Annex 11: Impact analysis of all policy measures

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A.1. Introduction

This appendix provides an assessment of the likely impacts of each of the 77 policy measures considered as part of the impact assessment study.

The presentation also includes the 10 pivotal policy measures that were identified from within the 77 measures, based on the initial assessment of the long list, as being of critical importance for the revisions to the legislation, and which have therefore been looked at in more depth. The pivotal measures are also presented in the main report of the study supporting the IA and the accompanying Staff Working Document. The assessment of the remaining policy measures is only presented here in the appendices.

For ease of reference, Table 1 presents the titles and reference number for each of the long list of 77 measures that have been assessed by the study team, the results of which are presented in some detail over the next 70 pages.

The measures are organised by policy block (e.g. antimicrobial resistance [AMR]), with the different combinations of policy elements set out under each of the three policy options. The tabular presentation allows the reader to more readily understand the different combinations of policy elements that have been brought together for each policy block, and with the common elements being tagged as such. For example, under the 'incentives for innovation' Policy Block, policy element C.1.1. is the same as policy element B.1.1. and C.1.8. is the same as B.1.8 and so on.

Option C is the most comprehensive of the three policy options and is expected to become the preferred option, having been able to strike the best balance between encouraging further innovation, supporting a strategic industry, while promoting improvements in access, affordability and environmental impact. The 77 measures are considered from the perspective of the current baseline and the specific policy option. The pivotal measures are listed in **bold**, to distinguish them visually from the other policy measures some of which may yet be included in the Commission's final proposals for the revisions.

Appendix B presents a similar overview of the 30+ horizontal measures that have been identified as a possible means by which to streamline the regulatory system in order to speed up assessments and otherwise reduce administrative burden. These measures would apply in principal to any of the three policy options, and have therefore been presented once only. The initial assessment of the long list of horizontal measures has been used as the basis for selecting a series of 10 pivotal horizontal measures, which are looked at in more depth and have been the subject of our cost-benefit analysis.

Table 1 Principal policy elements considered under each of the three policy options

Option A	Option B	Option C
Incentives for innovation, in particular to address unmet medical needs (UMNs)		
A.1.1. PRIME remains under the current scheme (i.e. not included in the legislation). A.1.2. Establish a non-binding system for scientific assessment of evidence for repurposing A.1.3 Add a special incentive bonus (+1 year): of regulatory (data) protection for products with a demonstrated ability to address an UMN A.1.4. Special incentive bonus: if data package includes	B.1.1. Codification of PRIME in the legislation B.1.2. Establish a binding system for scientific assessment for repurposing B.1.3. Obligation for MAHs to include a new indication when supported by scientific evidence	C.1.1. As B.1.1 Codification of PRIME in the legislation C.1.2. As B.1.2 Establish a binding system for scientific assessment for repurposing

Option A	Option B	Option C
comparative trial with standard of care (+6 months)	B.1.4. Reduce duration of incentives for originators from 8+2 to 6+2 years B.1.5. Medicines with demonstrated ability to address UMN get +2 years data protection. B.1.6. Breaking market protection in case of urgency B.1.7. Require transparency on any relevant public contribution or funding B.1.8. Give regulators the possibility to impose a post authorisation obligation for additional studies	C.1.3. Additional data protection period for the new evidence generated to support repurposing **C.1.4. Reduce duration of incentives for originators from 8+2 to 6+2 years (but with +2 years for launch in all markets [C.4.3.])** **C.1.5 As B.1.5 Medicines with demonstrated ability to address UMN get +1-year data protection.** **C.1.6. Same as A.1.4. Incentive bonus: if data package includes comparative trial (+6 months)** **C.1.7 Transparency on public contribution to clinical trials.** C.1.8 As B.1.8. Allow regulators to impose a post authorisation obligation for additional studies C.1.9. Breaking market protection in case of urgency
AMR specific		
A.2.1. Harmonisation of summary of product characteristics for nationally authorised antimicrobials to support prescription practices. A.2.2 Transferable voucher independent and in addition to data/market protection for antimicrobial products A.2.3. Consider adapted system for authorisation of phage therapies and other alternative products	B.2.1 Make central procedure mandatory for new antimicrobials. B.2.2. PRIME like support scheme, including rolling review B.2.3. Optimise package size B.2.4. Stricter rules on disposal B.2.5. Tighten prescription requirements B.2.6. Mandatory use of diagnostics B.2.7. Pay or play model B.2.8. Establish a monitoring system for consumption and use and the environment B.2.9. same as A.2.3	C.2.1. Novel antimicrobials fall in the CAP mandatory scope C.2.2. PRIME like support scheme, including rolling review C.2.3 Require companies to develop AMR lifecycle management plan C.2.4. same as B.2.3: Optimise package size C.2.5. same as B.2.5: Tighten prescription requirements for antimicrobials **C.2.6. Transferable voucher independent and in addition to data/market protection for antimicrobial products.** C.2.7. Consider adapted system for authorisation of phage therapies and other alternative products

Option A	Option B	Option C
Future proofing		
A.3.1. Maintain current exemptions from the scope of the legislation – add some clarifications/conditions *GMO OPTIONS* A.3.2. Clinical trials: a risk-based approach is applied to determine when a specific GMO assessment is required. A.3.3. An environmental risk assessment continues to be performed (by EMA) in the context of the marketing authorisation procedure.	B.3.1. Adapted regulatory framework for certain categories of novel products/technologies *GMO OPTIONS* B.3.2. same as A.3.2 but for clinical trials: Where required, the assessment of the GMO aspects of investigational medicinal products is performed at Member State level B.3.3. Adapt certain definitions, including that of medicinal product and *delink scope from industrial process*. B.3.4. Create a central *classification mechanism* for advice on whether products are medicines or not	C.3.1. Adapted regulatory framework for certain categories of novel products/technologies C.3.2. Clinical trials: a risk-based approach is applied to determine when a specific GMO assessment is required. C.3.3. Same as B.3.3. Adapt certain definitions, including that of medicinal product and *delink scope from industrial process.* For specific cell-based (ATMP) medicinal products [*-link with revision of BTC legislation*]: C.3.4. adapted regulatory requirements to facilitate production in the hospital setting C.3.5. less complex cell-based medicinal products to be defined on the basis of clear risk-based approach C.3.6. Introduction of a regulatory sandbox environment, in the context of complex/cutting-edge 'medicinal product' C.3.7. Same as B.3.4. Create a central [i]*classification mechanism* for advice on whether products are medicines or not.
Access		
A.4.1. Facilitate 'multi country packs' with labelling to allow their placing on the market in several Member States. A.4.2. Milestone incentive – +6 months data protection if product marketed in all MS within 6 years. A.4.3. (non-regulatory option) Voluntary reporting of market launches within 2 years of centralised authorisation. A.4.4. Promote placing on the market in all Member States within 5 years	B.4.1. Conditional marketing authorisation: more powers to regulators to enforce obligations for post-market evidence generation. B.4.2. Require MAHs to notify regulators of their market launch intentions. B.4.3. Obligation to place a centrally authorised medicine on the market in the majority of Member States within 5 years B.4.4. Requirement to MAH applying for MRP/DCP to include small markets	C.4.1. Conditional marketing authorisation: UMN incentives are only granted upon switching to standard MA. C.4.2. same as A.4.1. Facilitate 'multi country packs' with labelling to allow their placing on the market in several Member States. **C.4.3. 2 years of protection conditional to launch of all EU markets within 2 years** C.4.4. same as B.4.4.: Requirement to MAH applying for MRP/DCP to include small markets
Competition: generic, biosimilar entry		
A.5.1. New simpler regulatory pathway for generics A.5.2 No change to current situation and no restriction on duplicate marketing authorisations.	B.5.1. same as A.5.1. New simpler regulatory pathway for generics B.5.2. Interchangeability of biosimilars with their reference product will be generally recognised	C.5.1. same as A.5.1. New simpler regulatory pathway for generics C.5.2. same as B.5.2. Interchangeability of biosimilars with their reference product will be generally recognised

Option A	Option B	Option C
	B.5.3. Broaden Bolar exemption B.5.4. Extend Bolar exemption beyond generics B.5.5. Specific (regulatory) incentive for a limited number of first biosimilars B.5.6.a. Reforming the duplicates regime: No auto-biologicals. B.5.6.b. Duplicates restricted to cases of IP protection or co-marketing	C.5.3. same as B.5.3. Broaden Bolar exemption C.5.4. same as B.5.4. Extend Bolar exemption beyond generics C.5.5. same as B.5.6.b Duplicates restricted to cases of intellectual property protection or co-marketing
Security of supply		
A.6.1. Encourage use of HMA/EMA guidance definitions A.6.2. Notifications two months in advance A.6.3. Marketing authorisation offered to another MAH before a permanent withdrawal A.6.4. Use of the Falsified Medicines Directive (FMD) system to monitor shortages A.6.5. EU coordination to exchange information on supply and supply chains	B.6.1. Introduce an EU definition of a shortage B.6.2. Increase notification period to 6 months in advance B.6.3. Shortage prevention and mitigation plans added to GMP for all medicines B.6.4. Stockpiling requirements for MAHs and wholesalers for critical medicines B.6.5. Introduce an EU shortage monitoring system B.6.6. Require specific penalties for breaking supply obligations. B.6.7. Expanded requirements for key suppliers and back-ups to diversify supply chain B.6.8. Increase transparency of the supply chain, including active supply sites.	**C.6.1. Introduce an EU definition of a shortage** **C.6.2.a. Withdrawals: Increase notification period to 12 months** **C.6.2.b and at least 6 months in advance for all shortages (non-withdrawal).** **C.6.2.c Introduce a common template for reporting withdrawals and shortages.** **C.6.3. Stockpiling requirements for MAHs for unfinished critical medicines, as appropriate** **C.6.4. same as A.6.3 Marketing authorisation offered for transfer to another MAH before a permanent withdrawal** **C.6.5. MAHs to have shortage prevention and mitigation plans for all medicines** **C.6.6. Monitoring remains at MS level, with information exchange based on national monitoring, using a common format** **C.6.7. Same as B.6.7. Expand requirements to diversify supply chains.** **C.6.8. Establish a mechanism of information exchange to identify bottlenecks / vulnerabilities** **C.6.9. same as B.6.8. B.6.8. Increase transparency of supply chains**
Quality and manufacturing		

Option A	Option B	Option C
A.7.1. Strengthen enforcement by introducing harmonised system of sanctions. A.7.2. Inclusion of the information on the sustainability performance of supply chains actors by using international standards in the application dossiers. A.7.3. Adaptation of legislation/inclusion of specific provisions covering new manufacturing methods	B.7.1. Improve oversight of supply chains *by modifying the provisions on inspections* B.7.2. Reinforcing Member States GMP and GDP inspections capacity by setting up a mandatory joint audit scheme. B.7.3. Stronger overall responsibilities of MAH over the entire supply chain. B.7.4. same as A.7.3. Adaptation of legislation/inclusion of specific provisions covering new manufacturing methods	C.7.1. Strengthen the oversight of the sites within a supply chain *by extending the scope of mandatory inspections and modifying provisions on inspections* C.7.2. Stronger EMA role in oversight of coordination of inspections, including in setting up multinational inspection teams. C.7.3. same as B.7.2. Reinforcing Member States GMP and GDP inspections capacity by setting up a mandatory joint audit scheme. C.7.4. same as A.7.3. Adaptation of legislation/inclusion of specific provisions covering new manufacturing methods
Address environmental challenges[ii]		
A.8.1. No change A.8.2. Obligation to include information on sustainability performance of supply chain using international standards	B.8.1. Include assessment of the environmental risk of manufacturing into ERA, including main supply chain actors (API, raw materials). B.8.2. Strengthen the ERA requirements and conditions of use for medicines B.8.3. Include the AMR aspects in GMP to address environmental challenges.	**C.8.1. Include assessment of the environmental risk of manufacturing into ERA, including main supply chain actors (API, raw materials).** **C.8.2. same as B.8.2. Strengthen the ERA requirements and conditions of use for medicines** **C.8.3. Advisory role of EMA on ERA and green manufacturing aspects and quality (e.g. with relation to generics)** **B.8.4. Include the AMR aspects in GMP to address environmental challenges.**
COVID-19 lessons learnt to be applied during and beyond crises		
A.9.1. No further changes apart from the extension of the EMA mandate	B.9.1. Refusal of immature applications B9.2. Codification of rolling reviews for UMNs	C.9.1. same as B.9.1. Refusal of immature applications

A.2. The baseline situation

A.2.1. Policy Block A (Baseline): support for innovation, including unmet medical needs

Table 2 presents a qualitative assessment of the likely future impacts of the current regulatory arrangements on innovation. It acknowledges that the current system – the baseline – has been a catalyst for innovation over the past 15 years and would be likely to continue to encourage innovation going forwards, were it to continue unchanged from its present arrangements. In simple terms, the table presents a dynamic view of the baseline situation.

Table 2 Baseline situation: assessment of future impacts of current incentives for innovation

Assessments of innovation related sub-themes
1. Incentives
The current system provides incentives for innovation in terms of data (8 years) and market protection (2 years) to give time to developers to recoup their investment by delaying the entry of generics or biosimilars. These are without prejudice to intellectual property (IP) protection and specific rewards and market exclusivity for orphan and paediatric indications. The evaluation found the expanded scope and harmonised incentives of the current regulatory system had contributed to the growing numbers of applications for new medicines received by the EMA. Feedback from originators underlines support for the status quo and the relevance of current incentives, while other stakeholder groups and especially the representatives of generic companies and patients' groups see the current arrangements as favouring one particular model of innovation, and to a degree that is not optimal over other important objectives are considered (e.g. patients' access to affordable medicines). We identified several factors that present challenges for the current arrangements' ability to continue to encourage innovation to the extent that it has done in the past. These issues largely revolve around the exciting advances in science and technology and the increasing numbers of more complex medicinal products and a greater diversity of manufacturing methodologies. These trends are largely to the cost and time of making and assessing applications, rather than acting as a brake on innovation, however, it is conceivable that the current system is feeding forward into developers' planning and causing originators to look at less ambitious candidates or even to look to other regulatory systems in the first instance. Another external factor includes the increasing cost of medicines research, with statistics showing a long-run decline in research productivity overall (based on average success rates across phases of development), albeit these data point to an improvement in regulatory submission success rates. This trend is possibly driven in part by regulators' encouragement of and reward for increasingly risky or aspirational research.[1] Given the long-run nature of medicines development cycles, we assume historical growth rates – in the numbers of innovative medicines – will continue to hold in the medium term but may start to slow slightly in the longer term. In 2021, the EMA approved 92 new medicines and 53 new active substances[2]. As such, EU health care systems and patients would continue to see an expanding pool of novel medicines and treatment options in the next five years with some fall off in the rates
2. Expedited regulatory schemes
The current legislation successfully introduced several new schemes such as conditional marketing authorisation (CMA) and accelerated assessment (AE) to allow earlier authorisation of innovative products of major interest for public health. These regulatory pathways have supported the authorisation of more innovative medicines, and these expedited schemes have been given a further boost by the EMA's introduction of the Priority Medicines Scheme (PRIME), which is outside the legislation currently, but is nonetheless attracting a growing number of applications for promising medicines that address unmet medical needs. Our consultations confirmed the added value of these expedited regulatory schemes from an innovation perspective, with originators expressing strong support for the retention or enhancement of these existing pathways. By contrast, while national competent authorities and health payers acknowledge the potential boost to innovation, there was a concern that these expedited pathways were being used more for the convenience of industry and less for public health. Health payers and HTAs argued that the CMA had encouraged early submission of immature applications, and that the resulting conditional authorisations were difficult to assess in terms of cost-effectiveness – against standard treatments – and that there was a hardening of attitudes towards these regulatory pathways, with approvals for reimbursement become less likely in the absence of supporting evidence. Analysis of EMA statistics show increasing numbers of applications and authorisations running through these expedited schemes, especially CMAs and PRIME, many of which relate to major innovations relating to unmet medical needs. We would expect this expansion in interest and activity to continue over the next 5-10 years – and possibly intensify – even within the current regulatory system. There is a good pipeline of novel medicines in development, driven in part by more specific regulatory actions in the EU and the US, and relating to rare diseases and paediatric medicines in particular.[3] There is a substantial and growing interest across all stakeholder groups in addressing a number of key aspects around unmet medical needs, whether that is coming from patients groups and health systems or regulators and payers wanting to

[1] For a trend analysis, see exhibit 27 of 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022.

[2] https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2021_en.pdf

3 https://invivo.pharmaintelligence.informa.com/-/media/supporting-documents/in-vivo-issue-pdfs/iv2003_lrs.pdf

Assessments of innovation related sub-themes
frame a coherent definition / set of criteria or major public private research initiatives seeking to develop breakthroughs around specific UMNs, such as the €2.4bn Innovative Health Initiative (IHI) supported by Horizon Europe. Perhaps most critical, there is evident growth in investment in cell and gene therapies, and the EMA and other regulators are handling a growing number of CGT / ATMP applications. This next wave of pharma technology has the potential to improved research productivity, accelerate innovation, expand treatment options and address UMNs and all within the existing regulatory arrangements.[4]
3. Repurposing
There is an extended length of (market) protection available for new indications/repurposed medicinal products, whereby the 8+2+(1) major development would be maintained The current legislative arrangements include a special incentive that encourages and rewards originators for identifying opportunities to extend the use of existing medicines to include new indications. This is used largely with newer medicines and is used less often with off-patent or off-label products, which is the main focus of concerns to promote repurposing. While repurposing was one aspect where all stakeholder groups judged the current arrangements to have been less effective in driving a significant change in behaviour, the EMA annual reports and statistical highlights show the number of extensions of indications recommended is increasing over time: 51 recommendations in 2017, 65 in 2018, 60 in 2019, 83 in 2020 and 80 in 2021.[5] From this perspective, the current arrangements are likely to see a growing number of extensions, however, the commercial uncertainty around repurposing suggest the current level of incentives are unlikely to result in a substantive change in the underlying level of repurposing of medicines. This may be the case for older medicines in particular, where there is a weaker business case for extensions, as products near the end of the patent or regulatory protection periods, and paradoxically where there is a greater likelihood that wider health benefits have been identified through off-label uses of existing medicines. Originators are motivated to apply for extensions to new indications in the early years following the original marketing authorisation, taking advantage of the 8+2+1 incentive, however the incentive is not always strong enough to offset the costs / risks associated with repurposing medicines as they approach the end of the period of IP or regulatory protection. For novel medicines, a continuation in the expansion in the numbers of new medicines being submitted to the EMA for assessment – and the growing number of positive opinions – is likely to continue to drive, indirectly, an expansion in the numbers of new indications / variations extensions applied for. The current regulatory arrangements are therefore likely to accommodate an increase in demand for extensions of existing medicines to new conditions, which will continue to expand treatment options for patients. Support for repurposing will remain quite limited.

Table 3 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories. For most impact types, we have concluded that the baseline policy option would be likely to have a largely neutral effect. That is, there would be no substantive change, positive or negative, in impacts over time. We foresee several areas of positive impact that reflect the current regulatory arrangements past successes, relating primarily to the realms of research and innovation, treatment options for patients and support to Europe's research-intensive pharmaceutical industry. There are many exciting new developments already in progress, around advanced therapies, novel products, next generation manufacturing, real-world evidence, and more. The current regulatory system has not impeded these global developments, and as such, one could expect the current regulation to continue to accommodate this progress and the benefits that will follow from it.

The current arrangements have not been particularly influential in changing behaviour around repurposing, albeit we would expect the gradual increase in the number of extensions to continue. In terms of the downside, the current system's expedited pathways are causing difficulties for health technology agencies nationally, which struggle to determine the cost-

[4] https://www.marketwatch.com/press-release/europe-cell-and-gene-therapy-market---size-by-type-by-distribution-channel-and-forecast-till-2022-2031-2022-03-22

[5] https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines/medicine-evaluation-figures#annual-medicines-highlights-(2015-2021)-section

effectiveness of new medicines with only limited data, and where there is less likelihood that these innovative treatments will be approved for reimbursement and where they are there may be less good treatment outcomes for patients as a higher proportion of expedited medicines prove to be less effective than had been anticipated.

Table 3 Baseline – Summary assessment of incentives for innovation

Policy sub-themes	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
Incentives	+++	+/-	+/-	+/-	+/-	+++	+/-	++	+/-
Expedited pathways	++	+/-	+/-	+/-	+/-	+	-	-	+/-
Repurposing	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

A.2.2. Policy Block B (Baseline): Antimicrobial Resistance (AMR)

As noted in the problem analysis, the EC has several flagship projects underway that aim to restrict and optimise the use of antimicrobials, which are encompassed by the EU One Health Action Plan against AMR (June 2017)[6] built on 3 main pillars:

- Making the EU a best practice region
- Boosting research, development and innovation
- Shaping the global agenda

The Commission has also adopted the first deliverables of the plan, for example the EU Guidelines on the prudent use of antimicrobials in human health.

These commitments are underlined by the EC 2020 Pharmaceutical Strategy, which highlights the importance of AMR in the context of unmet medical needs, and presents two flagship initiatives in the field of AMR: (i) a public procurement mechanism to generate pull incentives; (ii) a role for the new Health Emergency Response Authority (HERA) in the process of promoting investment and coordinating research, development, manufacturing, deployment and use of novel antibiotics; and it furthermore commits to (iii) Review the pharmaceutical legislation with the aim of restricting and optimising the use of antimicrobial medicines.

From the perspective of the EU general pharmaceutical legislation, the baseline is clear: the current legislation includes no special incentives or obligations for the development of or prudent use of antimicrobials. As such, we see no change in impact (across the different impact dimensions) if the current scenario were to continue.

While the current legislation is silent on AMR, statistics show that the problem is wide ranging and expected to worsen without further interventions by governments and health systems around the world.

- The social costs of AMR are high and increasing
  - It is estimated that each year about 670,000 infections occur, and that 33,000 Europeans die as a consequence of antibiotic-resistant bacteria. With the burden

[6] https://ec.europa.eu/health/antimicrobial-resistance/eu-action-antimicrobial-resistance_en

being highest in the elderly and infants[7]. It is also estimated that AMR costs the EU €1.5bn per year in healthcare costs and productivity losses.

- The use of antimicrobials in Europe is reducing overall but with substantial unevenness across the EU
  - Stewardship measures are expected to continue to restrict and optimise the use of antimicrobials overall, however, there is considerable variability in stewardship policies and practices across the EU.
- The global AM pipeline is much weaker than other therapeutic areas

The development challenge is widely documented, with a weak global pipeline that is not expected to be rebuilt without substantive public support, as there are evident and growing market failures, with an evident gap between the typical cost and scale of the scientific challenge involved in developing new antimicrobials and the typical income and profit that can be derived from sales of these products. Global efforts to reduce use is increasing this gap between costs and benefits.

- The WHO Global Observatory on Health Research and Development monitors antibacterial products in development, and its April 2021 dashboard[8] shows that as of September 2020, there was a total of 41 antibiotics and 27 non-traditional antibacterial agents in clinical development globally. Those 68 products are distributed across the three phases of clinical trials. Overall, the WHO concludes that the clinical pipeline and recently approved antibiotics are insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance.
- We would expect to see increasing support for innovation and novel antimicrobials, through major public research programmes, such as Horizon Europe, and other regulators' actions (FDA), which should help to sustain and possibly improve the global pipeline, from its admittedly weak status currently.

A.2.3. *Policy Block C (Baseline): Future Proofing*

To regulatory system needs to be adaptive to adequately protect public health[9]. Exclusions exist to limit the scope of what medicinal products fall within the pharmaceutical legislation (currently there are seven product categories excluded from the scope). However, novel medicines, approaches and processes which do not naturally meet the scope or definitions or which the legislation does not fully fit can therefore find themselves unregulated or subject to unintended barriers.

Our consultations and desk research suggest that advances in science and technology have led to several regulatory challenges:

- Delays and inefficiencies due to uncertainty around the most appropriate regulatory pathway(s) resulting in applications being assessed in several committees rather than

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[7] Cassini, A., Högberg, L. D., Plachouras, D., Quattrocchi, A., Hoxha, A., Simonsen, G. S., Colomb-Cotinat, M., Kretzschmar, M. E., Devleesschauwer, B., Cecchini, M., Ouakrim, D. A., Oliveira, T. C., Struelens, M. J., Suetens, C., Monnet, D. L., Strauss, R., Mertens, K., Struyf, T., Catry, B., … Hopkins, S. (2019). Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *The Lancet Infectious Diseases*, *19*(1), 56–66. https://doi.org/10.1016/S1473-3099(18)30605-4

[8] https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens

[9] Klein, K., Stolk, P., de Bruin, M. L., & Leufkens, H. (2021). Regulatory density as a means to refine current regulatory approaches for increasingly complex medicines. *Drug Discovery Today*, *26*(10), 2221–2225. https://doi.org/10.1016/J.DRUDIS.2021.04.005

one, additional external advice being sought, and applicants being asked to clarify evidence or resubmit applications. The problem is exacerbated by the fact that each committee's mandate is narrow, fitting to the scope of the framework under which is set up, and there is a lack of coordination/consultation between the committees.

- Legislative barriers within regulatory pathways and processes due to definitions and guidance that do not apply to changing technology and heterogenous interpretation of such guidance by member states.
- Several new technologies, product combinations and innovative processes are causing uncertainty regarding their inclusion within the scope of the legislation in part as a result of the narrowness of current definitions and uncertainty on which legislative framework is most appropriate. For instance, certain technologies can also be subject to other EU legal frameworks that provide for safety, quality and efficacy requirements such as those for medical devices, substances of human origin, etc.

Challenges are particularly evident around these key areas:

1. Gene Therapy medicinal products:
   - Advanced therapy medicinal products (ATMPs): ATMPS are highly innovative and complex medicines based on genes, tissue or cells. Classification of these complex products can be complicated due to difficulties to distinguish between different biological subcategories.[10] These classification challenges are further complicated by the blood, cells, tissue (BTC) legislation where there are difficulties distinguishing between BTC and medicines because of (a) different criteria set in the general pharmaceutical legislation (industrial process, intention to put on market, hospital exclusion) and in the ATMP regulation (substantial manipulation, non-homologous use) as well as (b) lack of coordination between authorities/advisory bodies in relevant sectors on interpretation of these borderline criteria.[11]
   - Hospital exemption: Target markets for ATMPs are often small and not appealing for larger pharmaceutical organisations to invest in their development. The hospital exemption (HE) was implemented to encourage ATMP production in the hospital setting for non-commercial purposes to facilitate patient access to affordable novel therapies. For example, the price of a CAR-T developed under the HE-ATMPs pathway is one-third of the cost of commercial CAR-Ts available.[12] However, the HE has been interpreted and implemented differently across Member States, which risks undermining patient safety[13]. This is because there is no requirement to collect data on safety of efficacy of HE products. Furthermore, HE products do not fall under the centralised procedure (CP) limiting patient access. However, the HE has enabled the manufacture of a 'modest' number (~12) of ATMPs within EU between 2009 and 2017[14]. There are also concerns the HE is creating a competitive

[10] Iglesias-López, C., Agustí, A., Obach, M., & Vallano, A. (2019). Regulatory framework for advanced therapy medicinal products in Europe and United States. *Frontiers in Pharmacology*, *10*(JULY), 921. https://doi.org/10.3389/FPHAR.2019.00921/BIBTEX

[11] BTC impact assessment

[12] Trias, E., Juan, M., Urbano-Ispizua, A. et al. The hospital exemption pathway for the approval of advanced therapy medicinal products: an underused opportunity? The case of the CAR-T ARI-0001. Bone Marrow Transplant 57, 156–159 (2022). https://doi.org/10.1038/s41409-021-01463-y

[13] EuropaBio (2020) *EU ATMP Hospital Exemption*.

[14] Coppens, D. G. M., Hoekman, J., de Bruin, M. L., Slaper-Cortenbach, I. C. M., Leufkens, H. G. M., Meij, P., & Gardarsdottir, H. (2020). Advanced therapy medicinal product manufacturing under the hospital exemption and other exemption pathways in seven European Union countries. *Cytotherapy*, *22*(10), 592–600. https://doi.org/10.1016/J.JCYT.2020.04.092

disadvantage to commercial ATMP developers that incur higher development costs through the CP.

2. Combinational products: Medicines are increasingly being used in combination with a medical device, usually to enable the delivery of the medicine. Medical products are regulated through the pharmaceutical legislation, whereas devices are regulated through the medical device legislation. However, these combinational products have brought regulatory difficulties for NCAs in terms of uncertainty whether they should be classified as a medical product or medical device and what regulatory framework applies.
3. Industrial process/manufacture: Technological and scientific advances have raised issues regarding the definition of 'industrial process' or 'industrial manufacture'; these terms were to limit the scope of what products fall within pharmaceutical legislation. Differences in the interpretation of the definition has caused challenges for Member States in determining what legislation is appropriate or created legislative gaps where products are not regulated, meaning some products are not regulated under pharmaceutical legislation when they should be, thus potentially compromising the safety of patients. This has been particularly problematic for bedside production, personalised medicines, industrially prepared radionucleotides and medical products derived from blood in the hospital setting.
4. Novel technologies and approaches: There is an increasing number of novel technologies and approaches emerging that are transforming the development and production of medicines[15]. Notable examples include the application of novel manufacturing approaches to a range of areas from developing personalised medicines to addressing medicine shortages. Other areas of notable advancement include the application of artificial intelligence to medicines in a range of areas from improving medicine development, clinical trials, and medicine manufacturing[16]. These rapidly advancing technologies are bringing new regulatory challenges in terms of how best to accommodate them under the current legislation.

Medicinal products that contain or consist of GMOs, such as gene based and cell-based therapies, will increasing become more important as they have great potential to treat a range of diseases, including areas of unmet medical needs. There are specific requirement for products contain or consist of GMOs. During marketing authorisation: the evaluation of the environmental impacts of medicinal products for human use that contain or consist of GMOs is done, in accordance with the principles set out in Directive 2001/18/EC, by EMA or the national competent authority, as applicable, in the context of the assessment of the marketing authorisation application pursuant to the medicinal product legislation. Investigational medicinal products for human use (those in clinical trials) that contain or consist of GMOs are subject to the GMO legislation. Some Member States apply Directive 2001/18/EC, other Member States apply Directive 2009/41/EC and others decide on a case-by-case basis or apply both. This creates complexities for developers as different MSs have different requirements and stakeholders involved, ultimately causing regulatory burdens and delays in

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[15] Anklam, E., Bahl, M. I., Ball, R., Beger, R. D., Cohen, J., Fitzpatrick, S., Girard, P., Halamoda-Kenzaoui, B., Hinton, D., Hirose, A., Hoeveler, A., Honma, M., Hugas, M., Ishida, S., Kass, G. E. N., Kojima, H., Krefting, I., Liachenko, S., Liu, Y., … Slikker, W. (2022). Emerging technologies and their impact on regulatory science. *Experimental Biology and Medicine*, *247*(1), 1–75. https://doi.org/10.1177/15353702211052280

[16] Paul, D., Sanap, G., Shenoy, S., Kalyane, D., Kalia, K., & Tekade, R. K. (2021). Artificial intelligence in drug discovery and development. *Drug Discovery Today*, *26*(1), 80–93. https://doi.org/10.1016/J.DRUDIS.2020.10.010

market authorisations. To overcome these challenges, NCAs and the EC have updated and published good practice documents and common application forms concerning the conduct of clinical trials with GMOs to harmonise approaches across Member States. Specific ERA for GMO-containing medicinal products has been introduced for certain categories of investigational medicinal products containing GMOs that are highly unlikely to pose a risk to the environment or to public health to simplify requirements for developers.

According to our stakeholder consultation the current approach is still not ideal, and these main challenges were highlighted:

- Delayed authorisations of GMO-containing therapies and ultimately slower access to medicines[17]: GMO assessments are complex and vary across the EU leading to delays in clinical trials and authorisation of GMO-containing medicinal products[18]. Further harmonisation is needed for Contained Use versus Deliberate Release classification, risk classifications for the same GMOs (within Contained Use), and data requirements (content and format). GMO assessments are not always necessary as exemplified by the temporary derogation from some provisions of the GMO requirements for potential COVID-19 treatments and vaccines.
- Increased cost and burden of clinical trials in EU leading to reduced attractiveness to conduct trials in EU[19]: The EU is considered less attractive than other regions for conducting clinical trials. The number of new gene therapy clinical trials is proportionally lower in EU (55% of all new clinical trials) than in North America (71% of all new clinical trials)[20].
- Reduced investment and consequently development of GMO containing therapies[21]: In the US, a "categorical exclusion" exists for gene therapies, vectored vaccines, and related recombinant viral or microbial products[22]. However, in the EU, these types of GMO-containing products require a GMO assessment. This is seen to be delaying and restricting access to GMO-containing medicinal products in the EU[23]. Furthermore,

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[17] Technopolis. (2022). *Stakeholder Consultation Narrative Data: KIIs, OPC, Targeted Survey*.

[18] Beattie, S. (2021). Call for More Effective Regulation of Clinical Trials with Advanced Therapy Medicinal Products Consisting of or Containing Genetically Modified Organisms in the European Union. *Human Gene Therapy*, *32*(19–20), 997–1003. https://doi.org/10.1089/hum.2021.058;

Lambot, N., Awigena-Cook, J., Reimer, T., Persson, A., Romanetto, J., Friedeberg, B., Acha, V., Dandapat, S., Ruppert, T., Correas, C., Wonnacott, K., Fleischmann, T., Holzhauser, C., Galaup, A., Montes, F., Garcia, S., Tellner, P., & Beattie, S. G. (2021). Clinical trials with investigational medicinal products consisting of or containing genetically modified organisms: implementation of Clinical Trials Regulation EU 536/2014. *Cell and Gene Therapy Insights*, *7*(9), 1093–1106. https://doi.org/10.18609/CGTI.2021.143

[19] Technopolis. (2022). *Stakeholder Consultation Narrative Data: KIIs, OPC, Targeted Survey*.

[20] Alliance for Regenerative Medicine. (2019). *CLINICAL TRIALS IN EUROPE: RECENT TRENDS IN ATMP DEVELOPMENT*. www.alliancerm.org

[21] Technopolis. (2022). *Stakeholder Consultation Narrative Data: KIIs, OPC, Targeted Survey*.

[22] U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research. (2015). *Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products; Guidance for Industry*. https://www.fda.gov/media/91425/download

[23] Iglesias-Lopez, C., Obach, M., Vallano, A., & Agustí, A. (2021). Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States. *Cytotherapy*, *23*(3), 261–274. https://doi.org/10.1016/J.JCYT.2020.11.008

globally companies invested €20.1B in cell- and gene- based therapies in 2021; EU only raised €2.9B funding which was down 8% compared to 2020[24].

- EU patients are at risk of not having access to novel life-saving therapies[25]: Developers plan to submit ten market authorisation applications (MAAs) for gene therapies in the United States (USA) next year (2022), whereas they only plan to submit two of these MAAs in the EU[26]. However, a retrospective analysis until 2020 reported the EU authorised fifteen ATMPs, compared to nine in the USA[27].

This suggests EU regulatory framework is not well aligned with other regions, and a proportion of new medicines are being developed and launched in other markets (US) rather than the EU. Thus, further streamlining and harmonisation of the GMO assessment process would be desirable to avoid unnecessary delays in authorisation of GMO-containing medicines and for EU to be competitive concerning innovation of GMO medicines. Otherwise, EU patients may be at risk of not having timely access to novel life-saving therapies.

Table 4 presents an assessment of the likely future scenario if the existing scope, definitions GMO requirements for market authorisation and clinical trials continue without amendment. For most impact types, we have concluded that the effect of the baseline policy option would be largely negative. This reflects the continuing and rapid pace of technological change which will increasingly challenge the legislation in this baseline situation leading to decreasing efficiency, predictability and gaps in the regulatory framework.

Table 4 Baseline Policy Option: summary assessment of future proofing

Policy sub-themes	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
Scope and definitions	-	-	+/-	-	-	-	+/-	-	+/-
GMOs	+/-	+/-	+/-	-	-	-	+/-	+/-	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

A.2.4. Policy Block D (Baseline): Access

To promote timely access to innovative medicines, particularly those that meet a previously unmet medical need or would be used in a public health emergency, the EMA may fast-track approval by granting a conditional marketing authorisation (CMA). This allows for medicines to enter the market on less comprehensive clinical data than normally required. It does,

[24] Alliance for Regenerative Medicine. (2022). *Cell & Gene State of the Industry Briefing*. https://alliancerm.org/arm-event/sotibriefing/;

Lambot, N., Awigena-Cook, J., Reimer, T., Persson, A., Romanetto, J., Friedeberg, B., Acha, V., Dandapat, S., Ruppert, T., Correas, C., Wonnacott, K., Fleischmann, T., Holzhauser, C., Galaup, A., Montes, F., Garcia, S., Tellner, P., & Beattie, S. G. (2021). Clinical trials with investigational medicinal products consisting of or containing genetically modified organisms: implementation of Clinical Trials Regulation EU 536/2014. *Cell and Gene Therapy Insights*, *7*(9), 1093–1106. https://doi.org/10.18609/CGTI.2021.143

[25] Technopolis. (2022). *Stakeholder Consultation Narrative Data: KIIs, OPC, Targeted Survey*.

[26] Alliance for Regenerative Medicine. (2022). *Cell & Gene State of the Industry Briefing*. https://alliancerm.org/arm-event/sotibriefing/

[27] Iglesias-Lopez, C., Obach, M., Vallano, A., & Agustí, A. (2021). Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States. *Cytotherapy*, *23*(3), 261–274. https://doi.org/10.1016/J.JCYT.2020.11.008

however, require the MAH to fulfil specific obligations including the generation of additional post-authorisation evidence.

At present, there is no obligation on MAHs of centrally authorised medicines to enter a specific number or a particular set of EU markets. The only legal provision, known as the 'sunset clause', that applies is that the MA will cease to be valid if a medicine is not placed on any EU market within three years of the authorisation being granted or if the medicine is removed from the market for three consecutive years. This provision, however, is satisfied by placement on a single EU market. The EU pharmaceutical legislation currently also does not provide any incentives for MAHs to place their products on markets that, on their own, do not offer a sufficient business case for doing so.

Table 5 Baseline situation: Access

Continuation of baseline situation: effect on access
1. Accelerated assessment
Accelerated procedures, conditional marketing authorisations (CMA) exist.
2. Obligations and incentives for placement on the market
For centrally authorised medicines companies market the product as they see fit in one or more Member States. Placing on the market in a single Member State satisfies the obligation to place on the EU market. There is a sunset clause - a marketing authorisation can be withdrawn if the product is not placed on the market within 3 years.

Technopolis Group, based on information provided by client

A 2019 longitudinal analysis of the CMA instrument has suggested it has primarily been used as a path for regulators and companies to take when available evidence was not (yet) strong enough to support a regular authorisation[28]. This study furthermore suggested the pathway is plagued by substantial ambiguity about the need to balance patient's need for swift access to potentially life-saving medicines on the one hand with generation of sufficient evidence on effectiveness and risk on the other. These concerns have been echoed by interviewed representatives of NCAs and public health organisations who fear that increased use of accelerate access pathways places a heavy burden on health systems charged with deciding whether to allow these fast-tracked medicines into packages of reimbursed care based on limited evidence. It stands to reason that without changes to the procedure or to the ability of regulators to enforce post-authorisation evidence generation obligations, this trend will continue to put pressure on health systems.

In the market access and pricing environment the current trend is towards increasing use of 'gatekeeping' measures and price controls[29]. Such measures may have the effect of further limiting the number of markets in which products are launched or causing longer delays between authorisation and availability. Although a 2018 study by Ferrario found that, for medicines launched between 2010 and 2014, the time between authorisation and first use of

[28] Hoekman, J., & Boon, W. (2019). Changing standards for drug approval: A longitudinal analysis of conditional marketing authorisation in the European Union. *Social Science & Medicine (1982)*, *222*, 76–83. https://doi.org/10.1016/J.SOCSCIMED.2018.12.025

[29] Deloitte Centre for Health Solutions. (2019). *Patient access to innovative medicines in Europe A collaborative and value based approach*.

cancer medicines had shortened[30], analysis by IQVIA has suggested that between 2014 and 2018 in several countries the average delay had increased.

Thus, there is an assumption that, without EU intervention, the problems of selective market entry and delayed patient access to innovative medicines could remain or even worsen.

Table 6 Baseline – Summary assessment of incentives for innovation

Policy sub-themes	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
Accelerated assessment	+/-	+/-	+/-	+/-	+/-	++	-	-	+/-
Obligations and incentives for placement on the market	+/-	+/-	+/-	+/-	+/-	+/-	-	-	+/-
OVERALL	+/-	+/-	+/-	+/-	+/-	++	--	--	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

A.2.5. Policy Block E (Baseline): Competition

Table 7 presents an assessment of the likely future scenario if the current arrangements on competition are continued with no changes. The current system has resulted in more generics and biosimilars entering EU markets and led to improved access to medicines and lowered healthcare costs.

Evidence from 2005 to 2015 for 7 chronic conditions shows that patient access to treatment has doubled while overall spending has remained flat.[31] In Germany, the waiting time for patients with rheumatoid arthritis to be treated with a biologic has been reduced from 7.4 years to 0.3 years after the introduction of biosimilars.[32] Currently, generics offer 80%[33] savings on average and biosimilars 20%[34] compared to originator products.

Table 7 Baseline situation: assessment of competition-related themes

Continuation of baseline situation: effect on competition-related subthemes
1. Regulatory measures
There are specific, abridged pathways that are applicable for generics and biosimilars.

[30] Ferrario, A. (2018). Time to Entry for New Cancer Medicines: From European Union-Wide Marketing Authorization to Patient Access in Belgium, Estonia, Scotland, and Sweden. *Value in Health : The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, *21*(7), 809–821. https://doi.org/10.1016/J.JVAL.2018.01.003

[31] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[32] https://www.pharmatimes.com/magazine/2021/may_2021/15_years_of_biosimilar_access_in_europe

[33] Mestre-Ferrandiz, J., Towse, A. & Berdud, M. Biosimilars: How Can Payers Get Long-Term Savings?. *PharmacoEconomics* **34**, 609–616 (2016).

[34] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilarsv

Continuation of baseline situation: effect on competition-related subthemes
Development and submission times for generics under Art. 10 (1) i.e. standard generic (abridged) application and Art. 10(3) i.e. hybrid (abridged) application are 2-5 and 3-7 years respectively, and are 5-8 years for biosimilars under Art. 10 (4).[35] Generics account for the majority of DCP/MRP applications.[36] Of these, the assessment usually takes 210 days with the national phase of DCP/MRP taking between 4 weeks and 2 years.[35]
2. Faster market access of generics and biosimilars
The Bolar exemption makes it possible to conduct the testing required to obtain regulatory approval for the generic/biosimilar to take place during the patent/supplementary-protection-certificate (SPC) protection period of the reference medicine. According to NCAs, payers and industry representatives (including generic industry representatives) interviewed for this study, this has been beneficial for entry of generics/biosimilars but the provision is applied differently in different member states.[37] There is currently no additional regulatory protection for new biosimilar products.
3. Duplicates
Ordinarily only one market authorisation is granted to an applicant for a specific medicinal product, however the applicant/holder can obtain a duplicate authorisation at reduced cost for the same medicinal product where "*there are objective verifiable reasons relating to public health regarding the availability of medicinal products to healthcare professionals and/or patients, or co-marketing reasons*". MAHs have been making use of this exception to obtain a duplicate authorisation for the first generic product on the basis that its inaugural launch into the market can improve availability. No changes to the duplicate regime will have implications for the biosimilar market (including anti-competitive effects) and could also undermine the availability of treatment options for patients despite the intention behind the existence of the duplicate MA provision.

The EMA has recommended approval of 5 biosimilars on average each year (based on 84 biosimilars authorised between 2006 and 2021[38]). It is however foreseen that the number of biosimilars approved will increase over time with regulatory protection running out on many biologics esp. in oncology. About 139 biologics are due to lose regulatory protection between 2021 and 2030.[39] EMA has recommended approval of 19 generics on average each year (296 generics authorised between 2006 and 2021[40]) with around 1015 MA applications submitted via the MRP/DCP procedures per year (based on 8120 applications under Art. 10.1 between 2006 and 2013[41]). If current compound annual growth rates for generics and biosimilars (7.1%[42] and 10.5%[43] respectively) are maintained to 2035, the European markets for these product

[35] Mohammed, Y.M. (2019) Regulatory pathways for development and submission activities. *Medical Writing*, 28(2), 8–19.

[36] Ebbers, H. C., Langedijk, J., Bouvy, J. C., Hoekman, J., Boon, W. P., de Jong, J. P., & De Bruin, M. L. (2015). An analysis of marketing authorisation applications via the mutual recognition and decentralised procedures in Europe. *European journal of clinical pharmacology*, *71*(10), 1237–1244.

[37] https://cms.law/en/content/download/77965/2989749/version/1/file/BolarProvisioninEU.pdf

[38] GaBI Online - Generics and Biosimilars Initiative. Biosimilars approved in Europe. Mol, Belgium: Pro Pharma Communications International. Available from: www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe

[39] https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?_=1640100592119

[40] EMA website

[41] Ebbers, H. C., Langedijk, J., Bouvy, J. C., Hoekman, J., Boon, W. P., de Jong, J. P., & De Bruin, M. L. (2015). An analysis of marketing authorisation applications via the mutual recognition and decentralised procedures in Europe. *European journal of clinical pharmacology*, *71*(10), 1237–1244.

[42] https://www.marketdataforecast.com/market-reports/europe-generic-drugs-market

[43] https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?_=1640100592119

types would reach around €175 billion and €36 billion respectively from values of €67 billion and €8.8 billion in 2021.

Table 8 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories. For most impact types, we have concluded that the effect of the baseline policy option would be largely neutral. Considering the current regulatory regime, we expect the positive impacts relating to increased competition, savings for health systems and access to patients to continue.

Table 8 Baseline Policy Option - Summary assessment of competition

Policy sub-themes	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
Regulatory measures	+/-	+/-	+/-	+/-	+	+/-	+	+	+/-
Faster market access of generics and biosimilars	+/-	+/-	+/-	+/-	+	+	+	+	+/-
Duplicates	+/-	+/-	+/-	+/-	-	+/-	-	-	+/-
OVERALL	+/-	+/-	+/-	+/-	+	+/-	+	+	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

A.2.6. *Policy Block F (Baseline): Supply Chain Security*

The EU pharmaceutical legislation currently has two provisions that directly connect to security of supply. The first (Article 23a) places an obligation on MAHs to notify NCAs in the relevant Member States if they expect a temporary or permanent withdrawal of an authorised medicine from an EU market. The second (Article 81) obliged MAHs and wholesalers to ensure appropriate and continued supplies of authorised medicines. Both articles need to be transposed into national legislation by the Member States, who may opt to add more specific requirements.

In December 2016, the EMA and Heads of Medicines Agencies (HMA) set up a 'Task Force on the Availability of Authorised Medicines for Human and Veterinary Use'. To improve the collection and standardisation of information on shortages across the EU, in 2019 this task force published a 'Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)'[44]. The guidance includes a template detailing what information should be included. However, many elements are not mandatory and, thus far, are not required by NCAs.

Table 9 Baseline situation: Security of supply

Market withdrawal notification system
• *Obligation to notify a withdrawal two months before the interruption in the placing on the market of the product (Article 23a)* • *Obligation to ensure appropriate and continued supplies by MAHs and distributors (Article 81).*
Detecting and reporting shortages

[44] European Medicines Agency. (2019). *Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)*.

Market withdrawal notification system
The EMA/HMA guidance on detecting and reporting medicine shortages.

Despite several methodological challenges posed by lack of standardised comprehensive data, available evidence suggests that across the EU the frequency of shortages and their impact on patients and healthcare providers is increasing. The expectation thus is that, without further action, supply chain disruptions and shortages will continue to happen. At the same time, MS have already introduced a variety of actions at the national level to help protect their security of supply[45]. The impact of these measures on preventing and mitigating the impact of shortages is not yet sufficiently understood but it is likely that, at least at the MS level, they can be effective in protecting the national availability of medicines.

Many MS have invested in recent years in setting up and/or improving shortage notification systems. This has resulted in increased notification of shortages and better insight into key issues such as the extent of the problem, products affected and causes. Nonetheless, substantial space remains to further improve and standardise the collection of information. Given the increasing emphasis on data collection, it may be expected that the costs associated with notifying shortages (to MAHs and wholesalers) and administratively processing notifications (by NCAs) will continue to rise. Introduction of more automated systems for detection of supply problems and sharing of information between parties, however, could reduce these costs.

Table 10 Baseline Policy Option - Summary assessment of competition

Policy sub-themes	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
Market withdrawal notification	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
Detecting and reporting shortages	+/-	-	+/-	+/-	+/-	+/-	-	+/-	+/-
OVERALL	+/-	-	+/-	+/-	+/-	+/-	-	+/-	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

A.2.7. Policy Block G (Baseline): Quality and Manufacturing

Table 11 presents an assessment of the likely future scenario if the current arrangements on quality and manufacturing are continued with no changes.

Table 11 Baseline situation: assessment of quality and manufacturing-related themes

Continuation of baseline situation: effect on quality and manufacturing
1. Inspections and sanctions

[45] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages* (Issue December).

Continuation of baseline situation: effect on quality and manufacturing
GMP inspections are carried out by national competent authorities (NCAs). The HMA (Joint Human and Veterinary) established an audit programme among the GMP inspectorates of all EEA GMP human and veterinary medicines agencies known as the Joint Audit Programme (JAP) in 2002.[46] Mutual recognition agreements are in place between 44 inspectorates to optimise the use of inspection resources; grant mutual recognition of reports, certificates, authorisations issued by national authorities; reduce technical barriers to trade and avoid duplication of audit work. Under Article 84(1) of Regulation (EC) No 726/2004 and Article 111(8) of Directive 2001/83/EC, Member States are asked to penalise marketing authorisation holders (MAHs) who fail their obligations. The penalties must be dissuasive, proportionate and effective. Such penalties however vary from country to country. Moreover, Regulation 2019/5 has changed the scope of financial penalties by including Article 84a on Regulation 726/2004. This article ensures that financial penalties imposed by the Commission are applicable to the correct legal entities, for example legal entities that are part of the same economic entity as the MAH, legal entities that have decisive influence over the MAH or that could address a non-compliance issue.
2. Sustainability performance of supply chain actors
Sustainability performance of supply chain actors is currently not included. Environmental risk of the API is covered under the ERA (as discussed in the next section).
3. New manufacturing methods
Non-industrial manufacturing methods such as decentralised, continuous manufacturing, etc are not accommodated adequately by the current legislation.

Table 12 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories. For most impact types, our assessment is that the effect would be largely neutral. We expect that inspections and sanctions will continue to involve administrative burden on the part of MAHs and NCAs.

Table 12 Baseline Policy Option - Summary assessment of quality and manufacturing-related measures

Policy sub-themes	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
Inspections and sanctions	+/-	-	+/-	+/-	+/-	+/-	-	+/-	+/-
Sustainability performance	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
New manufacturing methods	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

A.2.8. Policy Block H (Baseline): Addressing environmental challenges

Table 13 presents an assessment of the likely future scenario if the current arrangements for addressing environmental challenges are retained.

The ERA is the main mechanism within the current legislation for ensuring environmental sustainability of pharmaceuticals. It is required for all new MA applications whether through a centralised, mutual recognition, decentralised or national procedure and ensures the

[46] https://www.hma.eu/about-hma/working-groups/hma/ema-joint-audit-programme-jap/hma/ema-joint-audit-programme-jap.html

potential environmental risks of pharmaceuticals are adequately assessed. While the outcome of the ERA does not affect the decision to award an MA, it serves as the basis for minimising the amount of pharmaceuticals released into the environment (using appropriate measures), identification of specific risk-minimisation activities to be undertaken by the user of the medicine and appropriate labelling to ensure correct disposal.[47]

Table 13 Baseline situation: assessment of themes addressing environmental challenges

Continuation of baseline situation: effect on addressing environmental challenges
1. Environmental risk assessment (ERA)
If no changes are made to current requirements, the ERA would continue to be performed by companies when applying for an MA. A 0.01 µg/L threshold value for predicted environmental concentration in surface water (PEC_{SW})[48] would continue to be used and any active substance with PEC_{SW} greater than this threshold would undergo further assessment as to its fate in the environment and potential effects on representative organisms. Thereafter precautionary measures or recommendations to minimise risk would be provided if necessary.

Table 14 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories. For most impact types, we have concluded that the effect of the baseline policy option would be largely neutral. Continued review of potential risks to environment from medicinal products and increased awareness of and promotion of prudent use of pharmaceuticals (outside the legislation e.g. based on the European Union Strategic Approach to Pharmaceuticals in the Environment[49]) could help drive down emissions of pharmaceuticals in the environment and improve waste management to some extent, at least for medicines requiring new MAs.

The impact of these measures on patient and public health is however unknown. There is not enough evidence to show the direct effect of pharmaceutical residues found in the environment e.g. drinking water on human health. The potential effect of long-term exposure on vulnerable populations is also as yet unknown. Potential impacts of AMR have already been covered above.

Table 14 Baseline – Summary assessment of measures to address environmental challenges

Policy sub-themes	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
ERA	+/-	+/-	+/-	+/-	+/-	+/-	+/-	unknown	+

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

A.2.9. Policy Block I (Baseline): Lessons from COVID-19

The pandemic has underlined the added value of an EU-level response to a global pandemic and has resulted in Member States agreeing to extend the role of the EMA in respect to future crises, with the publication of the Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices.

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[47] EMA. (n.d.). *Environmental risk-assessment of medicines*.

[48] Whomsley, R., Brendler-Schwaab, S., Griffin, E. *et al.* Commentary on the draft revised guideline on the environmental risk assessment of medicinal products for human use. *Environ Sci Eur* **31,** 17 (2019).

[49] European Commission, 2019. European Union Strategic Approach to Pharmaceuticals in the Environment

The EMA is now responsible for monitoring medicine shortages that might lead to a crisis, as well as reporting shortages of critical medicines during a crisis. It is also updating the role of the EU Single Point of Contact (SPOC) network, to improve the flow / exchange information on shortages among member states and provide recommendations on management of shortages. The EMA is also updating its plan for Emerging Health Threats; and establishing a list of the main therapeutic groups of medicines necessary for emergency care, surgeries and intensive care, to help prepare the lists of critical medicines to respond to public health emergencies or major events. The EMA will also invest in real-world evidence efforts through the establishment of DARWIN EU[50], a pan-European network of real-world data.

The pandemic focused attention on the EU's ability to forecast demand during crises, secure supplies and manage shortages of critical medicines going forwards.[51] There is an assumption that public health crises are highly likely to occur in future and that against the backdrop of a growing problem with medicines shortages more generally, there is a case for more concerted action at the EU level.

Moreover, learning from this exceptional experience, the EU has sought to improve the regulatory framework in two main areas: a) reducing the number of immature marketing authorisation applications, which can waste public authority resources and create uncertainty over decisions; b) providing a rolling review regulatory pathway for medicinal products addressing UMN, which will allow earlier engagement with developers around potentially critical new medicines.

Table 15 Baseline situation: assessment of lessons learned from the pandemic

Continuation of baseline situation: effect on shortages, resourcing and speed of assessment
Monitoring and mitigating shortages of medicines and devices
The EMA's extended mandate and the main actions agreed in respect to improving the management of shortages of critical medicines should produce improvements in the situation more generally, with greater coordination, data transparency and reallocation of medicines (cross-border) being expected to strengthen a Member State's ability to respond to any important shortages. The proposed European Shortages Monitoring Platform (ESMP) is planned to be implemented by early 2025 and should help to overcome some of the residual technical challenges relating to the fragmented and sometimes inconsistent implementation of reporting systems nationally. The question of interoperability will need to be tackled also through agreements on common data records, architectures, process definitions, etc.
Reducing numbers of immature marketing authorisation applications
Assessment procedures for CMAs usually involve resolving differences of opinions among regulators regarding the evaluability or suitability of a marketing authorisation application for processing through the CMA pathway. This can be time consuming and slow down the approval process. Between 2006 and 2016, the median number of days spent on assessment procedures for CMAs was 421 (329-491), in comparison to 337 (281-400) for standard applications in the same period. There were 30 CMA granted and 22 unsuccessful CMA applications in the same period. From these 52 applications, 24 did not include a proposal for CMA in the initial application, despite not qualifying for standard marketing authorisation.
Rolling reviews of innovative medicines addressing an unmet medical need
Unmet medical needs (UMN) are usually conditions that are complex and/or affect small patient populations, which creates uncertainty for medicinal product developers and results in a market failure. Creating better regulator/developer interaction and reducing the approval time for medicinal products addressing UMN can bring very important benefits for patients. The median approval time for medicinal products that address UMN (accelerated assessment) between 2016 and 2020 was 251 days, with an average reduction in the approval time

[50] https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu

[51] https://www.ema.europa.eu/en/documents/other/reflection-paper-forecasting-demand-medicinal-products-eu/eea_en.pdf https://www.ema.europa.eu/en/documents/other/reflection-paper-forecasting-demand-medicinal-products-eu/eea_en.pdf

Continuation of baseline situation: effect on shortages, resourcing and speed of assessment
of 1.5 days per year. Rolling reviews for medicinal products that address UMN could help to reduce the total approval time.

Table 16 presents our summary assessment of the likely future impacts of the baseline policy option on each of our main impact categories.

Table 16 Baseline – Summary assessment of lessons learned from the pandemic

Policy sub-themes	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
Managing shortages	+/-	-	+/-	+/-	+	+/-	+	++	+/-
Immature marketing authorisation applications	+/-	+/-	+/-	+/-	+/-	+/-	-	+/-	+/-
Rolling Reviews for UMN	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

A.3. Policy Option A

A.3.1. Policy Block A (A.A): support for innovation, including unmet medical needs

Assessment of the key impacts for the policy elements

Table 17 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

Table 17 Option A - Assessment of the proposed Incentives for Innovation

Assessment
1. Expedited regulatory schemes
A.1.1. PRIME – remains under the current scheme
This is business as usual (BAU) and as such there would be no additional impacts in comparison with the baseline policy option discussed earlier.
2. Repurposing
A.1.2. Establish a non-binding system for scientific assessment
The ability to include academic and other scientific evidence within applications for extensions might encourage MAHs to seek approvals for repurposing medicines that are being used off-label, albeit these tend to be older medicines where there is less opportunity to secure sufficient additional income to offset the costs of repurposing.

Research suggests that where new indications are added, this tends to happen earlier in the period of regulatory protection.[52]

Moreover, due to the non-binding nature of this policy element, companies are expected to keep deciding not to go on-label for certain extensions if this could affect their more lucrative on-label indications[53] or for liability reasons.

Given these competing pressures on MA holders, the initiative seems unlikely to have a significant impact on the level of repurposing overall.

Where it is implemented, the initiative would not impose significant additional costs for developers, as the use of this broader evidence base would be voluntary. Moreover, updating the SmPC and printing an indication on the product's label does not involve substantial extra costs. Small administrative costs are expected related to pharmacovigilance (smaller relative to a binding system).

EMA statistics show an upward trend in the annual number of extensions of indications it is recommending (87 in 2021, up from 83 in 2020 and 60 in 2019), with an annual growth rate of 5-10%.

We assume a non-binding system would at best increase that growth rate only marginally, by one or two percentage points, perhaps reaching an annual growth rate of 6-12%. In the longer term, even such a small boost to repurposing, would result in perhaps tens of additional treatment options for patients and expanded geographical access to those now on-label medicines.

3. Incentives: Adaptation of the period of regulatory protection

A.1.3 A special incentive bonus for products with a demonstrated ability to address an UMN.

An additional year of regulatory protection would increase the numbers of medicines being developed for UMNs

The baseline of c. 15 UMNs a year might be increased by 2-4 products a year

This would result in additional income for originators of perhaps €320m-€640m, associated with those products (based on €160m average peak sales in the EU)

The bonus would result in a delay in the market entry for generics for these additional products, which might amount to a loss of income of around €77m-€154m a year for the generics industry

A small additional administrative burden for originators, assuming the burden of proof for demonstrating that a product meets the UMN criterion falls on the MAH applicant

There would be some additional costs for health payers, which result from the delay in the market entry of generic competition. This may amount to €163m-€326m a year

A small additional cost for regulators involved in the development of the UMN criteria and the implementation of the UMN 'test'

There would be an improvement in patient benefits from the expansion in the flow of medicines addressing UMNs

A.1.4. Special incentive bonus: if data package includes comparative trial with standard of care (+6 months)

We assume a 6-month extension might increase the use of comparative trials for 8-10 products a year.

We assume the additional costs of a comparative trial design might amount to €10m.

With average additional peak income (EU) of €160m, a 6-month extension might secure an additional €80m in income, or €640m-€800m a year in additional protected sales for originators

The bonus would result in a delay in the market entry for generics for these additional products, which might amount to a loss of income of around €154m-€192m a year for the generics industry

There would be some additional costs for health payers, which result from the delay in the market entry of generic competition. This may amount to €326m-€408m a year

This should deliver faster access to markets and costs savings thanks to improved reimbursement decisions

Moore et al (2020) in a review of 101 new FDA medicines (225 individual clinical trials), found the median cost of an individual clinical trial was around $19m (range = $12m-$33m).[54] They found the Phase 3 development costs almost doubled with second trial (albeit the single biggest cost driver is the number of patients).

[52] Sahragardjoonegani, B., Beall, R.F., Kesselheim, A.S. *et al.* Repurposing existing drugs for new uses: a cohort study of the frequency of FDA-granted new indication exclusivities since 1997. *Journal of Pharmaceutical Policy and Practice* **14,** 3 (2021). https://doi.org/10.1186/s40545-020-00282-8

[53] https://www.fiercepharma.com/sales-and-marketing/sanofi-pulls-campath-to-clear-way-for-higher-priced-lemtrada

[54] Moore, T. J., Heyward, J., Anderson, G., & Alexander, G. C. (2020). Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015–2017: a cross-sectional study. *BMJ open*, *10*(6), e038863.

Moore et al identified 62 (27.5%) of the total set of 225 clinical trials had a comparison group rather than a placebo or uncontrolled trial.

Assessment of the principal costs and benefits by impact type

Table 18 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block A under Policy Option A and for each impact type.

Table 18 Option A - Summary assessment Incentives for innovation

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
A.1.1.	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
A.1.2.	+/-	+/-	+/-	+/-	+/-	+/-	-	+/-	+/-
A.1.3	+	-	+/-	+	+/-	+	-	+	+/-
A.1.4.	+	-	+/-	+/-	+/-	+	+	+	+/-
Overall impact	+	-	+/-	+	+/-	+	-	+	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

In summary, the introduction of:

- A special incentive bonus for UMNs should have a positive impact overall. It would bring additional costs for developers offset by an additional period of premium pricing, which should support an increase in R&D investment and expand the numbers of products in the pipeline. This should flow through to an increase in treatment options and benefit more patients. There may be substantial deadweight costs associated with the additional rewards granted to products that would have been developed without the bonus
- A special incentive bonus for comparative trials should have a positive impact overall. It would bring limited additional costs for developers that should be more than offset by the additional protected income and a more straightforward and robust assessment by regulators, with any positive recommendations being accompanied by a better evidence base for HTAs, which should lead to a greater proportion of authorised medicines being approved for reimbursement and thereby improving treatment options and benefiting more patients
- A non-binding system for the scientific assessment of new evidence would be unlikely to have any significant impact on the underlying situation regarding the numbers of extensions to new indications or the repurposing of older medicines more generally, given the commercial uncertainty around repurposing and potential additional liabilities of third-party evidence

Assessment of synergies and tensions

Within the Policy Block, the three policy elements proposed under Policy Option A are complementary, comprising additional special bonus incentives for both novel innovations (new medicines relevant to UMNs; and for the use of comparative trials) and incremental innovations (e.g. the inclusion of additional types of scientific evidence to encourage MA holders to consider extending their existing medicines for use with new indications).

Assessment of the proposed incentives for antimicrobial resistance

Policy Option A proposes measures to stimulate the development of novel antimicrobials and comprises three policy elements. Table 19 presents an overview of these three proposals, noting the key design assumptions and likely strengths and weaknesses.

Table 19 Option A - Assessment of the proposed incentives for antimicrobial resistance

Assessment
A.2.1 Harmonisation of summary of product characteristics for nationally authorised antimicrobials to support prescription practices
The harmonisation process will affect market authorisation holders, in as much as any referral for reassessment will result in the company being invited to carry out a wide-ranging review of evidence on efficacy, indications, posology, etc. to prepare an up-to-date technical dossier for consideration by the EMA and a resulting new SmPC and Product Leaflet for sharing with member states. The Opsalka et al study suggests the majority of updated SmPCs would result in a narrower set of more specific indications and more stringent dosage guidelines, resulting in a reduction in the numbers of prescriptions and the associated volume / sale of those antimicrobials. In simple terms, updated SmPCs supports more prudent use and would result in lower sales volumes for the 3-5 MA holders subject to a reassessment each year.[55]
The reassessment process will bring additional regulatory compliance costs that could amount to many tens of thousands of Euros, and the proposed policy element might be expected to increase the numbers of MAHs affected from 1-2 a year to 3-5.
This policy element would not have a significant impact on SMEs. Nationally authorised antimicrobials tend to be the older, broad-spectrum antimicrobials manufactured by larger (generics) companies.
The policy element could have a small negative impact on the competitiveness of the EU generics industry, since it would create additional costs for small numbers of generics companies while also reducing their income from the assessed medicines (more prudent use). Given the focus on the most widely used, older antimicrobials, it would disadvantage some MA holders rather than all. Given the relatively narrow geographical markets of these medicines, the policy element may also have a relatively greater (negative) impact on those companies based in or focused on addressing the biggest current users of antimicrobials in the EU (e.g. Greece, Italy, Spain). Indirectly, it should reduce consumption overall, but may increase the diversity of use and in limiting some medicines, it may boost demand for other antimicrobials.
The policy element could have a small positive impact on the functioning of the single market, inasmuch as the harmonised SmPCs should result in more consistent prescription practice across the EU and broader / more consistent demand for these generic medicines across EU member states.
The reassessment process might entail some limited additional research by the MA holders and could trigger a small increase in the demand for work by technology consultancies or academic researchers. However, the number of harmonisation exercises is likely to be limited. We have estimated 3-5 reviews a year initially, perhaps increasing to 5-10 a year, if the process proves to be useful and the resources can be found to coordinate the reviews and manage the resulting assessments. From this perspective, the total additional investment in research might be €1m-€3m a year. The policy element is unlikely to have a direct impact on innovation, albeit indirectly, it may make a small contribution to increasing demand for newer and more novel antimicrobials.
There would be an additional cost for the EMA in overseeing the increase in the number of reviews / assessments from the current baseline. There would be additional costs too for member state regulators in providing at least some of the staff and scientist that will be involved in the assessments. There would also be some limited costs in the implementation of the resulting SmPCs nationally.
Patients should benefit from improved prescription with medicines being prescribed only where they are likely to be effective and at more prudent levels. There would be a one-off cost to national health systems when implementing the new SmPCs, and the need to update relevant guidance and otherwise communicate about the required changes in prescription. There should be a reduction in the usage of the affected medicines, which could save money, albeit this may be offset by healthcare practitioners prescribing different antimicrobials (some more expensive, and a greater diversity of consumption may also reduce discounts and increase prices). Indirectly and in the longer term, the reductions in overuse and misuse should have a positive impact on the number of instances of AMR in the EU and the negative health impacts associated with that. This is the most critical social benefit, however, an increase in harmonisation may have only modest impacts here.
The more prudent prescription of antimicrobials should result in fewer and smaller prescriptions. Indirectly and over the longer term, this should reduce usage overall in the EU.

[55] Opalska, A., Kwa, M., Leufkens, H., & Gardarsdottir, H. (2020). Enabling appropriate use of antibiotics: review of European Union procedures of harmonising product information, 2007 to 2020. *Eurosurveillance*, *25*(45), 2000035.

Assessment
These improvements should result in fewer antibiotics entering the environment (whether through lower levels of manufacturing activity, better stewardship, or improved disposal practices). If the harmonised SmPCs do affect prescribing behaviour (and there are some major cultural factors that could frustrate ambitions here), then the policy element's targeting of the oldest and most widely used antimicrobials could result in quite significant reductions in usage (especially in those countries with the highest per capita usage), so the volume of releases to the environment may be equally positive affected.
A.2.2. Transferable voucher (TV) independent to data/market protection for antimicrobial products
The right to be transferred relates to the transfer of the right to extend the data protection by a length to be determined. The assumption/calculation is based on an extension of data protection by 1 year. The antimicrobials that would be applicable to generate this right are all antimicrobials or a subgroup e.g. antibiotics only or their alternatives which either (i) represent a new class and/or new mode of action, addressing new target or absence of known cross-resistance (WHO innovation criteria) or candidates targeting priority pathogens (WHO list for antibiotics) or innovative platform technologies able to confer break-through clinical benefit, (ii) ground-breaking innovation within an existing class. The average number of TVs we expect per year is 1. EU JAMRAI predicts fewer. Companies may use a TV on existing successful medicines that are still covered by data protection, and which are still at least 2 years (EFPIA proposal) away from the expiry of their data protection period.[56,57] The TV would be most relevant to products where the last defence before generic entry is the regulatory protection. For those where there is a 10+ years patent or SPC protection, the extended data protection does not give any benefit. Hence, only a part of all products could benefit from a TV. In principle the extension would need to be sufficient to provide a substantial incentive to compensate for the development of a new antibiotic, which is estimated to be on the order of €1.2bn. However, the EU market is some 20% of the total pharmaceutical market globally, and so a proportionate contribution to the development cost with the EU voucher may be a sufficient incentive. It would be possible for companies to receive the right to a TV for antimicrobial products that were already in the pipeline ahead of the implementation of the new regulation, to generate additional income / profits within 2-3 years of implementation, and thereby underpin an early expansion in investments in novel antimicrobials. Based on the application of a voucher to an average top-10 product, we estimate an originator would secure an additional €543m in non-contested sales because of the 1-year extension. There would be a cost to the generics industry of a year's delay on the order of €164m. There would a cost to the health system too, which we estimate at €283m. We further estimate the patient + payer monetised loss would be on the order of €441m Some vouchers may be sold rather than used directly by the developer of the antimicrobial and we have estimated the average sale value of a voucher at €360m. Each year, about 33,000 Europeans die as a consequence of antibiotic-resistant bacteria.[58] On average, a hospitalised patient with antibiotic-resistant infections costs an additional 10,000 to 40,000 USD.[59] The expansion in the development and authorisation of novel anti-microbials should help to manage and even reduce AMR, with fewer hospitalisations and deaths, although it has so far not been possible to estimate the scale of these potential benefits, in order to compare with the social costs of the incentives for taxpayers and health payers.
A.2.3. Adapted system for authorisation of phages therapies and other alternative products
This policy element would support the development of phage therapies potentially increasing the number of companies willing to invest and develop these therapies which will in turn increase competition, reducing prices of these therapies. The use of phage therapies may also reduce healthcare costs/budgets since phages are an inexpensive natural resource present in the environment, and offer immense potential as an alternative when

[56] There is also the TEE: https://www.ifpma.org/wp-content/uploads/2018/09/IFPMA_AMR_Position_Incentives_Pull_2018.pdf

[57] Recent paper: https://healthpolicy.duke.edu/sites/default/files/2022-01/Transferable%20Exclusivity%20Voucher%20Program.pdf

[58] Cassini, A., Högberg, L. D., Plachouras, D., Quattrocchi, A., Hoxha, A., Simonsen, G. S., Colomb-Cotinat, M., Kretzschmar, M. E., Devleesschauwer, B., Cecchini, M., Ouakrim, D. A., Oliveira, T. C., Struelens, M. J., Suetens, C., Monnet, D. L., Strauss, R., Mertens, K., Struyf, T., Catry, B., … Hopkins, S. (2019). Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *The Lancet Infectious Diseases*, *19*(1), 56–66. https://doi.org/10.1016/S1473-3099(18)30605-4

[59] https://www.oecd.org/els/health-systems/Antimicrobial-Resistance-in-G7-Countries-and-Beyond.pdf

Assessment
antibiotics are rendered ineffective due to bacterial resistance[60]. Finally, by reducing the use of antibiotics it would help reduce the presence of antibiotics in the environment.

Summary assessment by impact type

Table 20 Option A - Summary assessment of prudent use of antimicrobials

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
A.2.1	-	--	-/+	-/+	+	-/+	-/+	++	+
A.2.2.	+++	-/+	+++	++	-/+	+++	---	+	+/-
A.2.3.	+	-/+	-/+	+	+	+	-	+	+
Overall impact	+++	--	+++	++	+	+++	---	++	+

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Assessment of any synergies and tensions within the Policy Block

Within the AMR Policy Block, the policy elements proposed under Policy Option A are largely complementary to each other, whereby the proposal to accelerate the rate at which SmPCs are harmonised and updated would address one of the key sources of differences in prescribing practices across the EU in respect to older, lower cost, broad spectrum antibiotics and should restrict and support more prudent use in general. The Transferrable Voucher addresses one of the other key challenges around AMR, which is the inadequacy of the global pipeline for antimicrobials and the substantial gap that exists between the cost to develop innovative antimicrobials and their likely market performance. Lastly, the proposal to adapt the legislation to allow authorisation of phage therapy is an important step to allow this promising alternative to conventional antibiotics to be further developed for safe use in humans. These proposals also fit well with the EC's AMR Action Plan and its objectives to increase innovation and reinforce prudent use.

Assuming novel antimicrobials might be considered to address an unmet medical need (UMN), there would be an additional synergy between the Transferrable Voucher proposed here and the proposal to extend the period of regulatory protection for medicinal products addressing an UMN, under the Innovation Policy Block. An additional period of regulatory protection for the novel antimicrobial would generate a period of additional revenue at premium prices (before generic entry) and thereby deliver an additional profit stream to support investment in antimicrobial R&D.

A.3.3. Policy Block C (A.C): Future Proofing

Policy Option A is a refinement of the current arrangements, with three principal interventions around scope and definitions and GMOs. Table 21 presents our schematic overview of these three proposals, noting the key design assumptions and likely strengths and weaknesses.

[60] https://www.nesta.org.uk/blog/when-the-drugs-dont-work-could-bacteriophages/?gclid=Cj0KCQjw_4-SBhCgARIsAAlegrUn5LXTOVza5VKzwfA4XcfpeUXcHW8jiSFfDhOBM2_MUMNcQ0GrXVQaAtQVEALw_wcB

Table 21 Option A - Assessment of the proposed incentives for Future Proofing

Assessment
1. Scope and Definitions
A.3.1 Maintain **current** exemptions from the **scope** of the legislation –add some **clarifications**/conditions
Technological advances are providing innovative medicines that test the limits of the pharmaceutical legislative framework in terms of scope and definitions. Products can end up in a legislative gap (such as novel manufacturing processes) or there is risk of duplication or misalignment between frameworks (BTC, clinical trials, hospital exemption). A.3.1 has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. It would also address the issues of accommodating technological advancements in the legislation. For instance, by promoting coordination with concerned authorities in particular in the framework of medical devices and substances of human origin. However, these impacts may be short term and not sustained as technological change is ongoing and increasing in pace the changes could soon be outdated and may lack flexibility to keep pace.
2. GMO
A.3.2 Clinical trials: a **risk-based** approach is applied to determine when a specific GMO assessment is required. Where required, the assessment of the GMO aspects of investigational medicinal products is performed by **EMA**, within the maximum timelines defined in the Clinical Trial Regulation (centralised assessment).
Clinical trials for investigational medicinal products (IMPs) for human use that contain or consist of GMOs are subject to both clinical trials and GMO legislations under national competences. This causes delays in clinical trials as the directives are not uniformly interpreted or applied between MSs and is especially problematic for clinical trials that are conducted over multiple MSs. These differences in interpretations also impact on the authorisation of GMO-containing medicinal products that fall under the mandatory scope of the centralised procedure creating complexities for developers as different MSs have different requirements and stakeholders involved, ultimately causing regulatory burdens and delays in market authorisations. A3.2 has potential to improve the efficiency of GMO assessment and thus accelerate authorisation of GMO-containing medicinal products by focussing regulatory efforts on GMO containing medicines that pose the greatest threat to the environment. A centralised approach to GMO assessment has already been adopted by the United States where the review of medicinal products containing GMOs has been centralised within the FDA to improve efficiency and regulatory agility[61].
A.3.3. An environmental risk assessment continues to be performed (by EMA) in the context of the marketing authorisation procedure
This is the same as business as usual for this element.

Table 22 contains a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under Option A.

Table 22 Option A - Summary assessment of future proofing

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
A.3.1	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
A.3.2	+	+	+	+	+	+	-	+	+/-
A.3.3.	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-

[61] U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research. (2015). *Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products; Guidance for Industry*. https://www.fda.gov/media/91425/download

Overall impact	+/-	+/-	+/-	+/-	+/-	+/-	-	+	+/-

Assessment of any synergies and tensions within the Policy Block

Policy option A is most like the baseline policy option and least impactful in terms of future proofing as it risks not keeping pace with new products and technologies. It is the least 'friendly' towards innovation due to relying on 'hard law' changes that would suffer the same issues in a short time and are not flexible enough to consistently adapt moving forwards. Ultimately this creates a tension with the overarching policy option goal to: "use additional incentives to address unmet medical needs and to support public health objectives."

Future proofing elements in this policy option related to risk-based approach for GMO assessments (A3.2) have synergies with innovation in UMN (Block A) in creating incentives and removing barriers for innovation. The element related to reduction of regulatory burden - definitions and scope (A3.1) has synergies with horizontal streamlining measures. There are also complementary measures in Block E (Creating new simpler regulatory pathway for generics (A.5.1), Block F (Encourage use of HMA/EMA guidance definitions A.6.1.) and Block G (Adaptation of legislation to cover new manufacturing methods (A.7.3.))

A.3.4. Policy Block D (A.D): Access

Assessment of the key impacts for the policy elements

Table 23 presents our broad assessment of the likely costs and benefits of each of the proposed legislative actions. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

Table 23 Option A - Assessment of the proposed elements to improve access

Assessment
A.4.1 Facilitate 'multi-country packs' with labelling to allow their placing on the market in several Member States with the same packaging and pack sizes
Currently, information on the pack (outside and inside) must be in the official language(s) of the MS where a product will be placed on the market, bar a few exceptions for certain products that are not intended to go directly to a patient. This language requirement, along with other potentially country-specific requirements, means that MAHs must produce packs specifically designed for each market. This increases production costs and may make smaller markets, where these costs cannot sufficiently be offset by revenues, commercially unattractive. Additionally, country-specific requirements can hinder the movement of medicines between different EU markets when products need to be repacked and relabelled, to meet all requirements of the importing country. Facilitating 'multi-country packs' may result in more products being placed on a greater number of markets, in particular smaller or less economically attractive markets. In addition, medicines can be moved between EU countries more easily to mitigate or resolve shortages. This would improve security of supply and mitigate some of the risks resulting from product unavailability (e.g. treatment interruption, suboptimal treatment with alternatives). It will, however, be important to ensure that use of multi-country packs does not limit the ability of patients and healthcare providers to access information regarding, for instance, the correct use and safety profile of medicines. No studies were identified that detail experiences with multi-country packs as a way to overcome access challenges and that thus could inform an estimation of impact. In economic terms, it is expected that multi-country packs would result in a cost saving to MAHs by reducing the number of different presentations they need to produce and streamlining production lines. The magnitude of these savings will depend primarily on the number of countries and languages included, whilst the size of the markets reached by multi-country packs will further influence the profit potential for the MAH.

In theory, multi-country packs may have the added benefit of facilitating joint procurement between countries. Several initiatives already exist whereby smaller countries engage in joint procurement to increase their purchasing power. Such initiatives have the potential to negotiate lower prices. A 2020 study for WHO shows that whilst these initiatives hold promise, they often take months or years of cooperation before tangible results are achieved[62]. The study did not specifically look at the role of multi-country packs in facilitating joint procurement.

A.4.2 Additional period of data protection [6 months] if proven that the product has been placed on the market in all Member States within 6 years of authorisation.

If the incentive succeeds in encouraging MAHs to place their products in a greater number of EU markets, this can have substantial positive impacts on access to medicines and consequently on the health and wellbeing of people in previously unserved markets. These impacts scale with the size of the target populations that would be reached but are also dependent on the ability of health systems in those markets to adequately diagnose conditions and provide appropriate treatment. As such, not all countries stand to equally benefit from such incentives. The impacts will also depend on product characteristics, whereby expanded access to medicines that address high unmet medical needs will have greater impact than other medicines.

The incentives, however, may carry a significant cost to national health systems and payers by potentially delaying generic entry. The cost of this to authorities, and conversely the value of the reward to MAHs, depends on by how much the additional period of regulatory data protection would extend the overall protection on the product that delays generic competition and on the likelihood of such competition emerging more generally (e.g. competition for biological and orphan medicines is often slow or non-existent even after expiry of any protections).

Although data protection can have significant (economic) value for innovators, in various consultations, industry stakeholders have suggested that additional regulatory protection of six months will not be an adequate incentive for wider market launch. Whether this will be the case will most likely depend on the balance between the expected ratio between the costs of doing business in less commercially attractive markets and the value of the incentive.

A.4.3 Promote a voluntary reporting of market launches and a commitment to initiate pricing negotiations in all MSs within 2 years of centralised authorisation. (non-regulatory option)

It is assumed that the EMA would serve as the central point of contact for reporting but that the information may then be shared also with authorities in each of the Member States. The policy element additionally intends to obtain a commitment from MAHs to initiate price negotiations in all MS. However, it is assumed that neither the EMA nor any other regulatory authority will be granted powers to monitor or enforce these (voluntary) commitments and that there will be no sanctions on MAHs when these commitments are not fulfilled. As such, it is difficult to see how this measure intends to achieve the desired impact of launch in a greater number of countries or earlier launch and, consequently, increased access.

Nonetheless, if the measure succeeds in obtaining commitments from MAHs to initiate price negotiations in all MSs within two years of granting of the MA, this may lead to earlier and wider access. It is expected that other factors (e.g. market characteristics and price policies) that currently influence where and when MAHs enter a market will continue to shape decision-making. As such, the impact of such a non-regulatory and voluntary measure on access may be rather limited.

A.4.4 Allow generic competition entry in the EU market, in case a centrally authorised medicine is <u>not</u> placed on the market in the majority of Member States (small markets included) within 5 years of granting the MA

Any measure that promotes market entry into a greater number of EU countries or accelerates access, will be beneficial to patients who are otherwise unable to access these medicines. The impacts of this measure will scale with the number of countries and patients reached and with the importance of the medicine. Earlier access to generic medicines will also improve patient access to (generic versions of) these medicines when generic competition comes in, provided that those generic versions will be placed on these markets.

Pressure to enter a set number of markets, at the threat of generic competition, may force companies to market these products in countries where it does not make commercial sense to do so. The question is whether the threat of loss of protection and earlier generic competition will be sufficient to overcome the lack of financial incentive for MAHs to enter such markets voluntarily. SPCs, orphan market exclusivity and regulatory data protection each carry a significant financial value and industry has often cited these instruments as essential to stimulate innovation. Limiting access to these protections, by making them conditional, could thus risk slowing down innovation.

[62] Cross-country collaborations to improve access to medicines and vaccines in the WHO European Region, (2020).

Changes to the entire system of intellectual property and regulatory protections for medicines to make them contingent on market placement should be expected to make the system considerably more complex. It will require regular reporting by MAHs on market launches and potentially verification of this information by regulatory authorities to determine whether the MAH has fulfilled all the conditions to be, or remain, eligible for such protections. Questions also remain as to how eligibility for protections would be affected if countries decide not to admit the medicine into the package of reimbursed care (and consequently there is no possibility for the MAH to place the product on that market) or if the duration of the decision-making on reimbursement is such that the 5-year period after granting of the MA is exceeded. In these cases, the MAH may lose its protection from generic competition because of factors outside of its immediate control. This may introduce unpredictability into the system that could discourage companies from entering the EU market, although the risk of this may still be limited as the EU represents a major pharmaceutical market which MAHs are unlikely to forego.

Summary assessment of the principal costs and benefits by impact type

Table 24 presents a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under Option A, for each impact type.

Table 24 Option A - Summary assessment of access elements

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
A.4.1	++	+	+/-	+	++	+/-	+	+	+/-
A.4.2	++	-	+/-	-	+	+/-	+/-	+	+/-
A.4.3	+/-	-	+/-	+/-	+/-	+/-	-	+	+/-
A.4.4	---	--	+/-	--	+/-	-	++	++	+/-
Overall impact	+/-	---	+/-	--	++	-	++	+++	+/-

- Facilitating the use of multi-country packs is expected to result in cost savings for MAHs by reducing the need for country-specific packaging and presentations and streamlining production lines. It may also facilitate the movement of medicines within the EU internal market, thereby promoting competition.
- Access to additional incentives for market entry in all EU countries grants MAHs a longer period of exclusive prices, representing increased revenue.
- An expectation to place centrally authorised medicines on the market in a majority of EU MS and a concomitant disincentive for not doing so in the form of loss of protection, may result in loss of revenue for innovator companies. This may make the EU market overall less attractive to these companies. Generic manufacturers on the other hand may benefit from this measure, as they may be granted earlier market access in the whole of the EU.
- MAHs will have to provide additional information to regulators to demonstrate their eligibility for incentives. This implies increased administrative costs. Increasing the number of MS in which the MAH places a product on the market may also increase the administrative cost of filing for (MRP/DCP) authorisation and the subsequent costs for interacting with regulatory agencies and health technology assessment bodies in these countries.
- The existence of intellectual property rights and regulatory protections is generally considered a driver for research and development of new medicines. By making access to these market protection mechanisms conditional and forcing MAH to operate in markets where they have no commercial interest, developers could be discouraged from investing in R&D.

- To determine eligibility with new incentives and qualification for existing protections, regulators (presumably the EMA) would incur greater costs due to an increased workload. Regulatory authorities in the MS where products are placed in the market will see an increase in cost due to a greater number of medicines for which they provide regulatory oversight. Similarly, HTA bodies will have to conduct a greater number of assessments.
- The intended and expected impact of increased access to medicine is that patients will be provided with earlier and wider access to more effective and safer treatments. This will have a positive impact on their health status and wellbeing. Whilst increased access to medicines is an intended positive outcome, it may result in increased health care expenditure. At the same time, new medicines may displace less (cost-)effective treatments, resulting in net savings. Further indirect savings from increased access to medicines may result from improved health and productivity.
- Granting of additional incentives (extension of regulatory data protection) that delay access to cheaper generic versions of medicines will lead to higher costs to payers / health systems. Conversely, allowing earlier generic entry when launch expectations are not sufficiently met, represents a cost saving.

Assessment of any synergies and tensions within the Policy Block

Facilitating the wider use of multi-country packs not only may be a way to address problems with selective market launches that ignore the needs of smaller markets but could also facilitate the movement of product between countries in case of supply disruptions and shortages. It therefore is synergistic with other measures to improve supply chain security discussed in Block F.

Extending the regulatory data protection period as an incentive for wider market launch needs to be considered alongside other proposed revisions to the system to incentivise innovation, in particular in areas of unmet medical need (e.g. Policy element B.1.4).

Introducing a market placement expectation and allowing earlier generic entry in case the expectation is not fulfilled will require simultaneous revision of several other parts of the EU pharmaceutical legislation for medicines, in particular the EU Orphan and Paediatric Regulations.

A.3.5. Policy Block E (A.E): Competition

Policy Option A is a refinement of the current legislative arrangements for encouraging competition, with only one change overall: A new simpler regulatory pathway for generics.

No other changes to the current situation are envisaged, including to the current conditions for duplicate MAs.

Assessment of the key impacts for the policy elements

Table 25 presents our assessment of the key impacts of each of the proposed measures, drawing on our consultations, desk research and targeted literature review.

Table 25 Option A - Assessment of the proposed measures for competition

Assessment
A.5.1 New simpler regulatory pathway for generics
The key impact from a simpler regulatory pathway with shorter approval times will be faster availability of generics to patients. It should create more clarity and potentially less administrative burden for marketing authorisation applicants, encouraging more applications and increased development activity for generics.

We assume that generics will be on the market soon after approval and access to generics will be similar in all member states. The latter assumption has been adopted for ease of analysis as generics market penetration varies considerably across member states[63] and would add uncertainties to our assessment.
A.5.2 No change to current situation and no restriction on duplicate marketing authorisations
This is business as usual (BAU) and as such there would be no additional impact, as compared with the baseline policy option. As such we assume that the types of products being developed will not change (as no change in Bolar provision) and behaviour around duplicate marketing authorisations will also remain the same.

Summary assessment of the principal costs and benefits by impact type

Table 26 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block A under Policy Option A and for each impact type.

Table 26 Option A - Summary assessment of the proposed measures for competition

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
A.5.1	+	+	+	+	+	+	+	+	-/+
A.5.2	-/+	-/+	-/+	-/+	+	-/+	+	+	-/+
Overall impact	+	+	+	+	+	+	+	+	-/+

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

The following key impacts are envisaged based on interviews (industry representatives and payers) and literature:

- Greater certainty for businesses in terms of their development cycles and application requirements for generics with reduced complexity of the submission because of the simplified pathway. This would improve the situation compared to the lack of clarity that has been reported regarding which current abridged application procedures (generic or hybrid) should be followed[64]
- A high likelihood of positive impact through making medicines more readily available to those that need them and reducing costs for health systems (generics represent around 80% cost reduction compared to originators, and entry of a generic also reduces price of the off-patent medicine by 61%[65]; biosimilars are 20% cheaper[66] compared to originator products)
- Benefit to patients (and public health) through the greater likelihood that getting MA for generics will be easier and quicker, and thus access to medicines will be improved

[63] Wouters OJ, Kanavos PG, McKEE M. Comparing Generic Drug Markets in Europe and the United States: Prices, Volumes, and Spending. Milbank Q. 2017 Sep;95(3):554-601.

[64] *Klein, K., Stolk, P., De Bruin, M.L., Leufkens, H.G., Crommelin, D.J., & de Vlieger, J.S. (2019). The EU regulatory landscape of non-biological complex drugs (NBCDs) follow-on products: Observations and recommendations. European Journal of Pharmaceutical Sciences, 133, 228–235.*

[65] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[66] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilarsv

Assessment of any synergies and tensions within the Policy Block

This option does not present major changes compared to the current legislation, hence the opportunity for added impact in combination with other blocks is limited. Fundamentally, increasing competition via market entry of generics and biosimilars increases access and affordability and thus has added value in terms of improved patient health and lower costs for health systems. However, this added value will be in line with current benefits.

There is synergy with the horizontal measure of streamlining and harmonisation with making the regulatory pathway for generics simpler. No change to the duplicates regime creates some tensions with regard to timely availability of biosimilars on the market and thus access.

A.3.6. Policy Block F (A.F): Supply Chain Security

Option A includes a variety of measures aimed at improving the availability, quality, timeliness, and exchange of information about (potential) shortages (A.6.1, A.6.2, A.6.4, A.6.5). The underlying idea is that such information will allow authorities and other parties to better mitigate the impact of supply disruptions and thereby reduce negative health impacts and costs. It would furthermore also improve the understanding of the causes of shortages and of what products are at increased risk.

The option additionally seeks to preserve the availability of medicines that the MAH intends to withdraw from the market by mandating that the MA is first offered to another party (A.6.3).

Assessment of the key impacts for the policy elements

Table 27 presents our assessment of the key impacts of each of the proposed measures, drawing on our consultations, desk research and targeted literature review.

Table 27 Option A - Assessment of the proposed measures for Supply Chain Security

Assessment
A.6.1 Encourage the use of HMA/EMA guidance definitions
Overall, encouragement of the use of standardised guidance definitions can help create a more harmonised system of shortage monitoring across the EU. It should be noted though that adoption of such a definition itself cannot directly reduce the incidence of shortages, but rather is a stepping-stone in the introduction of further harmonisation measures. If wider adoption of a single harmonised definition contributes to improved information sharing between MS about shortage situations, this may in turn support earlier identification of potential supply disruptions and more effective mitigation strategies. The impact of this will still depend to a large extent on how national authorities further operationalise these guidance definitions within their own notification systems.
A.6.2. Notifications two months in advance, encouraging the use of the HMA/EMA reporting template.
The current notification timeframe under Article 23a of two months stipulates the minimum in all EU countries. As such, A.6.2. does not constitute a change to the current timing of notification. It also emphasises the use of the HMA/EMA reporting template. The main foreseeable impact thus relates to the type and amount of information MAHs may be expected to provide. Whilst possible that, compared to the current situation, the information requirements would increase in some MS, standardisation of requested information is more likely to facilitate central coordination of shortage reporting, thereby reducing transactional costs. Potential impacts on the security of the supply of medicines are primarily indirect. Greater standardisation of information collected as part of shortage notifications likely will improve information sharing between countries and allow for a better understanding of the causes of shortages. This may allow for the development of more tailored policy approaches to address the issue of shortages at both EU and national levels and ultimately improve security of supply.
A.6.3 Marketing authorisation offered for transfer to another MAH before a permanent withdrawal
Requiring a MAH to offer the MA to another party before allowing it to withdraw the product from a specific market could delay the original MAH's withdrawal decision, as it seeks to avoid enabling its own competitors. Hypothetically, requiring MAHs to offer the MA to another manufacturer could benefit such manufacturers who are enabled to market a product that already has an established patient base. However, as indicated previously,

a large proportion of product withdrawals can be traced to low product-level profitability[67]. It is not clear to what extent a MA transfer could effectively address these underlying profitability issues. Such transfers would only be feasible/interesting in case a product remains commercially interesting for the new MAH or if commercial viability is not required for another party to take over the MA (e.g. in case of transfer to a not-for-profit entity). The study team has identified no experiences with similar measures that could inform a (quantitative) estimation of potential impact. Moreover, the EU trade association for the generics industry (Medicines for Europe) has indicated that it considers this proposal unconstitutional and not compliant with the proportionality requirements of EU treaties. It indicates that permanent withdrawals for commercial reasons are often necessitated by national market conditions, such as pricing and reimbursement policies (e.g. price cuts, reference pricing, claw backs and rebates), that are imposed by Member States and over which the MAH has no control. Mandating that the MAH offers the authorisation to another party before allowing it to withdraw is therefore considered a form of regulatory expropriation in violation of Art. 16 of the European Charter of Fundamental Rights.
A.6.4. Use of the Falsified Medicines Directive (FMD) system to monitor shortages
EU-wide monitoring of shortages could reduce the need for decentralised notification and improve the quality of information available to stakeholders. Similar to B.6.1, better quality information could contribute to more effective prevention and mitigation strategies. Given the fact that the European Medicines Verification System (EMVS) is currently not yet deemed fit for purpose, this measure is likely to require a significant investment to develop the system in this direction. Some industry stakeholders have also called attention to the need for accelerating the implementation of IDMP/SPOR (IDentification of Medicinal Products[68]/Substances Products Organisations and Referentials) standards, which could improve data standardisation and linkage across systems and offer regulators more insight into supply chain structures, supply levels and demand.
A.6.5. EU coordination to exchange information on supply and supply chains to identify areas of consolidation

Summary assessment of the principal costs and benefits by impact type

Table 28 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block F under Policy Option A and for each impact type.

Table 28 Option A - Summary assessment of the proposed measures for supply chain security

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
A.6.1.	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+	+/-
A.6.2.	+/-	+	+/-	+/-	+/-	+/-	+/-	+	+/-
A.6.3.	-	-	+/-	-	+/-	+/-	+/-	++	+/-
A.6.4.	-	+	+/-	+/-	+/-	+/-	-	++	+/-
Overall impact	-	+/-	+/-	-	+/-	+/-	+/-	++	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

The following key impacts are envisaged:

- Collectively, the proposed measures are expected to allow for improved decision-making to prevent and mitigate the impact of shortages (A.6.1, A.6.2) and offer public authorities additional tools for protecting the domestic supply of medicines (A.6.3). If successful, this

[67] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages* (Issue December).

[68] IDMP is a suite of five standards developed within the International Organization for Standardization (ISO)

will in turn result in greater continuity of supply for medicines that are needed to offer appropriate healthcare to patients. Health care costs resulting from shortages would also be reduced.

- The costs associated with industry players are lower than in other policy options given that most measures are formulated in a non-binding language. The impact on industry players is therefore expected to be limited.

Assessment of any synergies and tensions within the Policy Block

The policy elements proposed for Security of Supply under the Option A are overall synergistic. The are no major areas where tensions are expected to arise if all these elements are implemented together.

A.3.7. Policy Block G (A.G): Quality and manufacturing

Assessment of the key impacts for the policy elements

Table 29 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing mainly on desk research and targeted literature review.

Table 29 Option A - Assessment of the proposed measures for quality and manufacturing

Assessment
A.7.1. Strengthen enforcement of responsibilities of MAH as regards the quality of the products by introducing harmonised system of sanctions
There is potential for more robust internal assessment before sanctions and less heterogeneity of sanctions across Member States. This would have a positive effect on quality standards in the long-term, with MAHs making sure to fulfil their obligations to avoid penalties. The harmonisation of sanctions may also positively impact the workload of the relevant competent authorities by streamlining the process. There may also be short and long-term negative effects on the EU pharma industry due to the financial costs of penalties incurred and reduction in international competitiveness of the sector if the sanctions regime is considered too severe. The burden of sanctions or threat thereof could present barriers for smaller actors such as SMEs, which could lead to companies leaving the sector or the EU.
A.7.2. Inclusion of the information on the sustainability performance of supply chains actors by using international standards in the application dossiers
The proposed measure would improve the sustainability of production of medicines, which would be favourable for the environment. However, companies (MA applicants) would be negatively affected due to the additional burden of collating and submitting this information and complexity of submission to comply with the environmental requirements. It may encourage more supplies to be sourced from the EU and will also have an impact on manufacturers in third countries.[69]
A.7.3. Adaption of legislation/inclusion of specific provision covering new manufacturing methods (decentralised, continuous manufacturing, etc) to ensure levels of quality and safety equivalent to current methods.
The proposed measure has the potential to bring several product categories that are currently excluded from the legislation into the fold and provide regulatory certainty to manufacturers. These include magistral formulae (pharmacy-based preparation for an individual patient), radionuclides in sealed sources, hospital-manufactured medicines, and single-batch medicines. In addition, manufacturing methods such as decentralised manufacturing (where manufacturing occurs at different locations) and 3D printing-based methods could be accommodated. Covering new manufacturing methods in the general pharmaceutical legislation has the main advantage of helping to standardise the methods themselves, quality control of the methods and resultant products and associated regulatory pathways at the EU level. Thus, there is a harmonisation benefit. Moreover, accommodating new technologies sends a positive signal to innovators as well as companies and will encourage more innovation

[69] Eeb. (2018). Policy options for regulating pharmaceuticals in the environment.

Assessment
and research activity and adoption of the new methods. There will be further knock-on effects on competition, competitiveness, and access to medicine. If greener manufacturing methods are used there will be an impact on environmental sustainability, but the likelihood and extent of that is unclear. With more certainty over the manufacturing methods and the resultant products as well as more medicine developers adopting these methods, we could imagine a very high increase in the number of new therapies in comparison to the baseline.

Summary assessment of the principal costs and benefits by impact type

Table 30 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block G under Policy Option A and for each impact type.

Table 30 Option A - Summary assessment of the proposed measures for quality and manufacturing

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
A.7.1	-	-	-	-	-	-/+	+	+/-	+/-
A.7.2	-	-	-	-	+	+/-	+/-	+/-	+
A.7.3	-/+	-/+	-/+	+	+	+	-/+	+	-/+
Overall impact	-	-	-	-	+	+	+	+	+

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

Some of the key costs and benefits are

- Additional transaction, compliance and administrative costs for businesses to adapt to the new regulatory and data requirements. These costs along with the threat of sanctions may have effects on international competitiveness and internal markets (e.g. security of supply)
- Future proofing for new manufacturing methods within the legislation could increase the competitiveness of the EU pharmaceutical sector, promote innovation and help improve sustainability (if new methods are greener)
- There is potential for public health impacts through improved sustainability (lower CO2 emissions) and new products coming on board (those manufactured using novel methods)

Assessment of any synergies and tensions within the Policy Block

There could be tensions between policy elements A.7.1 (harmonised system of sanctions) and A.7.3 (adaption of legislation for new manufacturing methods). While A.7.3 should ensure quality and safety standards of new manufacturing methods, which should result in more therapies being developed, A.7.1 may reduce this positive effect if the sanctions are not appropriately designed.

A.3.8. Policy Block H (A.H): Addressing environmental challenges

Policy Option A involves no changes to the ERA compared to the baseline. As such, there should be no change in impact compared with the baseline.

Table 31 Option B – Assessment of the proposed measures for addressing environmental challenges

Assessment
A.8.1. No legislative change; Continue the implementation of the actions under the EU Strategic approach to pharmaceuticals in the environment.
There should be no major change in impacts and costs compared to the baseline scenario except for positive environmental sustainability impacts to some extent owing to implementation of actions under the EU Strategic approach to pharmaceuticals in the environment outside the legislation.

Summary assessment of the principal costs and benefits by impact type

The table presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block H under Policy Option B for each impact type.

Table 32 Option A – Summary assessment of the proposed measures for environmental challenges

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
A.8.1.	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

A.3.9. Policy Block I (A.I): Lessons from COVID-19

Policy Option A refers to the EMA's extended mandate, which is the same as the baseline, and as such, the assessment of likely future benefits under the baseline / Option A is already presented above.

A.4. Policy Option B

A.4.1. Policy Block A (B.A): support for innovation, including unmet medical needs

Assessment of the key impacts for the policy elements

Policy Option B includes 3 sub-fields and 8 policy elements relating to Policy Block A and the legislation's support for innovation including unmet medical needs (UMNs).

Table 33 Option B - Assessment of the proposed Incentives for Innovation

Assessment
Expedited regulatory schemes
B.1.1. Codification of PRIME in the legislation
The inclusion of the PRIME scheme within the legislation would give a strong signal to developers that the EU is committed to increasing support for UMNs. It will also reassure developers that the scheme is permanent and that they continue to benefit from the active support that comes with PRIME designation (which is focused on medicines that promise a major therapeutic advantage in an area of unmet medical need). The scheme is well regarded by stakeholders (industry, regulators, health systems) and the EMA analysis of its first five years of operation found that PRIME designation is

Assessment
associated with faster assessment times and an improved likelihood of a positive recommendation for authorisation.[70] There should be no significant additional administrative or compliance costs for businesses, when compared with the current situation. Codification may increase the popularity of the scheme still further, and that may increase the number of companies that have to bear the administrative costs associated with making an unsuccessful PRIME-eligibility request. The popularity of the scheme has increased in the recent past (+15% between 2019 and 2020), and we would expect to see further growth in future. This would be even more likely should the EU implement an additional period of regulatory protection for UMNs. These additional costs (linked with unsuccessful requests) are being limited by an equivalent expansion in the number of medicines accepted onto the scheme, which has also increased (from 23% in 2018 to 33% in 2020). The impact on regulators should be broadly neutral, as while the scheme does involve additional effort to businesses with advice on the development of their PRIME-designated medicines, the resulting applications tend to be better framed and evidenced, making assessment more efficient and improving success rates for submissions (improving EMA productivity in this important area of UMNs). Small biopharma firms have a particular interest in advanced therapies relevant to UMNs, and the codification and expansion of PRIME ought to have positive impact of SMEs. They benefit disproportionately from EMA advice, where larger developers have considerably more experience in preparing an application for assessment. Moreover, for some startups (e.g. cell and gene therapy companies), PRIME may have the effect of a 'seal-of-approval,' which could improve their investability and market value. In the longer term, codification should reinforce the regulator's wider efforts to reduce UMNs, improving treatments, reducing hospitalisations and improving patients' quality of life. As with the other regulatory proposals designed to focus developers' attention on UMNs, there is a small risk this will displace investment in other areas of medical research, possibly even slowing down the rate of progress in other disease areas that have good treatment options currently, but which still constitute a major health burden.
Repurposing
B.1.2. Establish a binding system for scientific assessment of evidence
A binding system would increase the numbers of older off-patent and off-label medicines where available scientific evidence is brought together for assessment by the EMA, such that the wider EU healthcare system is informed about the safety and efficacy of medicines being used in for new indications. While the costs of obtaining the new evidence would have been incurred already by clinical researchers or academics, there may be some additional costs for MA holders where they look to review, replicate or challenge the new evidence. This element would work in conjunction with B.1.3, obliging MA holders to include a new indication when supported by new evidence. EMA statistics show an upward trend in the annual number of extensions of indications it is recommending (87 in 2021, up from 83 in 2020 and 60 in 2019), with an annual growth rate of 5-10%. We assume a binding system for new evidence may nudge that growth rate up by 1-2 percentage points annually, and more if applied in conjunction with B.1.3., perhaps reaching 8-15% CAGR within 3-5 years. This policy element will help broaden access to what are otherwise rather selective and uneven use of safe and effective medicines off-label. It will be a much stronger intervention than the non-binding system. In the longer term, we may see more treatment options for patients and improved geographical access.
B.1.3. Obligation for marketing authorisation holders to include a new indication when supported by scientific evidence and assessment.
The *obligation* for MAHs to include new indications when supported by scientific evidence will help reducing the problem of companies deciding selectively on which indications to include on-label.71 As such, it should help broaden patient access across the EU to safe and effective medicines that are used successfully off-label currently, but only in some but not all healthcare settings. This policy element would impose additional costs on MA holders, as they will be required to make an application for an extension that they would not have done otherwise. For originators, this might trigger a process that could take several years and costs tens of millions of Euros to conclude. The academic evidence may reduce the costs for developers, in some degree, however there will be additional information demands relating to the application – and possibly a need to replicate trials in order to manage the liability issues. There would also be post

[70] https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf

[71] https://www.fiercepharma.com/sales-and-marketing/sanofi-pulls-campath-to-clear-way-for-higher-priced-lemtrada

Assessment
authorisation processes and additional administrative costs are expected related to pharmacovigilance. While the additional costs may be similar on average for any MA holder, they may prove more problematic for generics companies, or developers that have withdrawn fully from a market, where the sales volumes / prices of the existing uses may not underwrite the costs for its extension to a new indication. EMA statistics show an upward trend in the annual number of extensions of indications it is recommending (87 in 2021, up from 83 in 2020 and 60 in 2019), with an annual growth rate of 5-10%. We assume a non-binding system may nudge that growth rate up only marginally, perhaps to 12-22% In the longer term, we may see more treatment options for patients and improved geographical access.
Incentives: Adaptation of the period of regulatory protection
B.1.4. Reduce the duration of incentives for originators from 8+2 years to a new combination (6+2 years) taking into account the interaction between data protection and intellectual property rights.
For originators, a reduction in the period of regulatory protection will reduce overall income and profitability for new medicines since generics companies will be able to enter markets and begin to erode monopoly prices a year earlier. The new period of protection may prompt developers to increase prices in general to protect their current business model or otherwise rebalance their portfolios towards those market segments with greater commercial potential. SMEs originators may find it more difficult to invest in riskier novel medicines given the reduction in future returns on investment and their relatively weaker market position when it comes to negotiating prices. It could weaken the global competitiveness of EU based originators overall, compared with the current situation, unless prices are adjusted upwards to reflect the new protection period, and ensure global ROI norms can continue to be achieved. The threat to EU-based originators will be offset to some degree by giving a boost to Europe's generic industries, broadening their portfolios and potentially creating a prime-mover advantage in global markets. Considering that this policy element affect SMEs more than larger firms and the latter are based in bigger economies, while the former may be based in smaller economies this may affect the functioning of the internal market and limit access to medicines across Europe. This will also be the case if some companies adjust prices upwards in response. Health payers may benefit from lower average lifetime costs for medicines due to earlier generic entry and patients may benefit if those savings are used in the health care sector. The extent of these benefits will depend on originators response to the reduced incentives, and it is highly likely that average prices will be adjusted upwards in some degree to offset the shortened period of protection.
B.1.5. Authorised medicines with demonstrated ability to address UMN get +2 years data protection. Other medicines will be entitled to additional protection only if they can demonstrate no return on investment in view of investment costs (including for research and development).
A +2 year period of premium pricing will offset the higher development costs and / or lower market volumes associated with a proportion of UMNs, whereby a larger number of all UMNs would pass the private sector's ROI thresholds. While companies cannot determine in advance which products will be successful and make a smaller or larger positive contribution to their overall income and profitability, the additional period of regulatory protection will have a positive impact on estimates of potential income and profitability used in stage-gate assessments. The additional period of protection would improve the competitiveness and investment flows towards EU based originators producing UMN medicines. Increasing developers focus on UMNs may increase their development and regulatory costs, in some limited degree, as applicants would need to meet the UMN criteria For other developers, with products that do not address a UMN, the focus would be on demonstrating the absence of a return on investment from their R&D should they not be able to secure a period of additional regulatory protection. This would increase administrative cost associated with the data-hungry and exacting ROI methodology businesses would need to follow). This would also imply higher administrative costs for the EMA and NCA partners involved in checking compliance with the ROI test. This incentive is expected to increase investments in R&D resulting in a higher number of novel medicines addressing UMNs as compared with the baseline and an increase in treatment options, treatments and improved patient health.
B.1.6. Breaking market protection in case of urgency and insufficient coverage by authorised medicines (compulsory licensing)

Assessment
There has only been one instance of an EU member state using a Compulsory Licence,[72] as such this is an ultra-low probability event, and the link with the EU general pharmaceutical regulation is about ensuring external coherence. There should be no or minimal direct impact on EU pharma in general, given it would be implemented indirectly and by exception and for a localised and time limited period. It may increase burden on regulators and expand the numbers of government bodies that have to become involved in explaining their use of this regulatory exception The time and costs involved in developing safe and effective copies of protected medicines may mean that the policy lacks the speed or certainty to respond with confidence to public health crises
B.1.7. Require public transparency on any relevant public contribution or funding, including of research and development costs
Commercial sensitivity around companies' willingness to disclose information about their use of public funding and tax reliefs to underpin their development costs makes it difficult for governments and healthcare organisations to judge the distance between manufacturers' costs and the prices they seek to realise. Greater transparency around public support for medicines development may strengthen reimbursement agencies' position when negotiating with MA holders, helping to place a downward pressure on prices and thereby helping to maintain or improve access to medicines with concomitant benefits to patient health. Indirectly and in the longer term, greater transparency may help public authorities justify higher healthcare budgets and thereby drive support for publicly funded medicines development. This in turn may increase the number of developers in the market and raise competition. The private sector may resist such measures where they require disclosure of commercially sensitive information that could be used by their competitors within the EU and globally. Moreover, the link between R&D grants / tax reliefs and individual medicines is complex and would demand the development of new costing models and assessment frameworks. The proposal to make this information available to the public may be in tension with EU competition and IP law and could result in legal challenges. Moreover, the proposal implies the EU pharmaceutical industry would need to tolerate a switch to cost+ pricing strategies in its dealings with EU payers as compared with value-based pricing that is in use currently and applies across all open markets globally. There may be substantial additional administrative costs for firms needing to prepare the required information using the templates and rules of thumb on the attribution of wide-ranging public supports to specific medicines. There would be substantial additional costs for the EMA compliance teams that need to develop the new procedures and tools (one off costs) and implement / assure the implementation of those protocols, including possibly upgrading the EMA's existing portals to provide better public access to individual dossiers.
B.1.8. Give regulators the possibility to impose a post authorisation obligation for additional studies on the effectiveness compared to the standard of care
Imposing a post-authorisation obligation for MAHs to include new information about the effectiveness of the medicines (i.e comparative clinical trials) may impose additional costs on MA holders, albeit this may be a matter of timing and degree, as many businesses carry out additional research on the cost-effectiveness of their medicines with a conditional approval. The EMA annual reports show that around one third of all medicines that have been granted a CMA since 2006 have gone on to be granted a full marketing authorisation (i.e. sufficient additional evidence has been gathered to confirm effectiveness). As such, it may increase and bring forward costs associated with such studies for tens of businesses. Those costs might amount to €20-€50m for each product. MA holders will have to bear some additional costs and there may be a small increase in the number of medicines that are found to be less cost-effective than had been anticipated. This last point could impact on the ability of individual companies to raise finance or otherwise weaken their competitive position, but there would be no substantive impact – positive or negative – on overall competitiveness, or the functioning of the internal market. This obligation would help to confirm the relative effectiveness of the products in question several years earlier than is the case currently. The EMA annual report (2020) shows that the 30% of CMAs that have been granted full marketing authorisation took an average of 3.5 years post-authorisation to get their products fully authorised. This would allow more timely action in respect to individual medicinal products – e.g. withdrawal or more widespread use – and would indirectly give HTAs and payers greater confidence in the CMA pathway. There would be some additional administrative costs for the EMA and NCA staff working with them following from the increasing numbers of assessments of these additional studies and consideration of the case for granting full authorisation.

[72] https://www.keionline.org/35558

Assessment
The improved clarity as regards the relative cost-effectiveness of medicines should increase confidence across health systems in making full use of those products, and thereby benefiting patient health.

Summary assessment of the Incentives for innovation

Policy Option B foresees several important changes to the current arrangements. With regard to the incentives for innovation, this option reviews the current protection periods with reduced standard regulatory protection periods and modulation subject to certain conditions. Authorised medicines with demonstrated ability to address UMN are entitled to longer protection than the standard protection.

Other medicines will be entitled to additional protection only if they can demonstrate no return on investment in view of investment costs, including for research and development.

MAH are given increased obligations regarding the repurposing of off-patent medicines. It gives regulators the possibility to impose a post-authorisation obligation for comparative studies on the effectiveness compared to the standard of care. This will facilitate decision-making throughout the lifecycle of medicines.

Table 34 Option B - Summary assessment of the Incentives for innovation

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
B.1.1.	+	+/-	+	+/-	+/-	+	-	-	+/-
B.1.2.	+/-	-	-	+/-	+	+	+/-	+	+/-
B.1.3.	-	--	--	+/-	++	+/-	+/-	+	+/-
B.1.4.	--	+/-	--	--	-	---	+	-	+/-
B.1.5.	++	--	--	+	+/-	+	-	+	+/-
B.1.6.	-	-	-	-	-	-	-	+/-	+/-
B.1.7.	-	--	-	-	+/-	-	-	+/-	+/-
B.1.8.	+/-	-	-	+/-	+/-	+	-	+	+/-
Overall impact	--	---	--	--	+	-	-	+	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact

Assessment of any synergies and tensions

Within the Innovation Policy Block, the policy elements proposed under Policy Option B are largely complementary to each other, whereby the proposal to reduce the period of regulatory protection for the standard innovative medicines pathway (by 2 year) is mirrored by a policy element to provide a +2 year special bonus for new medicines relevant to UMNs.

The ability to impose a requirement for additional studies would complement existing provisions relating to the EMA's various expedited regulatory pathways building support among member states (HTAs, health payers) for CMAs in particular.

Assessment of the incentives for innovation and prudent use of antimicrobials

Policy Option B encourages the development of antimicrobials through novel incentives. It introduces a 'pay or play' model. Either a company holds an antimicrobial in its portfolio, or it pays to a fund that is destined to finance the development of novel antimicrobials. It includes measures for prudent use of antimicrobials as well as monitoring consumption and use of human antimicrobials.

Table 35 Option B - Assessment of the proposed incentives for Innovation and prudent use of antimicrobials

Assessment
B.2.1 Make the central procedure mandatory for new antimicrobials.
As this policy element largely formalises what happens in practice already, there would be little or no additional impact on the development of novel antimicrobials or their more prudent use.
B.2.2. PRIME like support scheme, including rolling review
If the system in place for rolling reviews is easy for SMEs and large companies to navigate and flexible, there is potential for a large positive effect on EU pharma businesses by increasing company-regulator interactions in areas that may not be currently attractive for business to invest in R&D. This could result in a positive impact on innovation rates and overall EU pharma industry output. The targeted survey revealed that industry respondents were broadly in favour of codifying rolling reviews, in particular for new technologies or major innovations in medicinal products. However, the demands on Rapporteurs are high, with significant increase in workload; one NCA interviewed stated that the COVID-19 pandemic rolling review required approximately 50% increase in resources/workload. The demands on companies are also relevant, as the process requires more communication and clarifications (data packages may not be structured, may contain errors, etc). Furthermore, rolling reviews bring uncertainty on the added therapeutic value of medicines and inequity of access is larger for orphan medicines73. Considering these reasons, some civil society and public authority respondents were against codifying rolling reviews in a way that would expand the scope of use of this procedure outside exceptional medical conditions and public health emergencies.
B.2.3. Optimise package size
This policy element would encourage the use of smaller package sizes, thereby increasing manufacturers' costs relating to product packaging and distribution. It may also increase the cost of antimicrobials for health payers (smaller package sizes are more costly), including an increase in average prices for a course of treatment for an individual patient, albeit these price increases should be offset in some small degree by lower levels of consumption. It may have implications for storage costs (more space required) but may ease dispensing and take pressure off pharmacists' local storage requirements. We don't foresee additional extra administrative costs on the side of businesses and authorities. By helping to reduce overall levels of consumption, this policy element may contribute in some small degree to reducing AMR and avoiding AM releases to the environment. The smaller pack sizes will increase packaging waste, which would increase costs associated with waste management and recycling.
B.2.4. Stricter rules on disposal
The legislation and accompanying guidelines would have no direct impact on EU pharmaceutical manufacturers, wholesalers or pharmacies, indirectly it may lead to an expansion in overall sales volumes and income, as pharmacies buy smaller volumes more frequently, prescribers push for smaller pack sizes, and patients a less likely to self-medicate. In the longer term, and indirectly, the initiative should encourage industrial actors across the value chain and across member states to give more weight to these issues and adhere more closely to applicable legislation and professional guidance. Stricter disposal rules would bring additional costs for public authorities, with a substantial one-off cost for EU / MS authorities in developing and championing the roll-out / adoption of the guidelines and additional ongoing costs

[73] https://www.efpia.eu/media/602652/efpia-patient-wait-indicator-final-250521.pdf

Assessment
for national authorities in maintaining / monitoring adherence and for the EMA and its advisory groups in tracking developments and giving ad hoc advice. Stricter disposal rules / smaller pack sizes may increase the unit costs of antimicrobials and stricter management of stocks may also add costs and even increase susceptibility to shortages. Patients should see a benefit from a reduction in self-medication using unused and out of date medicines. Given the high proportion of citizens that hold onto medicines indefinitely or otherwise dispose of them inappropriately[74], improved advice and collection should reduce poor disposal and indirectly benefit the environment and help to curtail an important vector for AMR
B.2.5. Tighten prescription requirements for antimicrobials
While prescribing policies are a matter for national authorities in the first instance, the legislation can invite member states to do more to bring practice in line with international standards. These obligations and guidelines do not affect industry directly. Indirectly, and if successful, better prescribing would accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for the pharmaceutical industry overall and particularly those generics companies that supply older, lower-cost, broad-spectrum antimicrobials. Indirectly, there may be a differential impact on the generics industry and particularly that sub-set of pharma businesses that include older, broad-spectrum antimicrobials in their portfolio. There may be a small benefit for MA holders with more specific antimicrobials, if prescribers both reduce overall prescription numbers and switch from cheap, broad-spectrum medicines to more specific (more expensive) antimicrobials. Indirectly, tighter prescription is likely to reduce usage and that may weaken the return on investment for antimicrobials in general, worsening the investment case in an area of medicines research that is already regarded as being uneconomic. Indirectly, health systems may see savings because of better prescription practices and reduced consumption, albeit this may be offset by increased costs associated with diagnostic tests and a switch to more costly antimicrobials. If successful, this policy element should reduce consumption and that in turn should reduce the potential for negative environmental impacts.
B.2.6. Mandatory use of diagnostics prior to prescription of antimicrobials
Similar impacts as with B.2.5 but since this policy element is seeking to encourage EU member states to make the use of diagnostics a mandatory requirement, there may be a greater impact on prescribing behaviour and consumption (albeit, as with prescribing practice in general, the use of diagnostics is a matter for member states in the first instance, with many wider factors determining the use of such screening techniques[75]). There may be territorial issues around access and affordability with respect to diagnostic tests, whereby some of the proportionately largest consumers of antimicrobials are central and southern European member states, that rely heavily on low-cost broad-spectrum antibiotics supplied by generics manufacturers, and where there is less good access to more specific and costly branded antimicrobials and a similarly less good access to point-of-care tests, microbiologists, and test labs. These countries also have a stronger tradition in prescribing antibiotics as a first line of defence. Greater use of diagnostic tests should improve prescribing practice in some degree, which should have a positive impact on patients, avoiding unnecessary medication or poor therapeutic outcomes that result from using the wrong anti-microbials. Depending upon the success of the proposed legislation and guidelines, these changed practices could reduce consumption considerably and make a significant contribution to efforts to contain AMR.
B.2.7. Pay or play model: either a company holds an antimicrobial in its portfolio, or it pays into a fund that is destined to finance the development of novel antimicrobials.
A pay or play model would impose additional costs on EU pharma businesses, and while a minority may look to avoid a levy by beginning to develop antimicrobials, or by acquiring businesses with an antimicrobial in the portfolio, the majority would be likely to view the surcharge as an unavoidable additional cost to be factored into their wider pricing policies. Additional administrative costs related to the pay or play model are expected to be relatively small, with the sub-set of firms that are developing or supplying antimicrobials needing to certify that fact in order to avoid the surcharge.

[74] Mitkidis, K., Obolevich, V., Chrysochou, P. and Mitkidis, P., 2021. Harmonisation of Pharmaceutical Take-Back Systems in the EU. *European Journal of Health Law*, pp.1-27.

[75] https://www.imi.europa.eu/projects-results/project-factsheets/value-dx

Assessment
SMEs would not be impacted directly by this policy since it is expected that EMA continues to put in place preferential policies for these firms. Indirectly, and over time, the system could lead to a series of acquisitions and an expansion in demand among larger developers for the results of early-stage R&D involving SMEs. The proposed pay or play model would raise the cost of doing business in Europe, this could affect the competitiveness of pharma companies in Europe relative to US companies. It may encourage developers willing to avoid the fees to broaden their product portfolios through commercial activities (e.g. mergers, acquisitions, licences, etc. with smaller biopharma companies that develop antimicrobials). It will incentivise competition between large pharmaceuticals to win the research and development grants financed by the fund. The EMA would need to establish a new unit to decide on the allocation of the research grants to the best suited developers. This pay or play model would not increase substantially the number of novel antimicrobials in the market and may risk increasing prices in other markets, creating substantial social costs.
B.2.8. Establish a monitoring system for data collection on human antimicrobial consumption and use and potentially on the emission of APIs to the environment
Expanded surveillance would have no direct impact on EU pharmaceutical companies conduct of business. Indirectly, and in the longer term, improved surveillance data may help to accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for industry overall. Expanded surveillance would have no direct impact on EU pharmaceutical companies' administrative costs. Indirectly, and in the longer term, improved surveillance may facilitate the more robust scrutiny of MAH environmental risk assessments (ERA) and this would be expected to require all businesses to develop more comprehensive - possibly more costly - ERA presentations as part of their submissions to the EMA. This policy element would not have a direct impact on SMEs, however, indirectly, any implications for enhanced environmental risk assessments could be more challenging for SMEs to carry out / afford. Expanded surveillance would have no direct impact on EU pharmaceutical companies conduct of business. Indirectly, and in the longer term, the improved surveillance data would be expected to facilitate more robust scrutiny of MAH environmental risk assessments. More and better data may also accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for industry overall, but possibly with a relatively bigger negative impact on generic companies. This policy element would have no direct impact on the functioning of the single market; however, it is conceivable that an expanded surveillance system would reveal environmental hot spots across the EU that could trigger referrals to the EC / EMA and possibly change national procurement behaviour, with more interest in sourcing medicines from producers with the best environmental record no matter where they are based. Expanded surveillance would have no direct impact on EU pharmaceutical research and innovation. Indirectly, it is likely to reduce overall demand and thereby worsen the market failure associated with the development of new antimicrobials An expanded surveillance system could have a significant impact on the costs borne by public authorities, both one off and in the longer term. The additional costs would fall most heavily on national agencies. Environmental impacts go far beyond the mandate and competence of the network members and given the many routes by which such active ingredients may come into the environment (e.g., agriculture), there would need to be a considerable amount of work done to agree definitions and set up data collection systems. There would also be questions around the interpretation of the results and any causal relationship between the pharma legislation, human use and the environmental signature. An expanded surveillance system would not have a direct benefit to public health, however, indirectly it may provide a small additional impetus to encourage more prudent use of antibiotics. In this way, and in the longer term, it may help to combat AMR to some limited extent. On the negative side, and indirectly, it could weaken incentives slightly for industry to invest in the kinds of novel antibiotics that are needed to combat AMR more robustly. An expanded surveillance system could provide a good platform from which to improve the management of antimicrobial production and consumption, with more prudent use and more informed production and disposal helping to reduce the level of human-related active ingredients getting into the environment.
B.2.9 same as A.2.3. Consider adapted system for authorisation of phage therapies and other alternative products
This policy element would create the regulatory space to encourage an increase in ongoing efforts to develop phage therapies for routine use in human medicine, potentially increasing the number of companies willing to invest and develop these emerging alternatives to conventional antibiotics. In the longer term, the adaptation should ensure novel therapies can be authorised and this will in turn increase investment, develop a new market segment where the EU industry enjoys a competitive advantage, while also reducing prices of these therapies such that they will become affordable.

Assessment
In the longer term, the emergence and growing use of phage therapies may also reduce healthcare costs/budgets since phages are an inexpensive natural resource present in the environment and offer potential as an alternative when antibiotics are rendered ineffective due to bacterial resistance (AMR).[76] Finally, by reducing the use of antibiotics it would help reduce the presence of antibiotics in the environment.

Summary assessment of the incentives for innovation and use of antimicrobials

Policy Option B is largely concerned with enhanced prescribing practices and stewardship, which will have limited direct impact on industry or markets – beyond reinforcing the downward pressure on demand for antimicrobials in general – but should have benefits for patients and the environment. There is no substantive direct support for innovation, but rather Policy Option B proposes introducing a Pay or Play model to create a fund for reinvesting in AM R&D, which would add costs and administrative burden for industry in general without generating the volume of funds necessary to impact the AM pipeline. The adaptation of the system for the authorisation of phage therapies may catalyse increased investment in this emerging and innovative technology.

Table 36 Option B - Summary assessment of measures for innovation and use of antimicrobials

Policy elements	COB	Admin	SMEs	CTI	Internal Mar	I&R	PA	H&S	Sust
B.2.1	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
B.2.2.	+	-	+	+/-	+/-	+	-	+	+/-
B.2.3.	-	+/-	+/-	+/-	+/-	+/-	-	+	+
B.2.4.	+/-	+/-	+/-	+/-	+/-	+/-	-	+	+
B.2.5.	+/-	+/-	+/-	+/-	+/-	+/-	-	+	+
B.2.6.	+/-	+/-	+/-	+/-	+/-	+/-	-	+	+
B.2.7.	-	--	--	-	+/-	+	-	+/-	+/-
B.2.8.	+/-	+/-	+/-	+/-	+/-	+/-	-	+/-	+
B.2.9	+	+/-	+/-	+	+	+	-	+	+
Overall impact	+/-	--	-	+/-	+/-	+	-	+	+

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element. Policy Option C – Summary assessment of the Incentives for innovation

Assessment of any synergies and tensions

Within the AMR Policy Block, the policy elements proposed under Policy Option B are largely complementary to each other, with the mandating of the use of the Central Procedure dovetailing with the proposal for the EMA to create a PRIME-like scheme for AM products, while also introducing the Pay or Play model to create a fund for reinvesting in AM R&D. The adaptation of the system for the authorisation of phage therapies is a further complementary

[76] https://www.nesta.org.uk/blog/when-the-drugs-dont-work-could-bacteriophages/?gclid=Cj0KCQjw_4-SBhCgARIsAAlegrUn5LXTOVza5VKzwfA4XcfpeUXcHW8jiSFfDhOBM2_MUMNcQ0GrXVQaAtQVEALw_wcB

initiative that recognises the potential for this emerging and innovative technology to make a substantial contribution to combatting AMR through support for the development of a non-traditional technology trajectory. Moreover, the proposals on prescribing practices, package size, and disposal all work well together in supporting more prudent use. The expansion in the scope of the existing surveillance system would also provide an important means by which to track progress in optimising consumption across the EU.

Under Policy Option B, there is no specific policy element that will reward innovators with an additional period of regulatory protection, however, the proposals under the Innovation Policy Block do include a policy element to provide a +2 year special bonus for new medicines relevant to UMNs. This would be an important synergy across these blocks, assuming most innovative antimicrobials would be considered as being relevant to an UMN (e.g. targeting a WHO priority pathogen where there are no or too few effective treatment options) and therefore eligible for the additional protection.

A.4.3. Policy Block C (B.C): Future Proofing

Policy Option B is a refinement of the current arrangements, with four principal interventions.

Table 37 presents our schematic overview of these proposals, noting the key design assumptions and strengths/weaknesses of each one.

Table 37 Option B - Assessment of the proposed measures for Future Proofing

Assessment
1. Scope and Definitions
B.3.1. Adapted regulatory framework for certain categories of novel products/technologies or low volume products (hospital preparations) on the basis of well-defined conditions and respecting the principles of quality/safety/efficacy. Such frameworks could be adapted or expanded through delegated acts to set the technical framework that can be adapted to emerging scientific and technical advances (adaptive framework). Where applicable, such delegated acts should be developed in close coordination with other relevant competent authorities such as e.g. medical devices, IVDs or substances of human origin)
As changes to legislation can be lengthy with a high administrative burden especially in the case where legislation needs to change regularly (for example to adapt to emerging technologies) adaptive legislation can be an option. In an adaptive framework change can be more iterative and responsive, 'soft-law' tools such as best-practice guidance can be employed and can be developed more collaboratively with stakeholders (who bring in depth technical knowledge) and later certified or adopted by regulators. For novel products or technologies this is to respond to the emergence of new technologies that do not fit the legislation scope or definitions to ensure the legislation remains relevant. For low volume products this is assumed to respond to challenges with hospital preparations (via the hospital exemption, pharmacy exemption or as bedside manufacturing of a centrally authorised product) where regulatory gaps currently exist due to manufacturing process being out of scope or unsuitability of some aspects of GMP for hospital context. B.3.1. has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. It would also address the issues of current technological advancements that are not adequately legislated for and provide the legislation with a mechanism of keeping pace with technology through both facilitating adaptation and drawing on the expertise of deeply engaged stakeholders with in-depth technical knowledge of emergent areas. However, there would be an associated increase in administrative burden due to a likely expansion of the number of specific non-legislative (soft law) tools that would require development, maintenance, review etc. and ongoing need for feedback loops, iteration and adopting delegated acts. EMA and the regulators need to stay in control and ensure that the soft law tools are meeting the overall objectives of the legislation since the incentives and alignment of all stakeholders (some of whom have valuable technical expertise that this framework is designed to harness) is not implicit. With respect to low volume products specifically this will represent an increase in regulation and associated regulatory burden but will reduce gaps in the legislation and improve patient safety while providing the legislation with the tools to consistently adapt to this rapidly paced area of technological

Assessment
change (e.g. pharmacoprinting, bedside manufacture, personalised medicines etc.) contributing to hospital preparations as a legitimate and robust production mechanism.
2. GMO
B 3.2. Same as A.3.2 but for clinical trials: Where required, the assessment of the GMO aspects of investigational medicinal products is performed at Member State level, within the maximum timelines defined in the Clinical Trial Regulation (decentralised assessment).
This is as A3.2 however with the understanding that the assessment would take place at the Member State Level rather than EMA level. This element would likely have less potential to improve efficiency of assessment and thus speed of authorisation of GMO-containing medicinal products. This is because complications with assessments may arise if NCA apply risk-based approach differently. However, if implemented well regulatory efforts would be focused on assessing GMO containing medicines that pose greatest threat to the environment.
B.3.3. Adapt certain definitions, including that of medicinal product and *delink scope from industrial process* to address technological developments, gaps/borderline questions, taking into consideration the views of regulatory authorities for other relevant legal frameworks (e.g. medical devices and blood, tissue and cells) - linked to scope of the legislation.
The 2004 Directive 2001/83/EC covers all 'medicinal products' that are "either prepared industrially or that are manufactured by a method involving an industrial process". By "delinking" we assume removing the manufacturing process specification from the legislation scope such that it will automatically bring into scope products that could be considered as being exempted purely through not meeting that definition. By adapting 'certain' definitions we assume this is firstly 'medicinal product' to be less specific and more similar to that found fit for purpose in other markets, secondly 'batch' which is a cornerstone of GMP but ill-fitting for continuous manufacturing processes in addition to other more specific ones around different categories of medical product. This element has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. Delinking scope from industrial process would immediately bring under regulation a number of excluded or potentially excluded products and processes – most notably novel manufacturing such as bedside such as pharmacoprinting. It would be important that upon their being brought in scope the GMP was able to accommodate them or that sufficient alternative tailored guidance was available: the adaptive framework for low volume products in element B3.2 could be a facilitator to this. Addressing gaps in the legislation would impact positively on patient safety though could cause a (likely short term) reduction or delay in access while adaptations for compliance to greater regulation were made. There would be additional regulatory burden to implement the extended scope of the legislation. However, long term the efficiencies and predictability are anticipated to increase investment and innovation, reduce the time to access and improve patient safety.
B.3.4. Create a central *classification mechanism* for advice on whether products are medicines or not, building on the current EMA Committee for Advanced Therapies (CAT) mechanism for ATMPs to all medicinal products (borderline products) in close coordination with other concerned authorities in particular in the frameworks of medical devices and substances of human origin.
Medicines are increasingly being used in combination with a medical device, usually to enable the delivery of the medicine. However, these combinational products have brought regulatory difficulties for NCAs in terms of uncertainty whether they should be classified as a medical product or medical device and what regulatory framework applies. B.3.4 would improve consistency of the classification of borderline products and the resulting choice of the most appropriate pathway through the EMA committee structure. This should harmonise coordination between concerned authorities in particular in the framework of medical devices and substances of human origin, and thereby deliver some small efficiency gains and avoid assessment committees being distracted from their assessment work by definitional questions. It may also improve the overall timeliness of assessments. The creation of a central screening mechanism may be timely as more definition questions arise: for example, 1 in 4 centrally approved medicines typically include a

Assessment
medical device component[77]. Success would depend on EMA finding the capacity to deliver relevant advice at speed.

Assessment of the key impacts for the policy elements

Table 38 provides a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under option B.

Table 38 Option B - Summary assessment of future proofing

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
B3.1	++	+	+	++	+	++	--	++	+/-
B3.2	+/-	+/-	+	+/-	+	++	-	+	+/-
B3.3	+	+	+/-	+	++	+	-	++	+/-
B3.4	+	+	+	+	+	+	+/-	+	+/-
Overall impact	+	+	+	+	+	+	-	+	+/-

Assessment of any synergies and tensions

Within this block there is tension around significant ongoing administrative burden for legislators (and other stakeholders in complex novel technologies) associated with regular and continuous amendments via delegated acts. While this undoubtedly has positive impacts regarding efficiency of applications, reduction of legislative gap and therefore products reaching the market more quickly and better regulated it should be recognised that it does represent a transfer or trade-off of administrative burden (from scientific committees and applicants in navigating an ill-fitting framework) that it represents any overall reduction. This also creates a tension with some of the horizontal streaming measures looking to reduce administrative burden where otherwise there are synergies with B3.3 and B3.4 very much related to streamlining and reduction of burden.

The relationship of all medicinal products with industrial process is not the same. While generally a delinking from industrial process was regarded positively in stakeholder consultation and according to our research would have positive impacts overall particularly for resolving scope issues and preventing legislative gaps around novel manufacturing processes, certain sectors (plasma in particular) suggest this would for them create regulatory uncertainty.

Future proofing elements in this policy element related to improved mechanisms/approaches for innovation to promote access to novel medicines (B3.2, B3.3) complementing measures in Block A – innovation for UMN, Block D-access as well as competition (Block E). There are also definition synergies with Block F (Introduce EU definition of a shortage and a definition of a critical medicine (B6.1)) and G (Adaption of legislation/inclusion of specific provisions covering new manufacturing methods (B7.4)).

[77] European Medicines Agency. (2020). *ANNUAL REPORT 2020*.

A.4.4. Policy Block D (B.D): Access

Under Option B, four elements are included. The first (B.4.1) is aimed at regulating access to products that have been conditionally authorised by giving regulators greater powers to act when the generation of new evidence post-approval is not satisfactory or in case benefit is not confirmed. The other three measures (B.4.2, B.4.3 and B.4.4) have similar objectives to the elements previously discussed in Option B in that they are aimed at expanding the number of EU markets where products are launched. Unlike Option A, however, the measures under Option B exclusively focus on imposing greater requirements on MAHs and do not include incentives or voluntary options. Furthermore, whilst obligations under Option A were linked exclusively to products authorised through the centralised procedure, Option B also targets those that are authorised through the MRP/DCP route (B.4.4).

Assessment of the key impacts for the policy elements

Table 39 presents our high-level assessment of the likely costs and benefits of each of the proposed legislative actions. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

Table 39 Option B - Assessment of the proposed elements to improve access

Assessment
B.4.1 Conditional Marketing Authorisation: introduce more powers to regulators to take measures in case of non-compliance with obligations for post-market evidence generation or in case benefit is not confirmed
Whilst available evidence primarily points in the direction of issues with the *standards* of evidence imposed on post-market evidence generation, policy element B.4.1. aims at increasing the ability of regulators to *enforce compliance* with the SOB. For the measure proposed under B.4.1 to have meaningful impact on access to medicines, whilst maintaining rigorous standards of effectiveness, quality and safety it must thus be assumed that: • The standards for evidence generation imposed through the SOB are sufficient or will be further raised to a level whereby post-market evidence can better inform assessment of the risks and benefits • Delays in submitting data in compliance with the SOB are due to insufficient commitment on the part of the MAH to meet specified timelines and there is scope to accelerate fulfilment of the requirements. If regulators exercise their expanded powers to impose stricter obligations on the generation of post-marketing evidence (e.g. better quality study designs) and/or better enforce compliance with the SOB, this may raise the quality of evidence generated with regards to a medicine's effectiveness and safety. Earlier access to such information could mean that ineffective or unsafe medicines are removed from the market more quickly. This will have a positive impact on public health, as well as reduce the costs from use of ineffective or unsafe treatments. Conversely, when the generated evidence supports the conversion of the authorisation from conditional to full, this too will be beneficial for patients and health providers who can be better guaranteed of the medicine's continued availability. It also provides more certainty to payers and health systems about future health expenditures on such medicines.
B.4.2 Require the MAH to notify regulators, during the authorisation process, of their market launch intentions through a roll out plan for all centrally authorised medicines
The requirement to report on launch intentions is similar to the (voluntary) reporting proposed under A.4.3 except that voluntary reporting has here been converted into a requirement. It further differs in that it does not ask for a commitment to initiate pricing negotiations. In this regard it is both a stricter and a narrower proposal. Earlier notification of launch intentions allows regulators, health systems and payers to better prepare for (potential) entry of new medicines into the package of reimbursed care. It also facilitates timelier discussion between the MAH and authorities about pricing and reimbursement. It has been assumed that this requirement does not come with powers to regulators to enforce MAHs to follow up on their expressed launch intentions, nor imposes sanctions on MAH for not doing so. It is therefore highly uncertain whether, on its own, this measure could increase the number of markets in which MAH launch or encourage earlier launch. Additional obligations such as those proposed under B.4.3 would be needed to support this measure.
***B.4.3* Obligation to place a centrally authorised medicine on the market in the majority of Member States (small markets included) within 5 years of authorisation**
The proposed obligation is similar to that specified under A.4.4. but is less explicit in that it does not indicate what the sanction is for non-compliance. In the absence of this information, it is assumed the sanction will be withdrawal of regulatory protection that would allow generic competition from year 6.

Any measure that promotes market entry into a greater number of EU countries, will be beneficial to patients who are otherwise unable to access these medicines. The impacts of an obligation to place centrally approved products on the market will scale with the number of countries and patients reached and with the importance of the medicine. A potential risk is that MAHs of products that are within the optional, but not compulsory, scope of the CP will avoid the CP authorisation route to not fall under the obligations. This could result in a reduction in the number of countries where the product is authorised and decrease rather than promote equitable access.
B.4.3.1 Requirement to offer products to a majority of national health systems (including small markets)] within 5 years from authorisation
This element is offered as an alternative to B.4.3. The main difference is that it requires MAH only to *offer* the product to national health systems but does not make fulfilment of this obligation contingent on whether this results in actual market placement. Whilst not explicitly stated, it is assumed that – as an alternative to B.4.3 – this requirement would apply only to centrally authorised medicines. This element imposes somewhat less stringent obligations on MAHs by making its fulfilment dependent only on whether an MAH has entered into discussions with national authorities about pricing and reimbursement but not on a successful outcome of those discussions. Since this still allows MAHs to refrain from market entry if no mutually acceptable agreement can be reached, the direct impact of this element on improved access will likely be smaller than under option B.4.3. It may, however, be less of a deterrent for MAHs of products in the *optional* scope of the CP than B.4.3.
B.4.4 Requirement on MAH applying for MRP/DCP to include small markets (in particular address the post-BREXIT challenges) or possibility for MS to opt-in a pending MRP/DCP procedure
Most generic medicines are currently approved through the MRP/DCP route[78]. Because of this, these products would not fall within the scope of the requirements imposed by B.4.2 and B.4.3. By also extending greater obligations for inclusion of smaller markets in the application for approval via the MRP/DCP, the Commission aims to increase access to a wider group of products, in particular generic medicines, than would be achieved via marketing obligations on centrally approved medicines alone. It is assumed that the proposed element intends only to require the applicant to include specific countries into the MRP/DCP application, such that there is a valid MA in these markets, but does not require the applicant to directly place products on these markets. Requiring MAHs applying for an authorisation via the MRP/DCP route to include specific markets – or allowing countries to opt-in – will enable these countries to obtain medicines more easily from other EU MS (through parallel distribution), even when the MAH does not place the product directly on the market. This may have the effect of increasing access to medicines that are not within the scope of the CP, especially generic medicines. This, in turn, may be expected to positively affect both health outcomes for patients and the affordability of treatment by increasing access to low-cost generic versions. It will also improve security of supply for included countries by facilitating redistribution in case of shortages.

Summary assessment of the principal costs and benefits by impact type

Table 40 presents a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under Option B.

Table 40 Option B - Summary assessment of Policy Block D (Access)

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
B.4.1	--	-	-	--	+/-	++	++	++	+/-
B.4.2	+/-	-	+/-	+/-	+/-	+/-	+	+	+/-
B.4.3	---	--	--	--	+	-	++	+++	+/-
B.4.3.1	--	--	--	-	+	-	++	++	+/-
B.4.4	---	--	-	--	+	-	++	+++	+/-

[78] European Medicines Agency. (n.d.). *Authorisation of medicines*. Retrieved April 4, 2022, from https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

Overall impact	---	---	--	--	++	-	+++	+++	+/-

- Greater obligations on the quality of evidence generated may require additional activities by the MAH (e.g. larger and additional trials), that would increase the cost for conduct of business to the MAH. Estimation of the magnitude of any potential impact would require insight into the size and type of additional activities that would be requested to raise the post-market evidence generation to a more widely accepted level.
- Obligations on MAHs to place centrally authorised medicines on the market in a majority of MS, presumably at risk of penalty in case of non-compliance, may carry substantial costs to the MAH. They may either be required to operate in markets where they cannot generate a sufficient ROI or incur fines if they refuse to do so. The MAH will also have to provide additional information to regulators to demonstrate their compliance with obligations. This implies increased administrative costs.
- Increasing the number of MS in which the MAH places a centrally approved product on the market will increase the costs to MAHs for interacting with regulatory agencies and HTA bodies in these countries. Obligations for market placement in a minimum number of MS, including smaller markets, may be more challenging to meet for SMEs that do not yet have market presence or distribution channels in such markets.
- For products approved via the MRP/DCP, a separate fee for each country in which the application is recognised will also be required. Further fees are required to annually renew the authorisation and to submit variations. However, to promote inclusion of smaller MS, special procedures with shortened time schedules and reduced fees exist (20).
- The policy elements included under Option B impose a number of additional obligations on MAHs and do not offer any incentives in return. As such, they are likely to present a significant cost for any company operating in the EU. This will reduce the competitiveness of EU-based companies compared to those in, for instance, the United States.
- Inclusion of additional countries, in particular smaller MS, in the MRP/DCP application will facilitate the movement of medicines between markets where the product has been authorised. As such, this measure may be expected to promote the functioning of the EU internal market.
- Regulatory authorities in the MS where products are placed in the market will see an increase in costs due to a greater number of medicines for which they provide regulatory oversight (B.4.3 and B.4.4). Similarly, HTA bodies will have to conduct a greater number of assessments. Expansion of the number of countries included in MRP/DCP applications will result in more work for authorities in those countries to process applications. The resulting costs may be offset, at least in part, by application fees.
- The intended and expected impact of increased access to medicine is that patients will be provided with earlier, more effective and safer treatments. This will have a positive impact on their health status and wellbeing. Whilst increased access to medicines is generally positive, it may result in increased health care expenditure. At the same time, new medicines may displace less (cost-)effective treatments, resulting in net savings. Further indirect savings from increased access to medicine may result from improved health and productivity.

Assessment of any synergies and tensions within the Policy Block

Requiring additional, and in particular smaller, countries to be included in the MRP/DCP application procedure (or allowing countries to opt-in) may be considered synergistic with the

objectives of the policy elements in Block F to improve supply chain security, by facilitating the import of medicines from other EU countries in case of shortages.

A.4.5. Policy Block E (B.E): Competition

Policy Option B involves several changes to the current legislative arrangements for encouraging competition with a view to improving time to market entry for generics and biosimilars.

Assessment of the key impacts for the policy elements

Table 41 presents our assessment of the likely impacts (costs and benefits) of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected.

Table 41 Option B - Assessment of the proposed measures for competition

Assessment
B.5.1 New simpler regulatory pathway for generics (adapted EMA/CHMP working methods, shorter approval timelines, potentially distinguishing between complex generics/biosimilars – reducing requirements for known biologics)
As described for A.5.1. The key impact from a simpler regulatory pathway with shorter approval times will be faster availability of generics to patients. It should create more clarity and potentially less administrative burden for marketing authorisation applicants, encouraging more applications and increased development activity for generics. We assume that generics will be on the market soon after approval and access to generics will be similar in all member states. The latter assumption has been adopted for ease of analysis as generics market penetration varies considerably across member states and would add uncertainties to our assessment.
B.5.2 Interchangeability of biosimilars with their reference product will be generally recognised in guidance or e.g. through a recital in the legislation and will be scientifically assessed as part of the product assessment and indicated in the summary of product characteristics (SmPC, product information) to inform healthcare professionals and their patients as well as downstream decisions makers
Interchangeability, switching (by prescriber) and substitution (by pharmacy) of a reference medicine by its biosimilar currently fall within the remit of EU Member States. Guidance on interchangeability from one originator (reference) or biosimilar product to another at the EU level would enable all member states to make decisions on whether to allow switching and/or substitution for certain products, especially those countries where the relevant technical capacity is not available. There is potential to pool the best expertise from across the EU if product assessment is done as part of the centralised procedure, reducing burden on individual member state authorities. Inclusion of the guidance in a recital in the legislation and product information (SmPC) would inform prescribers, patients, and decision makers about interchangeability of specific products, potentially increasing uptake of biosimilars. This could improve access to biologics for patients and reduce health system costs if cheaper biologics were switched or substituted for more expensive ones. It is not clear if additional data will be requested for the scientific assessment of interchangeability e.g. switch studies.[79] Our assumption is that no additional data will be required – a study by Kurki et al. (2021) which analysed post-marketing surveillance data suggests that biosimilars approved in the EU are highly similar to and interchangeable with their reference products.[80] A recent qualitative study also shows that European and UK regulatory, legal and policy experts do not see any added value in additional data or switching studies.[81]
B.5.3 Broader Bolar exemption – allow additional beneficiaries (companies, producers of active pharmaceutical ingredients (APIs) and non-industry actors) to conduct studies/trials

[79] Alvarez, D.F., Wolbink, G., Cronenberger, C. *et al.* Interchangeability of Biosimilars: What Level of Clinical Evidence is Needed to Support the Interchangeability Designation in the United States?. *BioDrugs* **34,** 723–732 (2020)

[80] Kurki, P., Barry, S., Bourges, I. *et al.* Safety, Immunogenicity and Interchangeability of Biosimilar Monoclonal Antibodies and Fusion Proteins: A Regulatory Perspective. *Drugs* **81,** 1881–1896 (2021).

[81] Druedahl LC, Ka¨lvemark Sporrong S, Minssen T, Hoogland H, De Bruin ML, van de Weert M, et al. (2022) Interchangeability of biosimilars: A study of expert views and visions regarding the science and substitution. PLoS ONE 17(1): e0262537.

Assessment
Overall, the broader Bolar exemption is likely to increase legal certainty, access to medicines, cost savings and research activity in the EEA compared with a narrower exemption.[82]
B.5.4 Extend Bolar exemption beyond generics – Allow repurposing studies/comparative trials without infringing patent rights
Overall, the extended Bolar exemption is likely to increase legal certainty, access to medicines, cost savings and research and innovation activity in the EEA compared to a narrower exemption.[82]
B.5.5 Specific (regulatory) incentive for a limited number of first biosimilars [market exclusivity for 6 months]
The key expected impact would be new biosimilars on the market as a result of additional research and innovation related to biosimilars undertaken to capture the benefits of the incentive. However, any such impact is likely to be extremely limited according to feedback from industry in the impact assessment workshop. According to industry, the incentive proposed is unlikely to significantly alter R&D activity or availability of biosimilars. This point is supported by literature – for example, a one-year extension of market protection for approval of a new indication has rather marginal effects.[83] At this stage it is unclear, how the market exclusivity would work and whether it will be simultaneous or sequential as not all biosimilars within the group will enter the market at the same time.
B.5.6a Reforming the duplicates regime: No auto-biologicals OR B.5.6b Duplicates restricted to cases of intellectual property protection or co-marketing
The main effect of B.5.6.a will be increased competition in the biosimilars market with no monopoly conditions for the first entrant. This will mean greater choice for patients and health systems. In case of B.5.6.b, there will be a reduction in barriers to competition and monopolisation of the market by the first generic/biosimilar of an originator product to receive an MA. Consequently, there will be no delay in the second generic/biosimilar coming onto the market once it receives approval. This will mean greater consumer choice and price competition.

Summary assessment of the principal costs and benefits by impact type

Table 42 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block E under Policy Option B and for each impact type.

Table 42 Option B – Summary assessment of the proposed measures for competition

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
B.5.1	+	+	+	+	+	+	+	+	-/+
B.5.2	-/+	-/+	-/+	+	+	-/+	++	++	-/+
B.5.3	+	+	-/+	+	+	+	++	++	-/+
B.5.4	+	+	-/+	+	+	+	++	++	-/+
B.5.5	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/+
B.5.6	-/+	-/+	+	+	++	+	++	+	-/+
Overall impact	+	+	+	+	++	+	+++	+++	-/+

[82] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

[83] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, *Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe : final report*, Publications Office, 2018, https://data.europa.eu/doi/10.2873/886648

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Some of the key expected impacts are as follows:

- Increased international competitiveness through creation of a more favourable regulatory environment for generics/biosimilars (simplified generics pathway, specific incentive for first biosimilars), which might encourage more MAHs to apply for first filing in EU. The broader scope of the Bolar exemption will increase the share of EU-based API producers and API manufacturing jobs and lower costs of supply for European generics.[84] The cost savings would be more pronounced for European generics manufacturers of specialised products e.g. for oncology or central nervous system. Increased competitiveness may possibly encourage new entrants
- Improved consumer choice and competition through availability of both generics/biosimilars and originators on the market, resulting in lower prices and improved access for patients across member states. Modification of the duplicate regime will mean originator companies will not be able to severely undercut the price of potential biosimilar competitors through a duplicate authorisation for an autobiological while allowing the reference originator product to maintain a high price.[85]
- Market exclusivity for first biosimilars may allow higher prices to be charged[83]. It may also limit competition by preventing new biosimilars from entering the market during the exclusivity period. On the other hand, with protection being awarded to a set of biosimilars for the same originator product, price competition may also occur. The level of discounting is typically around 20% of the price of the originator product for a single new biosimilar entering the market, or 30–50 percent for multiple biosimilars entering the market simultaneously.[86]
- Increase in R&D for generics/biosimilars with regulatory pathway becoming quicker and clearer, Bolar exemption broadened to include additional beneficiaries, modification of the duplicate marketing authorisation regime and specific (regulatory) incentive for first biosimilars. The latter may encourage more investment in biosimilar development (there is a positive relationship between market protection and R&D investments by companies[87]), but this effect will be limited considering development costs[88] and only six months' market exclusivity as incentive.
- The extended scope of the Bolar exemption will increase returns to innovation and therefore increase incentives to innovate for European R&D based pharmaceutical companies in countries that currently have a narrow Bolar scope, such as Belgium, the Netherlands and Sweden. This might increase the number of regulatory tests/medicine trials

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[84] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

[85] https://www.biosliceblog.com/2019/11/update-on-eu-duplicate-marketing-authorisations/

[86] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilars

[87] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, *Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe : final report*, Publications Office, 2018, https://data.europa.eu/doi/10.2873/886648

[88] Mestre-Ferrandiz, J., Towse, A. & Berdud, M. Biosimilars: How Can Payers Get Long-Term Savings?. *PharmacoEconomics* **34**, 609–616 (2016).

conducted in these countries and can be expected to lead to an increase in the number of skilled jobs[84]

- A very high likelihood of positive impact on patients through making medicines more readily available and reducing costs for health systems (generics represent around 80% cost reduction compared to originators, and entry of a generic also reduces price of the off-patent medicine by 61%[89]; biosimilars are 20% cheaper[90] compared to originator products)
- An extended Bolar exemption will result in more timely access to medicines for patients.[91] If the measure leads to more clinical trials in a country, this will benefit the country patient population, as it has been shown that new medicine adoption is wider in countries where the clinical trial was run.[91]
- Increased access to medicines and security of supply through alternatives being defined (interchangeability)

Assessment of any synergies and tensions

There is synergy with the horizontal measure of streamlining and harmonisation with making the regulatory pathway for generics simpler. There is a high likelihood of synergistic effects on biosimilar adoption from the combination of interchangeability guidance and the other incentives and measures.

Changes to the duplicates regime should alleviate some tensions with regard to timely availability of biosimilars on the market and thus could improve access. On the other hand, the measures to promote earlier generic/biosimilar entry to the market e.g. extending/broadening the Bolar exemption and specific regulatory protection for first biosimilars may create tensions with the measures supporting innovation.

A.4.6. Policy Block F (B.F): Supply Chain Security

Compared to Option A, Option B introduces a considerably more extensive set of measures that introduce or increase various obligations and requirements on MAHs and wholesalers.

Assessment of the key impacts for the policy elements

Table 43 presents our assessment of the key impacts of each of the proposed measures, drawing on our consultations, desk research and targeted literature review.

Table 43 Option B - Assessment of the proposed measures for Supply Chain Security

Assessment
B.6.1. Introduce EU definition of a shortage, including a critical shortage and critical medicine
The measure has the potential to harmonise numerous definitions of shortages that exist across the EU. The clarification of criticality criteria can further help in making changes in shortage notification to cover shortages for most critical medicines. Overall, many stakeholders, and particularly industry representatives have advocated for the adoption of the concept of 'product criticality' into definitions of shortages and regulatory measures aimed at notification and prevention of shortages. The study of medicines shortages also called for the introduction of criticality criteria and further measures associated with it.[92]

[89] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[90] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilarsv

[91] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

[92] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages*

The clarification of shortage criticality criteria can further help in making changes in shortage notification to cover the most impactful shortages.
B.6.2. Increase notification period to 6 months in advance using a common template for reporting withdrawals and shortages including details of root causes, alternatives medicines and impact.
This option differentiates between planned (permanent) market withdrawals and temporary supply disruptions, setting different notification timeframes for each. There is more explicit recognition of the fact that not all shortages can be foreseen 6 months in advance. It is uncertain whether this element will result in earlier notification than presently the case, given that most shortage notification are currently made with less than 2 months' notice, citing 'exceptional circumstances'. There is no clear reason why extending the notification period would remedy this situation. Where potential shortages are notified more in advance, these situations often are resolved before they result in an actual shortage. Extending the notification period may thus increase the number of 'false alarms'. There is also a risk that a longer notification period will increase the administrative burden on both MAHs and public authorities without clear benefits. In some countries, parallel distributors also fall under a notification obligation. In consultation, this industry has indicated that a 6-month notification requirement would not be possible to meet since they typically do not hold stocks for more than 2-3 months. Earlier notification of planned withdrawals may be more feasible and provide authorities more time to identify and source alternatives. The obligation to utilise a common reporting template is received positively by the stakeholders. Common data collection approaches, particularly if linked to a standardised reporting portal and automatic sharing of information between MS could, in the longer term, result in cost savings for authorities. Greater standardisation of information may also enable a better understanding of the causes of shortages and allow for the development of better-tailored policy approaches to address the issue of shortages.
B.6.3. Shortage prevention and mitigation **plans added to GMP** for **all medicines**
Early identification of risks to the security of supply and of possible mitigation steps could reduce the occurrence and impact of supply disruptions. Fewer medicine shortages, as well as faster and more effective mitigation of the impact of shortages when these occur, improves patient access to (critical) medicines and leads to better health outcomes. The health system experiences fewer costs associated with dealing with medicine shortages. Depending on the level of detail required and the degree to which risk mitigation steps (e.g. contractual agreements with backup suppliers) are expected, MAHs may make additional costs not only in drawing up the plans but also in implementing the actions therein specified. Industry representatives have indicated that an important condition for the submission of shortage prevention plans would be that the company retains ownership of the plan, and that information remains confidential, as this could be commercially sensitive.
B.6.4. Stockpiling requirements for MAHs and wholesalers for unfinished critical medicines, as appropriate
Some further elaboration is needed to determine criteria to establish what constitutes 'as appropriate'. More detailing is also needed about the expected quantity of such stock, what state the product needs to be in (e.g. intermediates or finished but unlabelled/unpacked products), at what level the stock will be held (e.g. EU, national, regional), who has ownership and responsibility for the stock (e.g. MAHs, wholesalers or authorities) and whether stock may be redistributed according to need. All such factors may strongly influence the operational feasibility of this measure and its acceptability to involved stakeholders. Among wholesalers there is a sense that a limited level of additional reserve stockholding (~2-3 weeks) – with reserves dynamically rolled into normal stock – for critical measures may be a cost-effective measure against supply disruptions, holding larger volumes of stock is both unfeasible and unnecessary. It is expected that the costs of increased stock holding will either need to be shared between MAHs and public authorities, or if not, that MAHs will seek to recoup the increased costs by raising prices. For generic manufacturers, whose products are typically under strict price regulations and caps, this may not always be possible. Among generic manufacturers, there is therefore a fear that in the absence of a balanced cost/risk sharing arrangement, companies may be unable to continue operating in markets where these stock obligations apply.
B.6.5. Introduce an **EU shortage monitoring system**
Improved monitoring of supply and demand of shortages may enable earlier identification of potential supply problems and allow for mitigating actions to be taken before these can impact patients unduly. EU-wide monitoring of shortages would reduce the need for decentralised notification and national (mirror) reporting systems, which should improve the overall consistency / timeliness / quality of information available to stakeholders. This can be expected to result in cost savings for parties under a notification obligation if it is assumed that notification into an EU shortage system negates the need to report to one or more individual national authorities and for those national agencies to maintain their own reporting systems.

Most shortages are limited in geographic scope and are not the result of global supply disruptions but rather inequitable distribution. Improved monitoring at the EU level could allow to improve the balance between supply and demand across the EU and can support the functioning of the internal market by matching excess supply in one location to unmet demand in another. Standardisation of the information collected on shortages across the EU would overcome current reporting issues and would significantly aid research into understanding the characteristics of products most at risk and the causes of shortages. This, in turn, will inform better evidence-informed policy making.
B.6.6. Require specific **penalties** for breaking supply obligations.
If (the threat of) penalties are effective in improving the continuity of supply, this reduces the negative health and economic impacts to patients resulting from medicine shortages. If levied, financial penalties for failure to meet supply obligations represent an additional cost to suppliers (MAHs and wholesalers). The height of penalties and the conditions under which these are imposed in practice will determine the economic impact of this. In past, penalties have been imposed only rarely and often are not financially significant for companies. (DG SANTE, 2021) To enable more stringent monitoring of suppliers' obligations by authorities, suppliers will be expected to adequately document and communicate the steps they have taken to fulfil their responsibilities. This is likely to increase administrative costs associated with dealing with public authorities.
B.6.7 Expanded requirements for key suppliers and back-ups to diversify supply chain for critical medicines
B.6.7. aims to force MAHs to diversify their supply chains to prevent shortages and thus improve the availability of medicines and overall patient outcomes. Requiring more diverse supply chains most likely will result in increased production costs as MAHs may need to procure goods and services from less economically advantageous suppliers. These costs could be substantial, although no data was collected that would allow this impact to be quantified. There may be additional payments to backup suppliers, to reserve goods and space on production lines, even if not needed. These additional costs occurred by the pharmaceutical industry may result in higher medicine prices and greater costs to health systems and patients. If requirements are introduced by individual MS rather than at the EU level, this could discourage MAHs from operating in markets with such requirements and contribute to inequitable access to medicine. Importantly, the measure may not be feasible to implement for many medicines, for which globally a limited number of API and raw materials manufacturers exist, meaning that it may not be feasible for MAHs to sufficiently diversify their supply chains. Separate measures would be needed to enable this, e.g. economic incentives for industry to increase the manufacturing of APIs and raw materials.
B.6.8. Increase transparency of the supply chain, including: 1. active supply sites for all medicines, 2. volumes supplied, incl. supply quotas and remaining stocks for critical medicines upon request of NCA's/ EMA, 3. parallel traders and wholesalers' transactions for critical medicines upon request of NCAs/ EMA.
Improved transparency of the supply chain, at least for public authorities, has the potential of improving the security of supply by better matching supply and demand. MAHs and parallel distributors each have a clear commercial interest in keeping (aspects of) information about their transactions confidential and are not generally welcoming of disclosing this to the other. For instance, parallel traders fear that full public disclosure of information about their transactions will render their trade practically impossible by allowing MAHs to throttle their supply to the level where no surplus is created. For these parties to agree to share information with public authorities, it will be essential that strong agreements are made about what information is disclosed, for what purposes, how this will be used and who has access to it. Without this, it is unlikely that industry will cooperate. Mandatory disclosure of commercially sensitive information could furthermore distort competition between MAHs. It may be assumed that regular sharing of information between supply chain actors and authorities – particularly when not done though an automated system – entails substantial administrative costs on all sides.

Summary assessment of the principal costs and benefits by impact type

Table 44 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block F under Policy Option B.

Table 44 Option B – Summary assessment of Security of Supply elements

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
B.6.1	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
B.6.2.	-	-	+/-	-	+/-	+/-	+/-	++	+/-
B.6.3	-	+	+/-	+/-	+/-	+/-	-	++	+/-
B.6.4	+/-	+/-	+/-	-	+/-	+/-	+	++	+/-
B.6.5	+/-	+	+/-	+/-	+/-	+	+	++	+/-
B.6.6	---	--	-	+/-	--	+/-	+/-	++	+/-
B.6.7	---	---	--	--	-	+/-	+/-	++	--
B.6.8	+/-	--	+/-	--	-	+/-	+	++	+/-
Overall impact	-	+/-	+/-	-	+/-	+/-	+/-	++	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

The following key impacts are envisaged:

- Collectively, the proposed measures are expected to allow for improved decision-making to prevent and mitigate the impact of shortages (B.6.1, B.6.3, B.6.4) and offer public authorities additional tools for protecting the domestic supply of medicines (B.6.2). If successful, this will in turn result in greater continuity of supply for medicines that are needed to offer appropriate healthcare to patients. Health care costs resulting from shortages would also be reduced. With added coordination at EU level and use of an EU-wide monitoring system, the public health benefits will be greater compared to Option A.

Assessment of any synergies and tensions within the Policy Block

Overall, the elements are synergistic and do not contradict each other.

A.4.7. Policy Block G (B.G): Quality and manufacturing

Assessment of the key impacts for the policy elements

Table 45 presents our high-level assessment of the likely costs and benefits of each of the proposed policy elements.

Table 45 Option B – Assessment of the proposed measures for quality and manufacturing

Assessment
B.7.1. Improve the oversight of the sites within a supply chain (including distributors and active pharmaceutical ingredients (APIs) manufacturing sites) by modifying provisions on inspections (frequency, content, triggering points)
This measure will strengthen end-to-end oversight of the supply chain and could improve GMP/GDP compliance. However, it could impose significant additional burden on businesses and competent authorities if the frequency of inspections is increased and the triggering points are changed such that in effect more inspections take place. This would substantially increase the workload of inspectors, which would need to be met with more resources.
B.7.2. Reinforcing Member States GMP and good distribution practices (GDP) inspections capacity by setting up a mandatory joint audit scheme

Assessment
This policy element has the potential to increase inspection efficiency through more cooperation and knowledge transfer. This may have a positive effect on manufacturing and distribution practices within the EU and globally, which would ultimately positively impact public health in the long-term.
B.7.3. Stronger overall responsibilities of MAH vis a vis suppliers of raw materials and clarification of responsibilities of business operators over the entire supply chain. This would include transfer of information between each actor for each to fulfil their legal obligations with respect to quality, safety, efficacy.
Greater burden on MAHs and other business operators with additional responsibilities, complexity of submissions and costs could lead to reduction in international competitiveness and a decrease in companies within the sector, in particular SMEs. This may threaten security of supply of medicines. Depending on the information required to be provided by the manufacturers/suppliers and the mechanism for receiving, analysing and sharing this information with the stakeholders, sufficient safeguards should be introduced to ensure that information sharing does not run counter EU antitrust rules.
B.7.4. Adaption of legislation/inclusion of specific provision covering new manufacturing methods (decentralised, continuous manufacturing, etc). to ensure levels of quality and safety equivalent to current methods.
Same as A.7.3 The proposed measure has the potential to bring several product categories that are currently excluded from the legislation into the fold and provide regulatory certainty to manufacturers. These include magistral formulae (pharmacy-based preparation for an individual patient), radionuclides in sealed sources, hospital-manufactured medicines, and single-batch medicines. In addition, manufacturing methods such as decentralised manufacturing (where manufacturing occurs at different locations) and 3D printing-based methods could be accommodated. Covering new manufacturing methods in the general pharmaceutical legislation has the main advantage of helping to standardise the methods themselves, quality control of the methods and resultant products and associated regulatory pathways at the EU level. Thus, there is a harmonisation benefit. Moreover, accommodating new technologies sends a positive signal to innovators as well as companies and will encourage more innovation and research activity and adoption of the new methods. There will be further knock-on effects on competition, competitiveness, and access to medicine. If greener manufacturing methods are used there will be an impact on environmental sustainability, but the likelihood and extent of that is unclear. With more certainty over the manufacturing methods and the resultant products as well as more medicine developers adopting these methods, we could imagine a very high increase in the number of new therapies in comparison to the baseline.

Summary assessment of the principal costs and benefits by impact type

Table 46 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block G under Policy Option B and for each impact type.

Table 46 Option B – Summary assessment of the proposed measures for quality and manufacturing

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
B.7.1	-	-	-	-	-	-/+	-	+/-	+/-
B.7.2	+/-	+/-	+/-	+	+/-	+/-	+	+/-	+/-
B.7.3	-	-	-	-	+/-	+/-	+/-	+/-	+/-
B.7.4	-/+	-/+	-/+	+	+	+	-/+	+	-/+
Overall impact	-	-	-	+/-	+/-	+	-/+	+	-/+

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Overall, modifying provisions on inspections and expanding oversight to all sites within a supply chain (including distributors and API manufacturers) will create additional transaction,

compliance and administrative costs which might result in smaller players leaving the market and thus loss of choice and competition. Moreover, NCAs will need additional inspection capacity and training to accommodate the changes in the provisions and actors. On the other hand, a mandatory joint audit scheme for member states will allow greater efficiency, cooperation, and knowledge transfer across NCAs.

Adaptation of the legislation or inclusion of specific provisions to accommodate new manufacturing methods will improve international competitiveness, encourage greater research and innovation, and increase choice and competition in the sector. It would also have a direct impact on patients by making more treatments available. The other measures improve oversight of manufacturing but the quality standards are already high so there is unlikely to be greater added benefit to public health.

Assessment of any synergies and tensions within the Policy Block

Policy elements B.7.1, B.7.2 and B.7.3 have synergies as they aim to improve quality and safety of medicinal products through improved oversight. Stronger supply chain oversight through increased inspections should work well with setting up a mandatory joint audit scheme and should also help to enforce the stronger overall responsibilities of MAHs.

A.4.8. Policy Block H (B.H): Addressing environmental challenges

Assessment of the key impacts for the policy elements

Table 47 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

Table 47 Option B – Assessment of the proposed measures for addressing environmental challenges

Assessment
C.8.1 Include assessment of the environmental risk of manufacturing into ERA, including main supply chain actors (API, raw materials)
This measure represents considerable additional burden for medicine developers and supply chain actors, and public authorities in terms of compliance and administration costs and review costs respectively. On the other hand, it will allow tracking of the environmental risks of manufacturing across the supply chain providing a more comprehensive assessment of the potential environmental impact of a new medicine. For example, if risk associated with active pharmaceutical ingredient discharges from manufacturing sites is included in the ERA, it would increase the relevance of the assessments by including a part of the life cycle of the product responsible for the highest environmental concentrations detected.[93]
B.8.2 Strengthen the ERA requirements and conditions of use for medicines, while taking stock of research under the innovative medicines initiative
The proposed measure should enable robust assessment of the environmental risks of pharmaceuticals as well as promote prudent use, supporting sustainable consumption and helping to minimise the environmental footprint of medicines. However, this may place slight additional burden on public authorities for reviewing ERA submissions (in case of additional data requirements) and monitoring medicine use (if required) as well as on businesses and other stakeholders responsible for complying with said requirements and conditions.
B.8.3 Include the AMR aspects into GMP to address the environmental challenges
This measure would help minimise amounts of antibiotics entering the environment via manufacturing and thus prevent emergence of AMR from pharmaceutical manufacturing. Recent evidence indicates the presence of a

[93] Eeb. (2018). Policy options for regulating pharmaceuticals in the environment.

selection pressure for AMR within environments receiving wastewater from antimicrobial manufacturing, as opposed to environments receiving wastewater from municipal sewage treatment plants (containing antibiotics from human use) that do not receive waste from antimicrobial manufacturing.[94]

There would be the additional costs for businesses to comply with the AMR requirements in GMP and data requirements and for public authorities for enforcement of the requirements. This could present barriers for smaller actors.

The KPI would be amount of an antibiotic in waste and wastewater in µg/l. Suggested annual mean value for an erythromycin environmental quality standard (EQS) is 0.2 µg/l.95

For the current impact assessment, we would assume that compliance with the measure will result in levels below the EQS and thus there is a high likelihood of impact on sustainable production (environmental impact).

Summary assessment of the principal costs and benefits by impact type

Table 48 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block H under Policy Option B for each impact type.

Table 48 Option B – Summary assessment of the proposed measures for addressing environmental challenges

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
B.8.1.	-	-	-	-	-	+/-	-	+	++
B.8.2.	+/-	+/-	-	-	-	+/-	+/-	+	++
B.8.3.	-	-	-	-	+/-	+/-	-	+	+
Overall impact	-	-	-	-	-	+/-	-	+	++

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Policy Option B is unlikely to impact on areas other than sustainability and waste management since it does not mark a major departure from current requirements. The impact on patients and health systems will be neutral owing to the uncertain health impacts of pharmaceutical residues in the environment as well as lack of direct impact of the proposed measures on quality and safety of medicines.

Assessment of any synergies and tensions within the Policy Block

No synergies or tensions.

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[94] WHO Expert Committee. (2020). *Annex 6 Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance*.

[95] UBA – Umweltbundesamt (Hrsg.) (2018) Empfehlungen zur Reduzierung von Mikroverunreinigungen in den Gewssern, Hintergrund, February 2018, Dessau-Ro lau, https://www.umweltbundesamt.de/sites/default/files/medien/1410/publikationen/uba_pos_mikroverunreinigung_final_bf.pdf

A.4.9. Policy Block I (B.I): COVID-19 lessons learnt

Assessment of the key impacts for the policy elements

Table 49 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

Table 49 Option B – Assessment of the proposed policy elements for COVID-19 lessons learnt

Assessment
B.9.1. Refusal of immature marketing authorisation applications.
The most significant efficiency gains would be for public authorities, which could save time currently spent on assessing immature applications and resolving internal differences of opinion as regards their evaluability or suitability for processing through the CMA pathway. As per baseline, we assume that there could be **2 to 3** marketing authorisation applications every year that do not initially request a CMA despite not containing enough data for standard marketing authorisation. This would likely lead to 2 to 3 immature marketing authorisation applications refused every year in the first one or two years, possibly increasing to 5 to 10 refused applications every year in the next 3-5 years as the evidentiary threshold is established. Industry would begin to recalibrate the acceptable levels of evidence in parallel and the numbers of weak applications should fall back to some minimum within 5 years, perhaps never quite falling below 2-3 a year over the remaining years through to 2035. Overall, assuming an average annual reduction of 3-5% in the total number of applications for assessment and 100-120 applications annually, which are increasing at 5-10% a year (as per EMA annual report 2020), cutting assessments by 3-5% might result in a reduction of EMA / NCA costs of 2-3% (the work of the EMA committees is a major cost driver). There could be a negative impact on cost for developers that are currently submitting immature marketing authorisation applications for valid reasons. For example, addressing an UMN may be difficult in terms of conducting large clinical trials. This may discourage developers of medicinal products for UMN if it is not combined with other policy elements. On the other hand, less immature data means HTA bodies and P&R authorities would be more able to assess therapeutic value, which could have a positive impact on access and affordability. Thus, the impact on healthcare systems could be negative (less developers working on UMN) and positive (more streamlined and coherent procedure leading to faster market launch).
B.9.2 Codification of rolling review for UMN
The most significant benefit would be to developers of medicinal products for UMN. The increased interactions with regulators could reduce uncertainty, the timeline for EMA scientific opinion (baseline = 150 days) and the total approval time (baseline = 251 days). The impact will depend on the implementation of the system and the specific timeframes proposed by the EMA to respond to each rolling review cycle. As per baseline (COVID-19 pandemic), the average number of rolling review cycles was 2 cycles[96], and the number of days spent by the EMA on each rolling review cycle was 30 days[97]. Other factors will also be important, such as the details of the definition of UMN that will be applicable to the rolling review system and the specific requirements for each data package. As such, there would be significant cost to public authorities, even with our assumption that resources would be made available, new ways of working would have to be implemented and adapted over the years. It is expected that such system would streamline the process of evaluating evidence for medicinal products for UMN and therefore increase the number of medicinal products approved by speeding up the process and by attracting new investments areas of UMN. This could also result in a positive impact on innovation rates and overall EU pharma industry output. While patients and healthcare systems would benefit from more medicinal products available, there could be a negative impact on access due to more post-marketing authorisation requirements to allow P&R authorities to assess therapeutic value. Therefore, there is a risk that this policy element would increase the gap/time between availability (centrally approved) and accessibility (Member State market launch), which could affect poorer/smaller Member States disproportionately.

[96] https://doi.org/10.1016/j.clinthera.2022.01.001

[97] https://doi.org/10.1016/j.clinthera.2022.01.001

Summary assessment of the principal costs and benefits by impact type

Table 50 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block I under Policy Option B for each impact type.

Table 50 Option B – Summary assessment of the proposed policy elements for COVID-19 lessons learnt

Policy elements	COB	Admin	SMEs	CTI	Internal Mar	I&R	PA	H&S	Sust
B.9.1.	-	+/-	-	-	+/-	+/-	+	+/-	+/-
B.9.2	+	+	+	++	+/-	+	-	+/-	+/-
Overall impact	+/-	+	+/-	+	+/-	+	+/-	+/-	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element. Policy Option C – Summary assessment of the Incentives for innovation

Assessment of any synergies and tensions within the Policy Block

Within the COVID-19 lessons learned Policy Block, the policy elements proposed under Policy Option B are largely complementary to each other. Refusing immature marketing authorisation applications while codifying rolling reviews for UMN provides a clear pathway for developers to submit their immature data sets. In comparison to the current system, where immature data create challenges for regulators (often leading to ambiguous decisions and/or nudging developers towards CMA), this policy block B should decrease uncertainty, and facilitate developer/regulator interaction.

A.5. Policy Option C

A.5.1. Policy Block A (C.A): support for innovation, including unmet medical needs

Assessment of the proposed Incentives for Innovation

Table 51 Option C – Assessment of the proposed Incentives for Innovation

Assessment
Expedited regulatory pathways
C.1.1. Codification of PRIME in the legislation
same as B.1.1 The inclusion of the PRIME scheme within the legislation would give a strong signal to developers that the EU is committed to increasing support for UMNs. It will also reassure developers that the scheme is permanent and that they continue to benefit from the active support that comes with PRIME designation (which is focused on medicines that promise a major therapeutic advantage in an area of unmet medical need). The scheme is well regarded by stakeholders (industry, regulators, health systems) and the EMA analysis of its first five years of operation found that PRIME designation is associated with faster assessment times and an improved likelihood of a positive recommendation for authorisation. There should be no significant additional administrative or compliance costs for businesses, when compared with the current situation. Codification may increase the popularity of the scheme still further, and that may increase the number of companies that have to bear the administrative costs associated with making an unsuccessful PRIME-eligibility request. The popularity of the scheme has increased in the recent past (+15% between 2019 and 2020), and we would expect to see further growth in future. This would be even more likely should the EU implement an additional period of regulatory protection for UMNs. These additional costs (linked with unsuccessful requests) are

Assessment
being limited by an equivalent expansion in the number of medicines accepted onto the scheme, which has also increased (from 23% in 2018 to 33% in 2020). The impact on regulators should be broadly neutral, as while the scheme does involve additional effort to businesses with advice on the development of their PRIME-designated medicines, the resulting applications tend to be better framed and evidenced, making assessment more efficient and improving success rates for submissions (improving EMA productivity in this important area of UMNs). Small biopharma firms have a particular interest in advanced therapies relevant to UMNs, and the codification and expansion of PRIME ought to have positive impact of SMEs. They benefit disproportionately from EMA advice, where larger developers have considerably more experience in preparing an application for assessment. Moreover, for some start-ups (e.g. cell and gene therapy companies), PRIME may have the effect of a 'seal-of-approval,' which could improve their investability and market value. In the longer term, codification should reinforce the regulator's wider efforts to reduce UMNs, improving treatments, reducing hospitalisations and improving patients' quality of life. As with the other regulatory proposals designed to focus developers' attention on UMNs, there is a small risk this will displace investment in other areas of medical research, possibly even slowing down the rate of progress in other disease areas that have good treatment options currently, but which still constitute a major health burden.
Repurposing
C.1.2. Establish a binding system for scientific assessment of evidence for repurposing off-patent medicines (scientific opinions or monographs) that are used by marketing authorisation holders to include a new indication for their products. Plus simplify the obligations regarding certain activities associated with holding a market authorisation in order to facilitate non-commercial entities (e.g. academic) to become marketing authorisation holders. This could be combined with possibility for private, public partnerships for manufacturing and safety monitoring (e.g. for **repurposing** of authorised medicines or hospital preparations).
Same as B.1.2. The policy might lead to developers investing more heavily in new indications of their recently approved medicines, with the additional costs of seeking better, earlier scientific advice being offset by a greater likelihood of seeing a new use authorised There may be a reduction in administrative and compliance costs associated with repurposing, as compared with the authorisation of new medicines May provide opportunities for developers to cost-effectively expand their portfolio of medicines / indications (improving R&D productivity); may provide a platform for clinical researcher and academics to play a fuller role in development work and trials MAHs can be reluctant to apply for new indications of existing older medicines close to the end of their period of regulatory protection or where going on-label for new indications could affect the commercial value of any existing medicines used for the same indications[98] or otherwise for liability reasons. This policy element will help broaden access to what are otherwise rather selective and uneven use of safe and effective medicines off-label. It will be a much stronger intervention than the non-binding system. In the longer term, we may see more treatment options for patients and improved geographical access. Its impact would be strengthened by C.1.3 (a period of additional data protection for major public health interest) and C.1.4
C.1.3. Additional data protection period for the new evidence generated to support repurposing of existing products if considered as major public interest for public health or innovation (i.e. criteria for accelerated assessment).
Industry may benefit from the (lower cost) of repurposing an existing medicine for use with an UMN, where that insight has arisen based in part on evidence gathered by healthcare providers or academics. While repurposing costs are substantially lower than the costs for wholly new development programmes, the costs can run into the many tens of millions and take several years, and the ROI is often too weak for many older medicines. An additional period of data protection (+1 year becomes +2 years) could help offset that ROI challenge, at least for that subset of extensions where there is a major public health interest associated with an extension of an existing medicine. May increase the workload for regulators (more assessments, more enforcements). May increase the size of the medicines bill for health systems; may reduce the high costs associated with hospitalisations of people with complex conditions and no effective treatment.
Adaptation of the regulatory protection

[98] https://www.fiercepharma.com/sales-and-marketing/sanofi-pulls-campath-to-clear-way-for-higher-priced-lemtrada

Assessment

C.1.4. Reduce duration of incentives for originators from 8+2 to a new combination (e.g. 6+2) taking into account the interaction between data protection and intellectual property rights

same as B.1.4

For originators, a reduction in the period of regulatory protection will reduce overall income and profitability for new medicines since generics companies will be able to enter markets and begin to erode monopoly prices a year earlier. The new period of protection may prompt developers to increase prices in general to protect their current business model or otherwise rebalance their portfolios towards those market segments with greater commercial potential.

SMEs originators may find it more difficult to invest in riskier novel medicines given the reduction in future returns on investment and their relatively weaker market position when it comes to negotiating prices.

It could weaken the global competitiveness of EU based originators overall, compared with the current situation, unless prices are adjusted upwards to reflect the new protection period, and ensure global ROI norms can continue to be achieved.

The threat to EU-based originators will be offset to some degree by giving a boost to Europe's generic industries, broadening their portfolios, and potentially creating a prime-mover advantage in global markets.

Considering that this policy element affect SMEs more than larger firms and the latter are based in bigger economies, while the former may be based in smaller economies this may affect the functioning of the internal market and limit access to medicines across Europe. This will also be the case if some companies adjust prices upwards in response.

Health payers may benefit from lower average lifetime costs for medicines due to earlier generic entry and patients may benefit if those savings are used in the health care sector. The extent of these benefits will depend on originators response to the reduced incentives, and it is highly likely that average prices will be adjusted upwards in some degree to offset the shortened period of protection.

C.1.5. Authorised medicines with demonstrated ability to address UMN get +1 year data protection

A +1 year period of premium pricing (during the extra year of data protection) will offset the higher development costs and / or lower market volumes associated with a proportion of UMNs, whereby a larger number of all UMNs would pass the private sector's ROI thresholds.

While companies cannot determine in advance which products will be successful and make a smaller or larger positive contribution to their overall income and profitability, the additional period of regulatory protection will have a positive impact on estimates of potential income and profitability used in stage-gate assessments. It will also mean payers will have larger costs for the medicine for an additional year.

The additional period of protection would improve the competitiveness and investment flows towards EU based originators producing UMN medicines.

Increasing developers focus on UMNs may increase their development and regulatory costs, in some limited degree, as applicants would need to meet the UMN criteria.

This incentive is expected to focus and possibly increase investments in R&D resulting in a higher number of novel medicines addressing UMNs as compared with the baseline and an increase in treatment options, treatments and improved patient health.

The increased flow of medicines for UMNs would have a strongly positive benefit for patients that currently have to live with debilitating conditions with no effective treatment options. The health systems should also benefit from the availability of more effective medicines for these patient groups, making care more cost-effective and reducing costs associated with avoidable hospitalisations.

We assume this extension would increase by around 10% the numbers of UMN products being developed, which would amount to 2-4 new authorisations annually. Our modelling work suggests this would generate #320m-€640m in additional protected sales annually, based on the €160m annual EU revenue for the average product. The increasing number of UMNs – with a longer period of RDP – would lead to additional costs for health payers on the order of €163m-€326m, based on the difference between the premium priced product (in the final year of RDP) and the price of the first generics to enter the market (c. 50%). We estimate that the generics industry would see a loss of income on the order of €77m-€154m as a result of the +12-month delay in market entry.

C.1.6. Special incentive bonus: if data package includes comparative trial with standard of care (+6 months)

Same as A.1.4

We assume a 6-month extension might lead to the use of comparative trials for an additional 8-10 products a year. We assume the additional costs of a comparative trial design might amount to €10m.

With average additional peak income (EU) of €160m, a 6-month extension might secure an additional €80m in income, or €640m-€800m a year in additional protected sales for originators.

The bonus would result in a delay in the market entry for generics for these additional products, which might amount to a loss of income of around €154m-€192m a year for the generics industry

Assessment

There would be some additional costs for health payers, which result from the delay in the market entry of generic competition. This may amount to €326m-€408m a year.

This should deliver faster access to markets and costs savings thanks to improved reimbursement decisions

Moore et al (2020) in a review of 101 new FDA medicines (225 individual clinical trials), found the median cost of an individual clinical trial was around $19m (range = $12m-$33m). They found the Phase 3 development costs almost doubled with second trial (albeit the single biggest cost driver is the number of patients).

Moore et al identified 62 (27.5%) of the total set of 225 clinical trials had a comparison group rather than a placebo or uncontrolled trial.

C.1.7 Require transparency on public contribution to research and development costs in relation to clinical trials included in the marketing authorisation application (this information would be published)

This proposal for increased transparency around public support for R&D in clinical trials, is narrower than the proposal under Policy Option B, where the issue of transparency covers any aspects of public support for medicines development, including various tax reliefs.

This option would be simpler to implement as it relates to the direct support of specific clinical trials through publicly funded R&D grants. This information is more likely to be in the public domain already (through online, public grants databases) and does not require a complex financial exercise to link / attribute the public support to a specific trial and resultant application for a new medicine. It is therefore likely to meet with slightly less resistance from industry on the grounds of commercial confidentiality.

Greater transparency around public support for R&D may strengthen pricing and reimbursement agencies' position when negotiating with MA holders, helping to place a downward pressure on prices and thereby helping to maintain or improve access to medicines with concomitant benefits to patient health.

Administrative costs may increase for firms needing to prepare the required information.

Understanding the scale of public contributions to clinical trials research would need to be established over time, from the evidence submitted by applicants. We found no good data on this in the wider literature.

The analysis of public support would be reported by applicants in a section of the Common Technical Dossier. This would affect 4,000 clinical trials authorised each year in the EEA. This equals approximately 8,000 clinical-trial applications, with each trial involving two Member States on average.

The statistics show that around 60% of clinical trials are coordinated (sponsored) by industry and around 40% by non-commercial organisations, mainly academia. However, these trials do not necessarily relate to new medicinal products that will be submitted to the EMA and where an academic trial does feed into an industry application it is possible that trial would have been partly funded by industry or a research charity with little or no support from public R&D funders.

C.1.8 Give regulators the possibility, in the context of a marketing authorisation, including a conditional marketing authorisation, to impose a **post authorisation obligation** for **additional studies** on the effectiveness compared to the standard of care

same as B.1.8

Imposing a post-authorisation obligation for MAHs to include new information about the effectiveness of the medicines (i.e comparative clinical trials) may impose additional costs on MA holders, albeit this may be a matter of timing and degree, as many businesses carry out additional research on the cost-effectiveness of their medicines with a conditional approval. The EMA annual reports show that around one third of all medicines that have been granted a CMA since 2006 have gone on to be granted a full marketing authorisation (i.e. sufficient additional evidence has been gathered to confirm effectiveness). As such, it may increase and bring forward costs associated with such studies for tens of businesses. Those costs might amount to €20-€50m for each product.

MA holders will have to bear some additional costs and there may be a small increase in the number of medicines that are found to be less cost-effective than had been anticipated. This last point could impact on the ability of individual companies to raise finance or otherwise weaken their competitive position, but there would be no substantive impact – positive or negative – on overall competitiveness, or the functioning of the internal market.

This obligation would help to confirm the relative effectiveness of the products in question several years earlier than is the case currently. The EMA annual report (2020) shows that the 30% of CMAs that have been granted full marketing authorisation took an average of 3.5 years post-authorisation to get their products fully authorised. This would allow more timely action in respect to individual medicinal products – e.g. withdrawal or more widespread use – and would indirectly give HTAs and payers greater confidence in the CMA pathway.

There would be some additional administrative costs for the EMA and NCA staff working with them following from the increasing numbers of assessments of these additional studies and consideration of the case for granting full authorisation.

The improved clarity as regards the relative cost-effectiveness of medicines should increase confidence across health systems in making full use of those products, and thereby benefiting patient health.

C.1.9. **Breaking market protection** in case of urgency and insufficient coverage by authorised medicines (compulsory licensing)

Assessment
same as B.1.6 There has only been one instance of an EU member state using a Compulsory Licence, as such this is an ultra-low probability event, and the link with the EU general pharmaceutical regulation is about ensuring external coherence. There should be no or minimal direct impact on EU pharma in general, given it would be implemented indirectly and by exception and for a localised and time limited period. It may increase burden on regulators and expand the numbers of government bodies that must become involved in explaining their use of this regulatory exception The time and costs involved in developing safe and effective copies of protected medicines may mean that the policy lacks the speed or certainty to respond with confidence to public health crises

Summary assessment of the Incentives for innovation

Policy Option C reduces the current standard period of regulatory protection for new medicines and requires originators to disclose information in their applications regarding the level of public funding of their clinical trials. There is a special bonus available where the data package includes a clinical trial.

Policy Option C does not include any special incentives relating to UMNs, beyond the codification of PRIME in the legislation, which has some relevance to originators working on new medicines targeting UMNs and hoping to benefit from the additional advice that follows from PRIME designation.

MAHs are given increased obligations regarding the conduct of additional studies relating to for example, CMAs.

Policy Option C gives relatively more weight to repurposing, and the overarching objectives of improved access and affordability. It seeks to deliver a significant expansion in the number of extensions of existing medicines to new indications by targeting the under-exploited off-patent and off-label use of older medicines, through a combination of a more inclusive definition of scientific evidence for repurposing, with the simplified obligations for non-commercial entities to become MA holders (possibly through public private partnership) and the obligation on MA holders to include a new indication when supported by that scientific evidence and assessment.

There is an additional period of data protection available for these repurposed medicines, where the extension is judged to be a major public interest for reasons of public health or innovation.

Table 52 Option C – Summary assessment of the Incentives for innovation

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
C.1.1	+	+/-	+	+/-	+/-	+	-	-	+/-
C.1.2	+	+	+/-	-	++	++	+/-	+	+/-
C.1.3	+	-	+	+	++	+/-	+/-	+	+/-
C.1.4	--	+/-	--	--	-	---	+	-	+/-
C.1.5	++	+/-	-	+	+/-	+	-	+	+/-
C.1.6	+	-	+	+/-	+/-	+	+	+	+/-
C.1.7	-	-	-	+/-	+/-	+/-	+	+/-	+/-
C.1.8	+/-	-	-	+/-	+/-	+	-	+	+/-
C.1.9	-	-	-	-	-	-	-	+/-	+/-

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
Overall impact	++	--	-	-	++	++	+/-	++	+/-

Assessment of any synergies and tensions

Within the Innovation Policy Block, the policy elements proposed under Policy Option C are largely complementary to each other, whereby the proposal to reduce the period of regulatory protection for the standard innovative medicines pathway (by 1 year) is mirrored by a policy element to provide a +6 month special bonus for data packs that include comparative trials. The proposed new obligations around the transparency of public funding of clinical trials research may serve to reduce industry's interests in public R&D grants.

Relatively greater weight is given to repurposing under Policy Option C, with a general reduction in the level of support for innovation, at least through the standard EMA regulatory pathways. The ability to impose a requirement on MA holders to carry out additional studies post-authorisation would not reduce the attractiveness of the EMA's various expedited regulatory pathways, but should rebuild support among member states (HTAs, health payers) for conditional marketing authorisations in particular.

A.5.2. Policy Block B (C.B): Antimicrobial resistance

Assessment of the proposed incentives for innovation and prudent use

Policy Option C is similar to Policy Option B, regarding the proposed measures to encourage more prudent use of antimicrobials. It would reinforce these stewardship measures with the addition of a new requirement for MA holders, whereby developers must prepare an AMR lifecycle plan as part of their marketing authorisation application.

Policy Option C omits the play or pay model in favour of a stronger incentive, a transferrable voucher, similar to that in Policy Option A.

The proposed interventions are assessed in the table below:

Table 53 Option C – Assessment of the proposed incentives for Innovation and prudent use of antimicrobials

Assessment
C.2.1 Novel antimicrobials (new active substance, new mechanism of action, first in class) fall in the central procedure's mandatory scope
As this policy element formalises what happens in practice already, there would be no additional impact on the development of novel antimicrobials or their more prudent use.
C.2.2. PRIME like support scheme, including rolling review
Same as B.2.2 If the system in place for rolling reviews is easy for SMEs and large companies to navigate and flexible, there is potential for a large positive effect on EU pharma businesses by increasing company-regulator interactions in areas that may not be currently attractive for business to invest in R&D. This could result in a positive impact on innovation rates and overall EU pharma industry output. The targeted survey revealed that industry respondents were broadly in favour of codifying rolling reviews, in particular for new technologies or major innovations in medicinal products. However, the demands on Rapporteurs are high, with significant increase in workload; one NCA interviewed stated that the COVID-19 pandemic rolling review required approximately 50% increase in resources/workload. The demands on companies are also relevant, as the process requires more communication and clarifications (data packages may not be structured, may contain errors, etc). Furthermore, rolling reviews bring uncertainty on the added therapeutic value of medicines and inequity of access is larger for orphan medicines. Considering these reasons, some civil society and public authority respondents were against codifying rolling reviews in a way that would

Assessment
expand the scope of use of this procedure outside exceptional medical conditions and public health emergencies.
C.2.3 Require companies to develop AMR lifecycle management plan as part of marketing authorisation to set out coherent strategy for prudent use, stewardship monitoring and reporting (including consideration of optimised package size and rules on disposal) to address the environmental challenges as well).
The AMR Product life-cycle management (or PLCM) document would provide an opportunity for continuous development and improvement, a framework for change management to facilitate assimilation of novel control strategies, analytical procedures, and process tools as they become available to the industry.[99] It may involve reassigning some resources from other areas within companies to develop the AMR PLCM document required for antimicrobials. Expanded surveillance would have no direct impact on EU pharmaceutical companies conduct of business. Indirectly, and in the longer term, improved surveillance data may help to accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for industry overall. The legislation and accompanying guidelines would have no direct impact on EU pharmaceutical manufacturers, wholesalers or pharmacies, indirectly it may lead to an expansion in overall sales volumes and income, as pharmacies buy smaller volumes more frequently, prescribers push for smaller pack sizes, and patients a less likely to self-medicate. Even though preparing the AMR PLCM document may take some time, establishing appropriate mechanisms to share information with regulators and possessing records from inspection or assessment activities can mitigate increased burden on the MAH later on. Any implications for enhanced environmental risk assessments could be more challenging for SMEs to carry out / afford. The AMR PLCM document as any PLCM document could provide an opportunity for continuous development and improvement and assimilation of novel control strategies, analytical procedures, and process tools as they become available to the industry.[99] An expanded surveillance system could impact the costs borne by public authorities, both one-off costs associated with system development, capital investment and training and recurrent costs associated with additional data collection and additional data curation and storage costs. Stricter disposal rules would bring additional costs for public authorities, with a substantial one-off cost for EU / MS authorities in developing and championing the roll-out / adoption of the guidelines and additional ongoing costs for national authorities in maintaining / monitoring adherence and for the EMA and its advisory groups in tracking developments and giving ad hoc advice. Stricter disposal rules / smaller pack sizes may increase the unit costs of antimicrobials and stricter management of stocks may also add costs. Patients should see a benefit from a reduction in self-medication using unused and out of date medicines. The AMR PLCM document would cover the whole lifecycle of antimicrobials and help address AMR in the human and animal health and plant protection sectors. More prudent use and more informed production and disposal of medicines would help reduce the level of human-related active ingredients getting into the environment.
C.2.4. Optimise package size
Same as B.2.3. This policy element would encourage the use of smaller package sizes, thereby increasing manufacturers' costs relating to product packaging and distribution. It may also increase the cost of antimicrobials for health payers (smaller package sizes are more costly), including an increase in average prices for a course of treatment for an individual patient, albeit these price increases should be offset in some small degree by lower levels of consumption. It may have implications for storage costs (more space required) but may ease dispensing and take pressure off pharmacists' local storage requirements. We don't foresee additional extra administrative costs on the side of businesses and authorities. By helping to reduce overall levels of consumption, this policy element may contribute in some small degree to reducing AMR and avoiding AM releases to the environment. The smaller pack sizes will increase packaging waste, which would increase costs associated with waste management and recycling.
C.2.5. Tighten prescription requirements for antimicrobials
Same as B.2.5

[99] Schiel and Turner. The NISTmAb Reference Material 8671 lifecycle management and quality plan. Anal Bioanal Chem. 2018.

Assessment

While prescribing policies are a matter for national authorities in the first instance, the legislation can invite member states to do more to bring practice in line with international standards.

These obligations and guidelines do not affect industry directly. Indirectly, and if successful, better prescribing would accelerate the rate at which the EU reduces its overall consumption of antimicrobials, reducing income for the pharmaceutical industry overall and particularly those generics companies that supply older, lower-cost, broad-spectrum antimicrobials.

Indirectly, there may be a differential impact on the generics industry and particularly that sub-set of pharma businesses that include older, broad-spectrum antimicrobials in their portfolio. There may be a small benefit for MA holders with more specific antimicrobials, if prescribers both reduce overall prescription numbers and switch from cheap, broad-spectrum medicines to more specific (more expensive) antimicrobials.

Indirectly, tighter prescription is likely to reduce usage and that may weaken the return on investment for antimicrobials in general, worsening the investment case in an area of medicines research that is already regarded as being uneconomic.

Indirectly, health systems may see savings because of better prescription practices and reduced consumption, albeit this may be offset by increased costs associated with diagnostic tests and a switch to more costly antimicrobials. If successful, this policy element should reduce consumption and that in turn should reduce the potential for negative environmental impacts.

C.2.6. Transferable voucher – independent and in addition to data/market protection for antimicrobial products.

Similar to A.2.2

The right to be transferred relates to the transfer of the right to extend the data protection by a length to be determined. The assumption/calculation is based on an extension of data protection by 1 year.

The antimicrobials that would be applicable to generate this right are all antimicrobials or a subgroup e.g. antibiotics only or their alternatives which either (i) represent a new class and/or new mode of action, addressing new target or absence of known cross-resistance (WHO innovation criteria) or candidates targeting priority pathogens (WHO list for antibiotics) or innovative platform technologies able to confer break-through clinical benefit, (ii) ground-breaking innovation within an existing class.

Given the current pipeline, and the scale of the incentives foreseen, we assume the average number of TVs will be one a year (albeit U JAMRAI predicts fewer).

Companies may use a TV on existing successful medicines that are still covered by data protection, and which are still at least 2 years (EFPIA proposal) away from the expiry of their data protection period. ,

The TV would be most relevant to products where the last defence before generic entry is the regulatory protection. For those where there is a 10+ years patent or SPC protection, the extended data protection does not give any benefit. Hence, only a part of all products could benefit from a TV.

In principle the extension would need to be sufficient to provide a substantial incentive to compensate for the development of a new antibiotic, which is estimated to be on the order of €1.2bn. However, the EU market is some 20% of the total pharmaceutical market globally, and so a proportionate contribution to the development cost with the EU voucher may be a sufficient incentive. It would be possible for companies to receive the right to a TV for antimicrobial products that were already in the pipeline ahead of the implementation of the new regulation, to generate additional income / profits within 2-3 years of implementation, and thereby underpin an early expansion in investments in novel antimicrobials.

Based on the application of a voucher to an average top-10 product, we estimate an originator would secure an additional €543m in non-contested sales because of the 1-year extension.

There would be a cost to the generics industry of a year's delay on the order of €164m.

There would a cost to the health system too, which we estimate at €283m. We further estimate the patient + payer monetised loss would be on the order of €441m

Some vouchers may be sold rather than used directly by the developer of the antimicrobial and we have estimated the average sale value of a voucher at €360m.

Each year, about 33,000 Europeans die as a consequence of antibiotic-resistant bacteria. On average, a hospitalised patient with antibiotic-resistant infections costs an additional 10,000 to 40,000 USD. The expansion in the development and authorisation of novel anti-microbials should help to manage and even reduce AMR, with fewer hospitalisations and deaths, although it has so far not been possible to estimate the scale of these potential benefits, in order to compare with the social costs of the incentives for taxpayers and health payers.

C.2.7. Consider adapted system for authorisation of phages therapies and other alternative products

Same as A.2.3.

This policy element would support the development of phage therapies potentially increasing the number of companies willing to invest and develop these therapies which will in turn increase competition, reducing prices of these therapies. The use of phage therapies may also reduce healthcare costs/budgets since phages are an inexpensive natural resource present in the environment, and offer immense potential as an alternative when

Assessment
antibiotics are rendered ineffective due to bacterial resistance . Finally, by reducing the use of antibiotics it would help reduce the presence of antibiotics in the environment.

Summary assessment of prudent use of antimicrobials policy

Option C would be expected to catalyse an improvement in prescribing practices and stewardship by combining the stewardship measures set out here and under Policy Option B with the addition of an AMR lifecycle action plan.

Option C would provide substantive direct support for innovation, through the introduction of a transferable voucher, which would reinforce the investments of global MNCs active in the development of novel antimicrobials. The adaptation of the system for the authorisation of phage therapies may catalyse increased investment in this emerging and innovative technology.

Table 54 Option C – Summary assessment of the proposed incentives for prudent use of antimicrobials

Policy elements	COB	Admin	SMEs	CTI	Internal Mar	I&R	PA	H&S	Sust
C.2.1	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
C.2.2.	+	-	+	+/-	+/-	+	-	+	+/-
C.2.3	+/-	-	+/-	+/-	+/-	+/-	-	+	+
C.2.4	-	+/-	+/-	+/-	+/-	+/-	-	+	+
C.2.5.	+/-	+/-	+/-	+/-	+/-	+/-	-	+	+
C.2.6.	+++	-/+	+++	++	-/+	+++	---	+	+/-
C.2.7	+	+/-	+/-	+	+	+	-	+	+
Overall impact	+++	-	+++	++	+/-	+++	---	++	+

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Assessment of synergies and tensions within the Policy Block

Within the AMR Policy Block, the policy elements proposed under Policy Option C are largely complementary to each other, with the mandating of the use of the Central Procedure dovetailing with the proposal for EMA create a PRIME-like scheme for AM products. The Transferrable Voucher would reward antimicrobial innovators with an additional period of regulatory protection for their other medicines.

The adaptation of the system for the authorisation of phage therapies is a further complementary initiative that recognises the potential for this emerging and innovative technology to make a substantial contribution to combatting AMR. Moreover, the proposals on prescribing practices, package size, and disposal all work well together in supporting more prudent use. The expansion in the scope of the existing surveillance system would also provide an important means by which to track progress in environmental management across the EU. Lastly, the AMR PLCM would provide a framework for the optimal use and good stewardship of individual medicines.

A.5.3. Policy Block C (C.C): Future proofing

Option C is a refinement of the current arrangements, with seven principal interventions that are discussed in the table below.

Table 55 Option C – Assessment of the proposed measures for Future Proofing

C.3.1. Adapted regulatory framework framework (*e.g. adapted requirements, authorisation procedures, collection of post-authorisation monitoring data*) for certain categories of novel products/technologies (e.g. personalised medicine, medicines combined with self-learning artificial intelligence, medicines that contain or consist of GMOs, platform technologies) or low volume products (hospital preparations) on the basis of well-defined conditions and respecting the principles of quality/safety/efficacy. Such frameworks could be adapted or expanded through delegated acts to set the technical framework that can be adapted to emerging scientific and technical advances (adaptive framework). Where applicable, such delegated acts should be developed in close coordination with other relevant competent authorities such as e.g. medical devices, IVDs or substances of human origin.
C.3.1 has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. It would also address the issues of current technological advancements that are not adequately legislated for and provide the legislation with a mechanism of keeping pace with technology through both facilitating adaptation and drawing on the expertise of deeply engaged stakeholders with in-depth technical knowledge of emergent areas. However, there would be an associated increase in administrative burden due to a likely expansion of the number of specific non-legislative (soft law) tools that would require development, maintenance, review etc. and ongoing need for feedback loops, iteration and adopting delegated acts. EMA and the regulators need to stay in control and ensure that the soft law tools are meeting the overall objectives of the legislation since the incentives and alignment of all stakeholders (some of whom have valuable technical expertise that this framework is designed to harness) is not implicit
C.3.2 Clinical trials: a risk-based approach is applied to determine when a specific GMO assessment is required. Where required, the assessment of the GMO aspects of investigational medicinal products is performed by EMA, within the maximum timelines defined in the Clinical Trial Regulation (centralised assessment).
This is the same as A.3.2 Clinical trials for investigational medicinal products (IMPs) for human use that contain or consist of GMOs are subject to both clinical trials and GMO legislations under national competences. This causes delays in clinical trials as the directives are not uniformly interpreted or applied between MSs and is especially problematic for clinical trials that are conducted over multiple MSs. These differences in interpretations also impact on the authorisation of GMO-containing medicinal products that fall under the mandatory scope of the centralised procedure creating complexities for developers as different MSs have different requirements and stakeholders involved, ultimately causing regulatory burdens and delays in market authorisations. A.3.2 has potential to improve the efficiency of GMO assessment and thus accelerate authorisation of GMO-containing medicinal products by focussing regulatory efforts on GMO containing medicines that pose the greatest threat to the environment. A centralised approach to GMO assessment has already been adopted by the United States where the review of medicinal products containing GMOs has been centralised within the FDA to improve efficiency and regulatory agility.
C.3.3 Adapt certain definitions, including that of medicinal product and *delink scope from industrial process* to address technological developments, gaps/borderline questions, taking into consideration the views of regulatory authorities for other relevant legal frameworks (e.g. medical devices and blood, tissue and cells) - linked to scope of the legislation.
C.3.3 has the potential to improve efficiency and contribute towards stimulating innovation and investment by adding clarity and predictability to the existing legislative pathways. Delinking scope from industrial process would immediately bring under regulation several potentially excluded products and processes – most notably novel manufacturing such as bedside such as pharmacoprinting. It would be important that upon their being brought in scope the GMP was able to adequately accommodate them or that sufficient alternative tailored guidance was available. Addressing gaps in the legislation would impact positively on patient safety though could cause a (likely short term) reduction or delay in access while adaptations for compliance to greater regulation were made. There would be additional regulatory burden to implement the extended scope of the legislation. However, long term the efficiencies and predictability are anticipated to increase investment and innovation, reduce the time to access and improve patient safety.
C.3.4. For specific cell-based (ATMP) medicinal products adapted regulatory requirements under the pharmaceutical legislation to facilitate production in the hospital setting (improved "hospital exemption" mechanism) and respecting the principles of quality/safety/efficacy. [*link with revision of BTC legislation*]

ATMPs prepared "on a non-routine basis" for individual patients can by granted a hospital exemption by individual member states and can then be produced in the hospitals, exempt from the legislation scope which would require market authorisation and following GMP. This reflects a large proportion of ATMP development being undertaken by non-commercial entities (hospitals, research institutions, academia etc) for small patient numbers and was anticipated to increase ATMP development, improve timely access to ATMPs at affordable prices. The granting of the exemption has a lower evidence burden (including for safety and efficacy) than market authorisation and production of ATMPs in the hospital setting is not as strictly regulated in terms of batch-batch or patient-patient quality, safety and efficacy consistency.

Our understanding is that C.3.4 responds to this issue by the legitimising of hospital production increasing regulation such that it is more robust. In the context of ATMPs this would go alongside and require amendments to the hospital exemption which may include increased requirements of efficacy and safety demonstration in order to be granted, EU central oversight to harmonise pharmacovigilance across the same products, increased clarity to minimise differences in interpretation. In the case these were enacted then limitations of the number of patients treated could be removed thus facilitating hospital production under the new legitimate production method.

Increased patient safety through greater evidence burden for the exemption and then more consistent hospital production

More hospital production as patient numbers can be increased once this is removed from the exemption – better access and more data though we may expect a short-term reduction in ATMP access as production comes under regulation. Simultaneously as such an increase in production may make the market less attractive for commercial developers there could be a further withdrawal by them and potentially less ATMPs being picked up for MA as spin-offs by more commercial actors. Conversely, we may see commercial actors becoming more involved in development if they are able to access the hospital production route rather than MA – this may support more public-private partnerships.

There is some risk that research by SMEs, academics, and other non-commercial entities (currently the main stakeholder in ATMP development) reduce their activities as the costs increase through the need to have trial data and GMP manufacturing capability in order to be granted hospital exemption.

More transparent and predictable which may also encourage investment – by both commercial and non-commercial entities.

C.3.5. For specific products (named in annex – e.g. keratocytes etc.) less complex cell-based medicinal products to be defined on the basis of clear risk-based approach criteria - two sub-options could be explored in this regard:

C.3.5a. adapted requirements within the pharmaceutical legislation and authorisation by pharmaceutical national competent authorities (NCAs);

C.3.5b. to provide for a mechanism to exclude these medicinal products from the scope of the pharmaceutical legislation (in consultation with relevant authorities) and transfer them under the blood tissue and cells (BTC) legislation with authorisation by BTC NCAs

There are significant regulatory hurdles for less complex cell-based products (such as 'legacy products' existing before ATMPs) that are classed as ATMPs and subject to related standards. Many of these products could be produced in hospital settings. Additionally, there are borderline issues between the BTC and ATMP frameworks with some differing interpretation and classification between member states including some delineation reliant on the presence of an industrial process, no definition of which currently exists.

In theory, C3.5.a and C.3.5b should bring greater clarity around borderline products and simplify legislation for the less complex cell based medicinal products which would bring efficiencies and predictability. However, since both elements involve processes conducted at member state level there exists a potential for heterogenous interpretation and application. Such an outcome could impact negatively on patient safety as well as further exacerbate existing issues around ATMP classification and differentiation from BCT.

Depending on how C3.5.a and C.3.5b are implemented these measures may represent an increased regulatory burden for NCAs.

C.3.6. Introduction of a regulatory sandbox environment, especially in the context of the approval and oversight of complex/cutting-edge products especially those linked to the concept of a 'medicinal product'

We understand the purpose of the regulatory sandbox environment is to create an 'agile, evidence-based and resilient framework' which fosters competitiveness, growth, sustainability, and regulatory learning' to accelerate innovation of complex/cutting-edge medicinal products.

Sandboxes are increasingly being used in healthcare settings[100]. This has been inspired from the success of first regulatory sandboxes in the FinTech sector, which have helped businesses to attract investment and increase speed to market by 40% compared to the regulator's standard authorisation times[101]. Thus, sandboxes have the potential to facilitate EU patients getting faster access to complex /cutting edge medicinal products.
C.3.7. Create a central *classification mechanism* for advice on whether products are medicines or not, building on the current EMA Committee for Advanced Therapies (CAT) mechanism for ATMPs to all medicinal products (borderline products) in close coordination with other concerned authorities in particular in the frameworks of medical devices and substances of human origin.
This is the same as B.3.4. Medicines are increasingly being used in combination with a medical device, usually to enable the delivery of the medicine. However, these combinational products have brought regulatory difficulties for NCAs in terms of uncertainty whether they should be classified as a medical product or medical device and what regulatory framework applies. C.3.7. would improve consistency of the classification of borderline products and the resulting choice of the most appropriate pathway through the EMA committee structure. This should harmonise coordination between concerned authorities in particular in the framework of medical devices and substances of human origin, and thereby deliver some small efficiency gains and avoid assessment committees being distracted from their assessment work by definitional questions. It may also improve the overall timeliness of assessments. The creation of a central screening mechanism may be timely as more definition questions arise for example, 1 in 4 centrally approved medicines typically include a medical device component. Success would depend on EMA finding the capacity to deliver relevant advice at speed.

Table 56 Option C – Summary assessment of future proofing

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
C.3.1	++	+	+	++	+	++	---	+	+/-
C3.2	+	+	+/-	+	+	++	-	+	+/-
C.3.3	+	+	+	+	++	+	+/-	++	+/-
C.3.4	+/-	-	+/-	+/-	+/-	+	-	+	+/-
C3.5a.	+	+	+/-	+/-	+/-	+/-	-	+	+/-
C3.5b.	+	+	+/-	+/-	+/-	+/-	+/-	+	+/-
C3.6	+	+/-	++	+	+	++	---	+	+/-
C3.7	+	+	+	+	+	+	+/-	+	+/-
Overall impact	+	+	+	+	+	+	-	+	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

[100] European Commission. (2021). *Proposal for a regulation of the European Parliament and of the Council laying down harmonised rules on artificial intelligence (artificial intelligence act) and amending certain union legislative acts COM/2021/206 final*. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52021PC0206

Leckenby, E., Dawoud, D., Bouvy, J., & Jónsson, P. (2021). The Sandbox Approach and its Potential for Use in Health Technology Assessment: A Literature Review. In *Applied Health Economics and Health Policy* (Vol. 19, Issue 6, pp. 857–869). Adis. https://doi.org/10.1007/s40258-021-00665-1

[101] FCA. (2017). *regulatory-sandbox-lessons-learned-report*; FCA. (2019). *The Impact and Effectiveness of Innovate*.

Assessment of any synergies and tensions within the Policy Block

A tension exists in this block between promoting business – particularly around ATMP development by commercial entities – and the recognition that the majority of ATMP development is currently undertaken by academic, research and SMEs who are non-commercial and unsuited to be MAHs but represent the major stakeholder in this area. In this context promoting business, incentives and patent protections for commercial entities does not necessarily go hand in hand in with promoting innovation.

Future proofing elements in this policy options related to reducing regulatory burden to promote innovation and access: Adapted regulatory framework for certain categories of novel products/technologies (C.3.1); adapt definitions, including that of medicinal product and delink scope from industrial process (C3.3); risk-based classification of less complex cell-based medicinal products (C3.5); and creating a central classification mechanism for borderline products (C3.7) will add clarity and streamline existing legislative pathways that complement with horizontal measures such as streamlining of procedures, including avoiding duplicative processes (including GMO requirements, prioritisation of applications, better coordination within the regulatory network; streamline procedures to facilitate efficient interaction and synergies between different but related regulatory frameworks e.g. Medical Device (for certain type of products) and Health Technology Assessments and create an expert group to give advice/guidance on UMN – cross sector involving health technology assessment bodies (via the Coordination Group of HTA bodies set up under the new HTA Regulation), pricing and reimbursement bodies, patients, and academic representatives. There are also synergies and complementary measures around definitions with security of supply measures (definitions of critical medicine, critical shortage, critical medicine) as well as additional measures in manufacturing quality that would also focus on adapting to new manufacturing processes.

Future proofing elements in this policy element related to improved mechanisms/approaches for innovation to promote access to novel medicines: Introduction of regulatory sandboxes (C.3.6) will provide an adaptive mechanism to support novel innovation approaches to develop medicines. Adapted regulatory requirements to improve use of HE mechanism will facilitate production of non-commercial cell based (ATMP) medicinal products. While a risk-based approach for GMO assessments (C3.2) will focus regulatory efforts on assessment of GMOs posing highest risk to the environment. Together these elements will facilitate the development of novel medicines, GMOs (ATMPs) that have high potential to address UMNs. Element C1.2 also has good synergies in the support of non-commercial entities and making more robust hospital-based manufacturing processes.

A.5.4. Policy Block D (C.D): Access

Assessment of the key impacts for the policy elements

Option C incorporates two elements that were previously discussed in Options A (facilitating multi-country packs) and B (Requirement to include small markets in MRP/DCP applications) respectively, but also introduces two new elements.

C.4.1. Conditional marketing authorisation: UMN incentives are only granted upon switching to standard MA
This measure introduces a conditionality on the granting of the incentives proposed within Block A. It is assumed that this pertains specifically to the granting of an additional period of data protection for products with a demonstrated ability to address an UMN (elements A.1.3, B.1.5 and C.1.5). As such, this element does not introduce *new* impacts but rather limits the extent to which the expected impacts linked to these elements may materialise. The intent of C.4.1. is to further incentivize the generation of post-authorisation evidence for conditionally approved products and to ensure that their (cost-)effectiveness and safety can be sufficiently established. Thus, introduction of this conditionality may be expected to be beneficial for authorities tasked with

this assessment, as well as for health systems and patients who receive greater assurances that incentives are not granted to products not deserving of these.

C.4.2 Facilitate 'multi country packs' with labelling to allow their placing on the market in several Member States with the same packaging and pack sizes

Same as A.4.1

Currently, information on the pack (outside and inside) must be in the official language(s) of the MS where a product will be placed on the market, bar a few exceptions for certain products that are not intended to go directly to a patient. This language requirement, along with other potentially country-specific requirements, means that MAHs must produce packs specifically designed for each market. This increases production costs and may make smaller markets, where these costs cannot sufficiently be offset by revenues, commercially unattractive. Additionally, country-specific requirements can hinder the movement of medicines between different EU markets when products need to be repacked and relabelled, to meet all requirements of the importing country.

Facilitating 'multi-country packs' may result in more products being placed on a greater number of markets, in particular smaller or less economically attractive markets. In addition, medicines can be moved between EU countries more easily to mitigate or resolve shortages. This would improve security of supply and mitigate some of the risks resulting from product unavailability (e.g. treatment interruption, suboptimal treatment with alternatives). It will, however, be important to ensure that use of multi-country packs does not limit the ability of patients and healthcare providers to access information regarding, for instance, the correct use and safety profile of medicines. No studies were identified that detail experiences with multi-country packs as a way to overcome access challenges and that thus could inform an estimation of impact.

In economic terms, it is expected that multi-country packs would result in a cost saving to MAHs by reducing the number of different presentations they need to produce and streamlining production lines. The magnitude of these savings will depend primarily on the number of countries and languages included, whilst the size of the markets reached by multi-country packs will further influence the profit potential for the MAH.

In theory, multi-country packs may have the added benefit of facilitating joint procurement between countries. Several initiatives already exist whereby smaller countries engage in joint procurement to increase their purchasing power. Such initiatives have the potential to negotiate lower prices. A 2020 study for WHO shows that whilst these initiatives hold promise, they often take months or years of cooperation before tangible results are achieved. The study did not specifically look at the role of multi-country packs in facilitating joint procurement.

C.4.3 If a medicinal product is appropriately and continuously supplied in all MS (unless it is demonstrated that a certain MS does not wish supplies) within a period of 2 years from MA and not later withdrawn before the additional exclusivity kicks in, then the product receives an additional 2 years of data protection

This pivotal element seeks to encourage developers of innovative medicines to place products on all EU markets by offering a 2-year extension of regulatory data protection in return for doing so within two years of authorisation. To avoid potential abuse of the incentive and simultaneously address problems with access and continuity of supply, the incentive is linked not simply to market entry but to whether the product is appropriately and continuously supplied (subject to MS electing to reimburse / accept the product).

This element will complement the decision to reduce the standard period of regulatory data protection from 8+2 years currently to 6+2 years in future, with most MA holders being in a position to launch their new products in all member states willing to reimburse those medicines. This condition will bring the overall RDP back to the current 10 years (6+2+2) for the great majority of products.

We assume the 10-12 products annually may chose or fail to comply with the condition 'all markets within 2 years' and that these MAHs will see a loss of income (c. 22%; €352m-€422m a year) on those products, as a result of earlier generic entry (from year 8). We assume the cost of servicing say 25 EU markets on average rather than say 15 (more typical currently) would be cost neutral, with the higher sales volumes in the additional 10 smaller markets offsetting the additional marketing, distribution and other costs associated with smaller / marginal markets. EU health systems will also save money from earlier competition (€210m-€270m a year).

There are some practical issues to be tackled in the final detail design of this proposal. The element raises several questions as to how this should be operationalised. The first relates to the clock start. As most innovative medicines are approved via the centralised procedure, the most likely start time would be the date of central approval by the EMA. It has, however, not been specified whether medicines authorised via a national route would also be able to qualify and, if so, which date of authorisation should be considered.

Second, it is not clear how the measure would allow for the introduction of 'clock stops' to accommodate variability in the duration of pricing and reimbursement decision-making processes by public authorities. In the annually published results of the W.A.I.T. survey, conducted by EFPIA, it is estimated that the average time for a centrally approved medicine between marketing authorisation and the date at which products gain access to

the reimbursement lists, varies from 133 days in Germany to over 800 days in Bulgaria, Poland and Romania.[102] In these results, however, it has not been specified to what extent such differences are due to factors on the site of the MAH and of the public authority respectively. It is thus difficult to predict by how much an incentive for MAHs alone would be able to shorten this period if authorities are unable or unwilling to approve reimbursement within the required timeframes. This issue has not been discussed in consultations with public authorities and therefore it is not possible to indicate whether a two-year window would be sufficient.

Questions may also be asked about how to define 'appropriate and continuous' supply and how to apply this concept in determining whether eligibility criteria have been met. The concept exists in Article 81 of Directive 2001/83/EC which requires MAHs and wholesale distributors of a medicine that is placed on the market to ensure "appropriate and continued supplies", within the limits of their responsibility, to cover the needs of patients. This concept has, however, been interpreted differently in different countries and offers limited guidance on how to establish whether an MAH (or wholesaler) has acted appropriately to fulfil its obligations. It is therefore to be expected that similar difficulties will be encountered in its application in the context of the here proposed element, particularly if this assessment needs to be provided by the Member States where the products have been placed on the market.

C.4.4. Requirement to MAH applying for MRP/DCP to include small markets (in particular address the post-BREXIT challenges) or possibility for MS to opt-in a pending MRP/DCP procedure

Same as B.4.4

Most generic medicines are currently approved through the MRP/DCP route . Because of this, these products would not fall within the scope of the requirements imposed by B.4.2 and B.4.3. By also extending greater obligations for inclusion of smaller markets in the application for approval via the MRP/DCP, the Commission aims to increase access to a wider group of products, in particular generic medicines, than would be achieved via marketing obligations on centrally approved medicines alone. It is assumed that the proposed element intends only to require the applicant to include specific countries into the MRP/DCP application, such that there is a valid MA in these markets, but does not require the applicant to directly place products on these markets.

Requiring MAHs applying for an authorisation via the MRP/DCP route to include specific markets – or allowing countries to opt-in – will enable these countries to obtain medicines more easily from other EU MS (through parallel distribution), even when the MAH does not place the product directly on the market. This may have the effect of increasing access to medicines that are not within the scope of the CP, especially generic medicines. This, in turn, may be expected to positively affect both health outcomes for patients and the affordability of treatment by increasing access to low-cost generic versions. It will also improve security of supply for included countries by facilitating redistribution in case of shortages.

Summary assessment of the principal costs and benefits by impact type

Table 57 presents a summary assessment of the principal impacts of the main policy elements proposed for this Policy Block under Option C, by impact type. Whilst the impact of some of the individual elements has been detailed previously under Options A and B, the introduction of new ones, as well as the new combination of elements will have intrinsically different synergies and tensions and thus result in a different assessment of the overall impact.

Table 57 Option C – Summary assessment of access elements

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
C.4.1	+/-	+/-	+/-	+/-	+/-	++	++	++	+/-
C.4.2	++	+	+/-	+	++	+/-	+	+	+/-
C.4.3	-	-	+/-	--	+	+/-	++	++	+/-
C.4.4	---	--	-	--	+	-	++	+++	+/-
Overall impact	---	---	--	--	++	+/-	+++	+++	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and

[102] https://www.efpia.eu/media/636821/efpia-patients-wait-indicator-final.pdf. Last accessed 23 May 2022.

production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

- The proposed elements impact different groups of industry stakeholders differently. For innovative medicine developers, the package of measures is skewing positively, by introducing a new incentive for market placement and removing some barriers to operating in smaller markets by facilitating multi-county packs. At best, these elements will enable innovators to increase their operating profits whilst on the other hand there are no new obligations introduced that could cause harm to their cost of business. Generics manufacturers on the other hand are not likely to benefit from the new incentive, as their products are normally not under regulatory protection, yet face a new requirement to include smaller markets in their MRP/DCP applications. Additionally, the incentive offered to innovative developers means a longer exclusion from the market for generic companies. Jointly, these measures thus most likely represent a substantial net negative for generic manufacturers.
- Inclusion of additional countries, in particular smaller MS, in the MRP/DCP application (C.4.4 will facilitate the movement of medicines between markets where the product has been authorised. This measure is substantially synergistic with the measure to facilitate use of multi-country packs (C.4.2). Jointly, these measures may be effective in facilitating the movement of medicines within the EU internal market to countries that are comparatively underserved or where medicines are in shortage.

Assessment of any synergies and tensions within the Policy Block

As under Options A and B.

A.5.5. Policy Block E (C.E): Competition

Assessment of the key impacts for the policy elements

Table 58 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements.

Table 58 Option C – Assessment of the proposed measures for competition

Description
C.5.1 New simpler regulatory pathway for generics (adapted EMA/CHMP working methods, shorter approval timelines, potentially distinguishing between complex generics/biosimilars – reducing requirements for known biologics)
As described for A.5.1. The key impact from a simpler regulatory pathway with shorter approval times will be faster availability of generics to patients. It should create more clarity and potentially less administrative burden for marketing authorisation applicants, encouraging more applications and increased development activity for generics. We assume that generics will be on the market soon after approval and access to generics will be similar in all member states. The latter assumption has been adopted for ease of analysis as generics market penetration varies considerably across member states and would add uncertainties to our assessment.
C.5.2 Interchangeability of biosimilars with their reference product will be generally recognised in guidance or e.g. through a recital in the legislation and will be scientifically assessed as part of the product assessment and indicated in the summary of product characteristics (SmPC, product information) to inform healthcare professionals and their patients as well as downstream decisions makers
As described for B.5.2. Interchangeability, switching (by prescriber) and substitution (by pharmacy) of a reference medicine by its biosimilar currently fall within the remit of EU Member States. Guidance on interchangeability from one originator (reference) or biosimilar product to another at the EU level would enable all member states to make decisions on whether to allow switching and/or substitution for certain products, especially those countries where the relevant technical capacity is not available. There is potential to pool the best expertise from across the EU if product

Description
assessment is done as part of the centralised procedure, reducing burden on individual member state authorities. Inclusion of the guidance in a recital in the legislation and product information (SmPC) would inform prescribers, patients, and decision makers about interchangeability of specific products, potentially increasing uptake of biosimilars. This could improve access to biologics for patients and reduce health system costs if cheaper biologics were switched or substituted for more expensive ones. It is not clear if additional data will be requested for the scientific assessment of interchangeability e.g. switch studies. Our assumption is that no additional data will be required – a study by Kurki et al. (2021) which analysed post-marketing surveillance data suggests that biosimilars approved in the EU are highly similar to and interchangeable with their reference products. A recent qualitative study also shows that European and UK regulatory, legal and policy experts do not see any added value in additional data or switching studies.
C.5.3 Broader Bolar exemption – allow additional beneficiaries (companies, producers of active pharmaceutical ingredients (APIs) and non-industry actors) to conduct studies/trials
Overall, the broader Bolar exemption is likely to increase legal certainty, access to medicines, cost savings and research activity in the EEA compared with a narrower exemption.[103]
C.5.4 Extend Bolar exemption beyond generics – Allow repurposing studies/comparative trials without infringing patent rights
Overall, the extended Bolar exemption is likely to increase legal certainty, access to medicines, cost savings and research and innovation activity in the EEA compared to a narrower exemption.[82]
C.5.5 Duplicates restricted to cases of intellectual property protection or co-marketing
As described for B.5.6b. There will be a reduction in barriers to competition and monopolisation of the market by the first generic/biosimilar of an originator product to receive an MA. Consequently, there will be no delay in the second generic/biosimilar coming onto the market once it receives approval. This will mean greater consumer choice and price competition.

Summary assessment of the principal costs and benefits by impact type

Table 59 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block E under Policy Option C and for each impact type.

Table 59 Option C – Summary assessment of the proposed measures for competition

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
C.5.1	+	+	+	+	+	+	+	+	-/+
C.5.2	-/+	-/+	-/+	+	+	-/+	++	++	-/+
C.5.3	+	+	-/+	+	+	+	++	++	-/+
C.5.4	+	+	-/+	+	+	+	++	++	-/+
C.5.5	-/+	-/+	+	+	++	+	++	+	-/+
Overall impact	+	+	+	+	++	+	+++	+++	-/+

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and

[103] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Some of the key expected impacts are as follows:

- Increased international competitiveness through creation of a more favourable regulatory environment for generics/biosimilars (simplified generics pathway) and broader scope of activities and actors covered under the Bolar exemption. The broader Bolar exemption will increase the share of EU-based API producers and API manufacturing jobs and lower costs of supply for European generics.[104] The cost savings would be more pronounced for European generics manufacturers of specialised products e.g. for oncology or central nervous system
- Improved consumer choice and competition through availability of both generics/biosimilars and originators on the market (including guidance on interchangeability), resulting in lower prices and improved access for patients across member states. Modification of the duplicate regime will mean originator companies will not be able to severely undercut the price of potential biosimilar competitors through a duplicate authorisation for an autobiological while allowing the reference originator product to maintain a high price.[105]
- The extended scope of the Bolar exemption will increase returns to innovation and therefore increase incentives to innovate for European R&D based pharmaceutical companies in countries that currently have a narrow Bolar scope. This would increase R&I for generics and biosimilars and can be expected to lead to an increase in the number of skilled jobs[84]
- If the extended Bolar exemption leads to more clinical trials in a country, this will have impacts on access as it has been shown that new medicine adoption is wider in countries where the clinical trial was run[91]
- A very high likelihood of positive impact on patients through making medicines more readily available and reducing costs for health systems (generics represent around 80% cost reduction compared to originators, and entry of a generic also reduces price of the off-patent medicine by 61%[106]; biosimilars are 20% cheaper[107] compared to originator products)

Assessment of any synergies and tensions within the Policy Block

There is synergy with the horizontal measure of streamlining and harmonisation with making the regulatory pathway for generics simpler. Changes to the Bolar exemption will have synergy with elements introduced to improve access, but may have some negative implications for innovation activity if ROI figures change for originators. Change to the duplicates regime improves background conditions for timely availability of biosimilars on the market and thus access.

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[104] European Commission, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, Fischer, R., Débarbat, G., Koustoumpardi, E. (2017). *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, Publications Office. https://data.europa.eu/doi/10.2873/673124

[105] https://www.biosliceblog.com/2019/11/update-on-eu-duplicate-marketing-authorisations/

[106] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[107] https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilarsv

Assessment of the key impacts for the policy elements

Table 60 presents our assessment of the key impacts of each of the proposed measures, drawing on our consultations, desk research and targeted literature review.

Table 60 Option C – Assessment of the proposed measures for Supply Chain Security

Assessment
C.6.1. Introduce EU definition of a shortage, including a critical shortage and critical medicine
The measure has the potential to harmonise numerous definitions of shortages that exist across the EU. The clarification of criticality criteria can further help in making changes in shortage notification to cover shortages for most critical medicines. Overall, many stakeholders, and particularly industry representatives have advocated for the adoption of the concept of 'product criticality' into definitions of shortages and regulatory measures aimed at notification and prevention of shortages. The study of medicines shortages also called for the introduction of criticality criteria and further measures associated with it.[108] The clarification of shortage criticality criteria can further help in making changes in shortage notification to cover the most impactful shortages.
C.6.2. a) Increase notification period to 12 months for all withdrawals of products that have been on the market for more than two 2 years b) Notification at least 6 months in advance or as soon as identified for all shortages (non-withdrawal) c) Introduce a common template for reporting withdrawals and shortages including details of root causes, alternatives medicines and impact.
This option differentiates between planned (permanent) market withdrawals and temporary supply disruptions, setting different notification timeframes for each. There is more explicit recognition of the fact that not all shortages can be foreseen 6 months in advance. It is uncertain whether this element will result in earlier notification than presently the case, given that most shortage notification are currently made with less than 2 months' notice, citing 'exceptional circumstances'. There is no clear reason why extending the notification period would remedy this situation. Where potential shortages are notified more in advance, these situations often are resolved before they result in an actual shortage. Extending the notification period may thus increase the number of 'false alarms'. There is also a risk that a longer notification period will increase the administrative burden on both MAHs and public authorities without clear benefits. In some countries, parallel distributors also fall under a notification obligation. In consultation, this industry has indicated that a 6-month notification requirement would not be possible to meet since they typically do not hold stocks for more than 2-3 months. Earlier notification of planned withdrawals (element a), however, may be more feasible and provide authorities more time to identify and source alternatives. The obligation to utilise a common reporting template (Element c) is received positively by the stakeholders. Common data collection approaches, particularly if linked to a standardised reporting portal and automatic sharing of information between MS could, in the longer term, result in cost savings for authorities. Greater standardisation of information may also enable a better understanding of the causes of shortages and allow for the development of better-tailored policy approaches to address the issue of shortages.
C.6.3. Stockpiling requirements for MAHs for unfinished critical medicines, as appropriate
Some further elaboration is needed to determine criteria to establish what constitutes 'as appropriate'. More detailing is also needed about the expected quantity of such stock, what state the product needs to be in (e.g. intermediates or finished but unlabelled/unpacked products), at what level the stock will be held (e.g. EU, national, regional), who has ownership and responsibility for the stock (e.g. MAHs, wholesalers or authorities) and whether stock may be redistributed according to need. All such factors may strongly influence the operational feasibility of this measure and its acceptability to involved stakeholders. Among wholesalers there is a sense that a limited level of additional reserve stockholding (~2-3 weeks) – with reserves dynamically rolled into normal stock – for critical measures may be a cost-effective measure against supply disruptions, holding larger volumes of stock is both unfeasible and unnecessary. It is expected that the costs of increased stock holding will either need to be shared between MAHs and public authorities, or if not, that MAHs will seek to recoup the increased costs by raising prices. For generic

[108] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages*

manufacturers, whose products are typically under strict price regulations and caps, this may not always be possible. Among generic manufacturers, there is therefore a fear that in the absence of a balanced cost/risk sharing arrangement, companies may be unable to continue operating in markets where these stock obligations apply.
C.6.4 (as in A.6.3.) Marketing authorisation offered for transfer to another MAH before a permanent withdrawal
Requiring a MAH to offer the MA to another party before allowing it to withdraw the product from a specific market could delay the original MAH's withdrawal decision, as it seeks to avoid enabling its own competitors. Hypothetically, requiring MAHs to offer the MA to another manufacturer could benefit such manufacturers who are enabled to market a product that already has an established patient base. However, as indicated previously, a large proportion of product withdrawals can be traced to low product-level profitability[109]. It is not clear to what extent a MA transfer could effectively address these underlying profitability issues. Such transfers would only be feasible/interesting in case a product remains commercially interesting for the new MAH or if commercial viability is not required for another party to take over the MA (e.g. in case of transfer to a not-for-profit entity). The study team has identified no experiences with similar measures that could inform a (quantitative) estimation of potential impact. Moreover, the EU trade association for the generics industry (Medicines for Europe) has indicated that it considers this proposal unconstitutional and not compliant with the proportionality requirements of EU treaties. It indicates that permanent withdrawals for commercial reasons are often necessitated by national market conditions, such as pricing and reimbursement policies (e.g. price cuts, reference pricing, claw backs and rebates), that are imposed by Member States and over which the MAH has no control. Mandating that the MAH offers the authorisation to another party before allowing it to withdraw is therefore considered a form of regulatory expropriation in violation of Art. 16 of the European Charter of Fundamental Rights.
C.6.5. Marketing authorisation holders to have shortage prevention and mitigation plans for all medicines.
Early identification of risks to the security of supply and of possible mitigation steps could reduce the occurrence and impact of supply disruptions. Fewer medicine shortages, as well as faster and more effective mitigation of the impact of shortages when these occur, improves patient access to (critical) medicines and leads to better health outcomes. The health system experiences fewer costs associated with dealing with medicine shortages. Depending on the level of detail required and the degree to which risk mitigation steps (e.g. contractual agreements with backup suppliers) are expected, MAHs may make additional costs not only in drawing up the plans but also in implementing the actions therein specified. Industry representatives have indicated that an important condition for the submission of shortage prevention plans would be that the company retains ownership of the plan, and that information remains confidential, as this could be commercially sensitive. In consultations, industry stakeholders have strongly opposed applying this measure to all authorised medicines rather than limiting it to critical medicines and those medicines at high risk of shortage. Amongst these stakeholders the measure is widely viewed as unnecessary, impractical, and burdensome as these plans would need to be regularly updated to remain relevant. It is expected this will create a very significant administrative burden for both regulators and MAHs. There is greater support for this measure should it be limited in scope to critical medicines and products at risk of shortage. Even under these circumstances, however, industry stakeholders note that MAHs may not be able to offer alternatives as this is the responsibility of physicians and prescribers.
C.6.6. Monitoring of supply remains at MS level, with information exchange at EU level for critical shortages based on national monitoring, using a common methodology/format to ensure compatibility & exchange at EU level.
This policy element is economically advantageous for MAHs and NCA as it builds upon the existing system of national monitoring. The implementation of the element is also feasible: existing initiatives and networks such as SPOC can be used for the purposes of the exchange. However, countries would still need to adopt the definitions of critical medicines in order to make the exchange efficient.
C.6.7 Expanded requirements for key suppliers and back-ups to diversify supply chain for critical medicines
C.6.7. aims to force MAHs to diversify their supply chains to prevent shortages and thus improve the availability of medicines and overall patient outcomes. Requiring more diverse supply chains most likely will result in increased production costs as MAHs may need to procure goods and services from less economically advantageous suppliers. These costs could be substantial, although no data was collected that would allow this impact to be quantified. There may be additional payments to backup suppliers, to reserve goods and space on production lines, even if not needed.

[109] de Jongh, T., Becker, D., Boulestreau, M., Davé, A., Dijkstal, F., King, R., Petrosova, L., Varnai, P., Vis, C., Spit, W., Moulac, M., & Pelsy, F. (2021). *Future-proofing pharmaceutical legislation — study on medicine shortages* (Issue December).

These additional costs occurred by the pharmaceutical industry may result in higher medicine prices and greater costs to health systems and patients. If requirements are introduced by individual MS rather than at the EU level, this could discourage MAHs from operating in markets with such requirements and contribute to inequitable access to medicine.

Importantly, the measure may not be feasible to implement for many medicines, for which globally a limited number of API and raw materials manufacturers exist, meaning that it may not be feasible for MAHs to sufficiently diversify their supply chains. Separate measures would be needed to enable this, e.g. economic incentives for industry to increase the manufacturing of APIs and raw materials.

C.6.8 Establish a mechanism of exchange of relevant information on supply chains between Member States to identify the supply chains bottlenecks and vulnerabilities

It is assumed this refers to sharing of information about the structure of supply chains, including the upstream aspects such as production and sourcing of raw materials and APIs, e.g. identifying the number, location and production capabilities of suppliers. Whilst improved insight into these structures certainly would be beneficial to understand which products may be at higher risk for supply disruptions, it is unclear who would be expected to provide the information or how it would be used. MAHs likely will consider such information commercially sensitive. It is, however, also unlikely that NCAs would be able to collect such information without the input from MAHs and other parties that make up the supply chain. It is thus difficult to understand the foreseen impact pathway and the actions needed to implement these policy elements. Consequently, we are presently not able to predict their potential impacts.

C.6.9. (same as B.6.8) Increase transparency of the supply chain, including:

1. active supply sites for all medicines,
2. volumes supplied, incl. supply quotas and remaining stocks for critical medicines upon request of NCA's/ EMA,
3. parallel traders and wholesalers' transactions for critical medicines upon request of NCAs/ EMA.

Improved transparency of the supply chain, at least for public authorities, has the potential of improving the security of supply by better matching supply and demand.

MAHs and parallel distributors each have a clear commercial interest in keeping (aspects of) information about their transactions confidential and are not generally welcoming of disclosing this to the other. For instance, parallel traders fear that full public disclosure of information about their transactions will render their trade practically impossible by allowing MAHs to throttle their supply to the level where no surplus is created.

For these parties to agree to share information with public authorities, it will be essential that strong agreements are made about what information is disclosed, for what purposes, how this will be used and who has access to it. Without this, it is unlikely that industry will cooperate. Mandatory disclosure of commercially sensitive information could furthermore distort competition between MAHs.

It may be assumed that regular sharing of information between supply chain actors and authorities – particularly when not done though an automated system – entails substantial administrative costs on all sides.

Summary assessment of the principal costs and benefits by impact type

Table 61 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block F under Policy Option B and for each impact type.

Table 61 Option C – Summary assessment of Policy Block F (Security of Supply)

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
C.6.1	+/-	+	+/-	+/-	+/-	+/-	+/-	+	+/-
C.6.2	--	--	+/-	+/-	+/-	+/-	+/-	++	+/-
C.6.3	--	--	+/-	--	+/-	+/-	-	+	--
C.6.4	-	-	+/-	-	+/-	+/-	+/-	++	+/-
C.6.5	-	--	+/-	--	+/-	+/-	+	++	+/-
C.6.6	+/-	+	+/-	+/-	+/-	+/-	+	++	+/-
C.6.7	---	---	--	--	-	+/-	+/-	++	--
C.6.8	+/-	+/-	+/-	+/-	+/-	+/-	+	++	+/-

C.6.9	+/-	--	+/-	--	-	+/-	+	++	+/-
Overall impact	--	--	+/-	-	-	+/-	++	+++	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Assessment of any synergies and tensions within the Policy Block

Similar to Option B, several policy elements (C6.6. and C.6.7) are dependent on element C.6.1. (Introduce EU definition of a shortage, including a critical shortage and critical medicine). Overall, the elements are synergistic and do not contradict each other.

A.5.7. Policy Block G (C.G): Quality and manufacturing

Assessment of the key impacts for the policy elements

Table 62 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on desk research and targeted literature review.

Table 62 Option C – Assessment of the proposed measures for quality and manufacturing

Assessment
C.7.1. Strengthen the oversight of the sites within a supply chain (including distributors and APIs manufacturing/importing sites) by extending the scope of mandatory inspections and modifying provisions on inspections (frequency, content, triggering points)
This measure will strengthen end-to-end oversight of the supply chain and could improve GMP/GDP compliance. However, it would impose significant additional burden on businesses and competent authorities. It would substantially increase the workload of inspectors (because of the extended scope and depending on the modified provisions), which would need to be met with more resources.
C.7.2. Stronger EMA role in ensuring proper oversight of the manufacturing sites via adapted IT tool and by increased role in coordination of inspections, including in setting up multinational inspection teams
The proposed policy element would have efficiency benefits with regard to oversight of manufacturing sites in the long term through better data management, transparency, resilience, and interoperability. However, this effect would depend on the quality, content and implementation of the IT tool, and would require additional resources in the short term. A stronger role for the EMA and setting up of multinational inspection teams would allow harmonisation of approaches. The latter would promote knowledge exchange and efficiency, benefitting national competent authorities. In the short-term, there may be high costs involved in restructuring capabilities.
C.7.3. Reinforcing Member States GMP and good distribution practices (GDP) inspections capacity by setting up a mandatory joint audit scheme
Same as B.7.2. This policy element has the potential to increase inspection efficiency through more cooperation and knowledge transfer. This may have a positive effect on manufacturing and distribution practices within the EU and globally, which would ultimately positively impact public health in the long-term.
C.7.4. Adaption of legislation/inclusion of specific provision covering new manufacturing methods (decentralised, continuous manufacturing, etc). to ensure levels of quality and safety equivalent to current methods
Same as A.7.3 The proposed measure has the potential to bring several product categories that are currently excluded from the legislation into the fold and provide regulatory certainty to manufacturers. These include magistral formulae (pharmacy-based preparation for an individual patient), radionuclides in sealed sources, hospital-manufactured medicines, and single-batch medicines. In addition, manufacturing methods such as decentralised manufacturing (where manufacturing occurs at different locations) and 3D printing-based methods could be accommodated. Covering new manufacturing methods in the general pharmaceutical legislation has the main advantage of helping to standardise the methods themselves, quality control of the methods and resultant products and associated regulatory pathways at the EU level. Thus, there is a harmonisation benefit. Moreover,

Assessment
accommodating new technologies sends a positive signal to innovators as well as companies and will encourage more innovation and research activity and adoption of the new methods. There will be further knock-on effects on competition, competitiveness, and access to medicine. If greener manufacturing methods are used there will be an impact on environmental sustainability, but the likelihood and extent of that is unclear. With more certainty over the manufacturing methods and the resultant products as well as more medicine developers adopting these methods, we could imagine a very high increase in the number of new therapies in comparison to the baseline.

Summary assessment of the principal costs and benefits by impact type

Table 63 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block G under Policy Option C and for each impact type.

Table 63 Option C – Summary assessment of the proposed measures for quality and manufacturing

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
C.7.1	-	-	-	-	-	-/+	-	+/-	+/-
C.7.2	+	+	+/-	+/-	+/-	+/-	+	+/-	+/-
C.7.3	+/-	+/-	+/-	+	+/-	+/-	+	+/-	+/-
C.7.4	-/+	-/+	-/+	+	+	+	-/+	+	-/+
Overall impact	-/+	-/+	-	+	+/-	+	+	+	-/+

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Extending the scope and modifying provisions of inspections and expanding oversight to all sites within a supply chain (including distributors and API manufacturers) could create additional transaction, compliance and administrative costs which could put a large burden on SMEs in particular. Moreover, NCAs will need additional inspection capacity and training to accommodate the changes in the scope, provisions and actors. On the other hand, a mandatory joint audit scheme for member states and stronger coordination of inspections by EMA will create efficiencies and savings for NCAs (and to some extent for businesses in the long term).

Adaptation of the legislation or inclusion of specific provisions to accommodate new manufacturing methods will improve international competitiveness, encourage greater research and innovation, and increase choice and competition in the sector. It would also have a direct impact on patients by making more treatments available and require additional transaction, compliance and administrative costs for oversight (both for businesses and NCAs). The measures to improve oversight of manufacturing but the quality standards are already high so there is unlikely to be greater added benefit to public health.

Assessment of any synergies and tensions within the Policy Block

Policy elements C.7.1, C.7.2 and C.7.3 have synergies with regard to enabling stronger supply chain oversight through different mechanisms.

A.5.8. Policy Block H (C.H): Addressing environmental challenges

Assessment of the key impacts for the policy elements

Table 64 presents our broad assessment of the likely costs and benefits of each of the proposed policy elements, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

Table 64 Option C – Assessment of the proposed measures for addressing environmental challenges

Assessment
C.8.1 Include assessment of the environmental risk of manufacturing into ERA, including main supply chain actors (API, raw materials)
This measure represents considerable additional burden for medicine developers and supply chain actors, and public authorities in terms of compliance and administration costs and review costs respectively. On the other hand, it will allow tracking of the environmental risks of manufacturing across the supply chain providing a more comprehensive assessment of the potential environmental impact of a new medicine. For example, if risk associated with active pharmaceutical ingredient discharges from manufacturing sites is included in the ERA, it would increase the relevance of the assessments by including a part of the life cycle of the product responsible for the highest environmental concentrations detected.[110]
C.8.2 Strengthen the ERA requirements and conditions of use for medicines, while taking stock of research under the innovative medicines initiative (IMI)
The proposed measure should enable robust assessment of the environmental risks of pharmaceuticals as well as promote prudent use, supporting sustainable consumption and helping to minimise the environmental footprint of medicines. However, this may place slight additional burden on public authorities for reviewing ERA submissions (in case of additional data requirements) and monitoring medicine use (if required) as well as on businesses and other stakeholders responsible for complying with said requirements and conditions.
C.8.3 Advisory role of EMA on ERA and green manufacturing aspects and quality (e.g. with relation to generics)
Constitution of a new advisory body/bodies and ongoing costs of providing advice will be the main drivers of administrative burden for EMA. However, the advice will help companies to better address ERA requirements and adopt green manufacturing practices, which will in turn aid pharmaceutical sector businesses to be more sustainable.
C.8.4 Include the AMR aspects into GMP to address the environmental challenges
This measure would help minimise amounts of antibiotics entering the environment via manufacturing and thus prevent emergence of AMR from pharmaceutical manufacturing. Recent evidence indicates the presence of a selection pressure for AMR within environments receiving wastewater from antimicrobial manufacturing, as opposed to environments receiving wastewater from municipal sewage treatment plants (containing antibiotics from human use) that do not receive waste from antimicrobial manufacturing.[111] There would be the additional costs for businesses to comply with the AMR requirements in GMP and data requirements and for public authorities for enforcement of the requirements. This could present barriers for smaller actors. The KPI would be amount of an antibiotic in waste and wastewater in µg/l. Suggested annual mean value for an erythromycin environmental quality standard (EQS) is 0.2 µg/l.112 For the current impact assessment, we would assume that compliance with the measure will result in levels below the EQS and thus there is a high likelihood of impact on sustainable production (environmental impact).

[110] Eeb. (2018). Policy options for regulating pharmaceuticals in the environment.

[111] WHO Expert Committee. (2020). *Annex 6 Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance*.

[112] UBA – Umweltbundesamt (Hrsg.) (2018) Empfehlungen zur Reduzierung von Mikroverunreinigungen in den Gew ssern,Hintergrund, Februar 2018, Dessau-Ro lau, https://www.umweltbundesamt.de/sites/default/files/medien/1410/publikationen/uba_pos_mikroverunreinigung_final_bf.pdf

Summary assessment of the principal costs and benefits by impact type

Table 65 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block H under Policy Option C for each impact type.

Table 65 Option C – Summary assessment of the proposed measures for addressing environmental challenges

Policy elements	COB	Admin	SMEs	CTI	Int Mar	I&R	PA	H&S	Sust
C.8.1.	-	-	-	-	-	+/-	-	+	++
C.8.2.	+/-	+/-	-	-	-	+/-	+/-	+	++
C.8.3.	+/-	+/-	+/-	+/-	+/-	+/-	-	+	+
C.8.4.	-	-	-	-	+/-	+/-	-	+	+
Overall impact	-	-	-	-	-	+/-	-	+	++

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

The key impact of the measures to address environmental challenges in Policy Option C are expected to be increased sustainable production and waste management owing to improved ERA, inclusion of AMR in GMP and green manufacturing. This may have an indirect effect on public health local to manufacturing sites due to reduced emissions and the possibility of fewer AMR strains emerging.

There may be additional burden on SMEs to meet the new requirements either in terms of administrative costs or need for specialised expertise with implications on competitiveness and the internal market. Similarly, the EMA and NCAs may require additional capacity or incur greater administrative burden in reviewing and assessing products based on the additional requirements for ERA and GMP.

Assessment of any synergies and tensions within the Policy Block

There are no major synergies or tensions within this block for Policy Option C. Policy element C.8.1. is in line with elements in other blocks that aim to increase transparency and obligations about supply chain actors, but conflicts with the horizontal measure aimed at simplification. C.8.2. has synergy with the horizontal measure aiming to strengthen and harmonise ERA across member states, while reducing duplication of testing. C.8.4. has complementarities and synergies with measures to restrict and monitor use of antimicrobials, especially B.2.4. (Stricter rules on disposal) and B.2.8 (Establish monitoring system for data collection on human antimicrobial consumption and use and potentially on the emission of APIs to the environment). However, there is a risk of duplication of effort/data in the GMP/environment reporting requirements for companies, which should be covered in the revision.

The additional advisory role of the EMA has potential synergy with the measures to strengthen ERA and modify GMP and could support industry in smooth transition to and harmonised implementation of the new requirements.

Assessment of the key impacts for the policy elements

Table 66 presents our broad assessment of the likely costs and benefits of the proposed policy element, drawing on our consultations, desk research and targeted literature review. It focuses on the main costs and benefits for the key actors affected, with a short and long-term view where appropriate.

Table 66 Option C – Assessment of the proposed measures for COVID-19 lessons learnt

Assessment
C.9.1. Refusal of immature marketing authorisation applications
Same as B.9.1 The most significant efficiency gains would be for public authorities, which could save time currently spent on assessing immature applications and resolving internal differences of opinion as regards their evaluability or suitability for processing through the CMA pathway. As per baseline, we assume that there could be 2 to 3 marketing authorisation applications every year that do not initially request a CMA despite not containing enough data for standard marketing authorisation. This would likely lead to 2 to 3 immature marketing authorisation applications refused every year in the first one or two years, possibly increasing to 5 to 10 refused applications every year in the next 3-5 years as the evidentiary threshold is established. Industry would begin to recalibrate the acceptable levels of evidence in parallel and the numbers of weak applications should fall back to some minimum within 5 years, perhaps never quite falling below 2-3 a year over the remaining years through to 2035. Overall, assuming an average annual reduction of 3-5% in the total number of applications for assessment and 100-120 applications annually, which are increasing at 5-10% a year (as per EMA annual report 2020), cutting assessments by 3-5% might result in a reduction of EMA / NCA costs of 2-3% (the work of the EMA committees is a major cost driver). There could be a negative impact on cost for developers that are currently submitting immature marketing authorisation applications for valid reasons. For example, addressing an UMN may be difficult in terms of conducting large clinical trials. This may discourage developers of medicinal products for UMN if it is not combined with other policy elements. On the other hand, less immature data means HTA bodies and P&R authorities would be more able to assess therapeutic value, which could have a positive impact on access and affordability. Thus, the impact on healthcare systems could be negative (less developers working on UMN) and positive (more streamlined and coherent procedure leading to faster market launch).

Summary assessment of the principal costs and benefits by impact type

Table 67 presents a summary assessment of the principal costs and benefits of the main policy elements proposed for Block I under Policy Option C and for each impact type.

Table 67 Option C – Summary assessment of the proposed policy elements for COVID-19 lessons learnt

Policy elements	**COB**	**Admin**	**SMEs**	**CTI**	**Int Mar**	**I&R**	**PA**	**H&S**	**Sust**
C.9.1.	-	+/-	-	-	+/-	+/-	+	+/-	+/-

COB=conduct of business; Admin=Administrative costs on businesses; CTI= Competitiveness, trade and investment flows; Int Mar= Functioning of the internal market and competition; I&R= Innovation and research; PA= Public authorities; H&S=Public health and safety; Sust= Sustainable consumption and production. Colour coding: Red=negative impact; amber=neutral; green=positive impact; White=cannot say or depends on actual implementation of the element.

Overview of proposed horizontal measures

A.6. Introduction

The impact assessment identified the need to improve the flexibility of the regulatory framework, to futureproof the system and ensure its effectiveness over the next 15-20 years.

In response, the EC and the wider regulatory 'family' has developed a long list of proposals for improving efficiency of the regulatory system, which are listed below in Table 68. The impact assessment has explored each of these areas through our consultations and wider desk research, which suggest there may be substantial opportunities for streamlining and reducing regulatory burden.

The initial assessment of this long list is shown below and has been used to identify a series of 10 pivotal horizontal measures, which have been the subject of a more detailed assessment and cost benefit analysis.

Table 68 Original long list of horizontal measures that have been considered by the IA study

Streamlining proposals
Abolish the sunset clause for all medicinal products
Abolish requirement for renewal of marketing authorisation for all medicinal products
Abolish the additional monitoring requirement and accompanying black symbol.
Abolish risk management plans for generics, biosimilars, hybrid and informed consent products
Certification of active substance master file (ASMF)
Shorter timeline for MRP and DCP – what is the impact bearing in mind the market protection period?
Repeat use procedure (RUP) – legal basis for administrative zero-day MRP/RUP to prevent or address shortages
Establish legal basis for a platform for EMA to facilitate alignment of evidence requirements
Building in structured exchanges to ensure that the advice given is taken into account by the other bodies
Efficient governance of European Medicines Regulatory Network
Digitalisation through electronic submissions, variations to MA (see below)
Electronic submission of applications or registrations by companies.
Legal basis for Electronic Product Information (i.e. electronic labelling and package leaflet
Streamline procedures to facilitate efficient interaction and synergies between different regulatory frameworks
Closing potential gaps in Benefits/Risk of combination products where medicinal products have the primary role
Introducing joint scientific advice for developers of combination products
Data sharing for centrally authorised medicines with downstream decision makers
Increase collaboration between MS and trusted strategic partners to ensure better supervision
Additional leverage of regulators on summary of product characteristics (SmPC)
Increase or optimise the regulatory support to SMEs, academia and public innovators
Address availability issues related to radiopharmaceuticals
Empowering new concepts

Streamlining proposals
Strengthen the environmental risk assessment (ERA)
Empower regulatory authorities to access raw data
Use experts outside national competent authorities to ensure capacity and expertise for assessment
Opening certain procedures for third country participation to strengthen global attractiveness
Adapt where necessary the regulatory system to support the use of new concepts including real world evidence
Information from application dossiers available to authorities
Introduce an EU-wide centrally coordinated process for early dialogue
Create an expert group to give advice/guidance on UMNs
Creation of an emergency use authorisation (EUA) at EU level

Table 69 presents our light touch assessment of each of these horizontal measures. There are 10-15 specific examples of proposals that would abolish certain current procedures, which have been found to be of limited effectiveness as regards their original objectives (e.g. the sunset clause and medicines shortages) or otherwise largely duplicative (e.g. risk management plans for generics). There are a similar number of proposals to improve the level of coordination, integration and harmonisation of the many working parts of the overall regulatory ecosystem, which are often intertwined with proposals to make fuller use of digital solutions across the system. There are also several measures that relate to growing concerns around new types of products and production processes, which are raising questions about where they fit in the overall regulatory architecture. Challenges are particularly evident around: Advanced therapy medicinal products (ATMPs); Combinational products; Products containing genetic modified organisms (GMOs).

Several concepts overlap with the issues raised through the IA consultations, and these are addressed briefly here and in the main body of the IA report (e.g. the abolition of the need to renew marketing authorisations after 5 years). Most of the individual proposals will only be considered here in this technical annexe.

A.7. The strengths and weaknesses of the various proposals

Table 69 presents our qualitative assessment of the 20 or so streamlining measures and Table 70 presents our assessment of a further 10 horizontal measures that relate to new regulatory concepts and structures.

The treatment has included a brief review of what was found in the related evaluation of the EU general pharmaceutical regulation and the Impact Assessment consultation and literature review. Column three provides a synopsis of any advice or feedback from the Impact Assessment stakeholder workshop, and in particular Break Out Group 4, which focused on regulatory burden and flexibility. The final two columns provide qualitative reflections on the likely direction and intensity of future costs and benefits. The study team has sought to identify data and studies that would help to quantify and monetise these impacts, however, the proposals are so particular in their design, that we have been unable to find any relevant data or statistics to support a more granular cost benefit analysis. This absence of data holds even where proposals relate to major development initiatives (e.g. the EMA's digital transformation

programme, which is being implemented by around 80 FTEs) or existing legislative activities that have been evaluated (e.g. the EMA's international cooperation programmes and joint inspections have been evaluated, but no attempt was made to quantify costs or benefits).[113]

We have assessed each proposal against the current situation (baseline) using the same 7-point scale used in the assessment of the policy options, however, with such highly particular measures and no or few data, these assessments have had to be more cautious. We have had to be content for the most part in signalling the direction of costs or benefits with a single plus or minus, as there is simply no basis for determining likely real costs or benefits. In two or three instances, we have assigned two pluses or two minuses, where the proposal relates to a process or activity that is extensive and where our evaluation or impact assessment have picked out the issue as a source of substantial additional costs, time delays or other inefficiencies.

Based on our assessment of this long list, the biggest opportunities for efficiency gains appear to relate to the abolition of various redundant procedures (e.g. 5-yearly renewals), increased integration and collaboration among regulators within and beyond the EU and the need to pursue digitisation in a more determined and holistic manner.

Several points emerge from our assessment of this long list of proposals, whereby the feedback from our wider consultations and literature reviews suggests that these proposals may need to be appraised finally based on a more strategic view of the organisation and resourcing of the overall ecosystem. We see a risk in principle that this elemental approach could lead to piecemeal implementation of the easier fixes, and miss the opportunity to achieve more substantive and lasting improvements:

- The overall system is complex and in danger of becoming more so, and that creating new coordination units or advisory structures is likely to add to the costs and the confusion, without bringing any substantive improvements in functional effectiveness. Our consultations revealed widespread criticism by industry as regards the complexity, rigidity and levels of duplication that the experience with the current system. While these stakeholders can offer numerous examples of difficulties experienced or delays in decision making, they were unable to quantify these inefficiencies overall. Their concerns are echoed by the regulators too, who point to the challenges of fragmentation and resourcing that accompany the EU regulatory model, as compared with the more centralised and integrated US system. There are also concerns being expressed publicly by the chair of the CHMP who told the DIA Europe 2022 conference delegates that the EMA struggles to do its job as a result of its limited resources and its reliance on experts from national regulators to carry out a large part of the work of the committees, given these experts have day jobs and may not be available or allowed to invest the time needed. He noted the duplication of regulatory work across the EU, with numerous regulators carrying out their own reviews of the same products, between sectors and across countries, even within the EEA. The concerns about resourcing, complex committee structures and organisational efficiency were underlined in another presentation, by the head of the EMA's regulatory science and innovation task force, noting problems with approval times. He commented on the use of the clock-stop methodology, which was hiding issues with turnaround times. He also cited the study carried out for EFPIA looking into the 67-day

[113] https://www.ema.europa.eu/en/documents/other/programme-rationalise-international-good-manufacturing-practice-inspections-active-pharmaceutical/active-substance-manufacturers-terms-reference-procedures-participating-authorities_en.pdf

decision making process (33-198 days in practice)[114] at the EC for the issuing of a marketing authorisation decision following the CHMP opinion, and whether it could be shortened.

- The many proposals for organisational reform and digitalisation should be considered together, in the round, with a view making a step change in the level of systemic integration, data sharing, collaborative working and the findability of relevant data and information from across the system.
- Many of these proposals have merit and could be taken forward to the benefit of the system overall, however, it is not clear that many should be a matter for the regulation specifically, inasmuch as they have no need to be detailed specifically in the primary legislation and possibly not even in the accompanying technical guidelines and other 'soft law.' Most of the proposals are about the organisational coherence and dynamism of the whole regulatory system and its integration with other contiguous areas of regulator interest in the health, environment, innovation, and industrial policy realms. There is a risk that hardwiring these elements in the legislation will reduce the long-run effectiveness of the overall ecosystem, adding costs rather than adding speed, efficiency, and agility.

Table 69 Qualitative assessment of proposals for streamlining

Streamlining proposals	Consultation	IA workshop (BG4)	Costs	Benefits
Abolish the sunset clause for all medicinal products	Evaluation revealed feedback suggesting this procedure had not been used greatly EMA monitors withdrawals (I think), which relate to all regulatory pathways and can be triggered by EU / MS regulators	Industry sees little added value in this procedure, which would create some small savings National regulators are more positive about having an ability to formally register that a medicine has been withdrawn and thereby close a file	No quantitative data identified No substantive costs expected (+/-)	No quantitative data identified Would reduce costs to a very limited degree for MAHs (+)
Abolish requirement for renewal of marketing authorisation for all medicinal products	Evaluation confirmed this was problematic IA feedback	Almost universal support for this proposal The 2-3 environmental groups in the room disagreed	No quantitative data identified No substantive costs expected (+/-)	No quantitative data identified There would be substantial time-related cost savings for regulators and industry (++) (could we use pharmacovigilance fees as a proxy?)
Abolish the additional monitoring requirement and accompanying black symbol.	Eval: No feedback IA: not asked The EMA maintains a current list of	The EFPIA delegation suggested they would be supportive of this proposal	No quantitative data identified No substantive costs expected (+/-)	No quantitative data identified There would be time-related cost savings for

[114] https://www.vintura.com/news/every-day-counts-improving-regulatory-timelines-to-improve-time-to-patient-access-across-europe/

Streamlining proposals	Consultation	IA workshop (BG4)	Costs	Benefits
	medicines subject to additional monitoring (c. 375) and black label	No other delegates offered any remarks		regulators and industry (+) (could we use pharmacovigilance fees as a proxy?)
Abolish risk management plans for generics, biosimilars, hybrid and informed consent products, unless the reference medicinal product has requirement for additional risk minimisation measure in its risk management plan or unless specifically requested for generics etc.	Eval: No feedback IA: asked as part of a composite question, which received a very strong positive response from industry (and regulators	RMPs for generics were not discussed in BG4	No quantitative data identified The introduction of a risk-based approach to the development of RMPs should not create any meaningful additional costs, beyond the initial costs to develop, pilot and refine a robust system (-)	No quantitative data identified The introduction of a risk-based approach to the development of RMPs should deliver cost savings to the generics industry (++)
Certification of active substance master file (ASMF) – an independent procedure prior to application for marketing authorisation for generics	Eval: No feedback IA: not asked	Medicines for Europe said they support this proposal 'very strongly,' but it didn't attract wider comments	No quantitative data identified The design and implementation of this new certification system would create additional one-off / ongoing costs for regulators (-)	No quantitative data identified A certified file may reduce the need for generics companies to prepare a separate document (+)
Shorter timeline for MRP and DCP – what is the impact bearing in mind the market protection period?	Eval: No feedback IA: not asked	Not discussed	No quantitative data identified Shortening timelines implies more resources and or further simplification of procedures by regulators (-)	No quantitative data identified Industry generally benefits from shorter decision-making periods (+)
Repeat use procedure (RUP) – legal basis for administrative zero-day MRP/RUP to prevent or address shortages	Eval: No feedback IA: not asked The current RUP arrangements allow member states up to 90 days accept an assessment by the reference member state	Not discussed	No quantitative data identified Creating this exceptional legal basis would require national regulators to develop / agree / implement 'emergency' assessment procedures, which will create additional costs	No quantitative data identified Accelerated approval in an EU MS of an alternative medicine(s) authorised in another MS may help to address critical shortages, to the benefit of patients (+)

Streamlining proposals	Consultation	IA workshop (BG4)	Costs	Benefits
			at the design stage and would create additional costs and risks at each time of use (-)	
Establish legal basis for a platform for EMA to facilitate alignment of evidence requirements through parallel scientific advice (building on mechanisms introduced by the HTA Regulation)	Eval: No feedback IA: not asked The chair of the CHMP presented a paper on regulatory governance at the DIA 2022 Conference, where he talked about duplication of efforts within EMA and between EMA and other regulators	Not raised as an issue by stakeholders	No quantitative data identified There would be costs – and political challenges – involved in designing, setting up and maintaining a more open and integrated system for obtaining, sharing and reusing scientific advice across regulators (-)	No quantitative data identified There could be substantial efficiency gains – and speed enhancements – across the system (++)
Building in structured exchanges to ensure that the advice given at each step of the development is known and taken into account by the other bodies (e.g. scientific advice given by EMA should be aligned with the authorisation processes of the clinical trials related to this advice).	Eval: No feedback IA: not asked Harald Enzmann chair of the CHMP presented a paper on regulatory governance at the DIA 2022 Conference, where he talked about duplication of efforts within EMA and between EMA and other regulators	Industry delegates cited the work done by their various representative bodies on the biggest opportunities for streamlining, from an industry perspective, which include 1. Iterative regulatory advice and agility 2. Expedited, flexible and dynamic assessment and decision-making pathways. The top 5 issues were identified through a poll at the DIA 2022 Conference	No quantitative data identified There would be costs – and political challenges – involved in designing, setting up and maintaining a more open and integrated system (-)	No quantitative data identified There could be substantial efficiency gains – and speed – across the system (++)
Efficient governance of European Medicines Regulatory Network	Eval: No feedback IA: not asked The European Medicines Regulatory Network strategy to 2025 includes	Not discussed	No quantitative data identified Strengthened coordination would bring some small additional costs (ongoing) for regulators, for	No quantitative data identified Strengthened coordination may deliver more timely / effective / even contributions to the

Streamlining proposals	Consultation	IA workshop (BG4)	Costs	Benefits
	a section on governance, operational excellence and sustainability. But no references to or expected scale of impact.[115]		secretariat / governing body / individual members (-)	work of the network (+)
Digitalisation through electronic submissions, variations to MA (see below)	Eval: industry and regulators argue that the regulatory system had fallen behind on digital IA: all stakeholders are strongly supportive of further digitalisation to improve timeliness, efficiency and consistency The EMA is investing heavily in digital transformation, and is closely involved with wider projects on digital health. EMA Digital Business Transformation task force (17 FTE); EMA Data Analytics and Methods Task Force (62 FTEs)[116]	All stakeholders were supportive of the need for the regulatory system to exploit digitalisation more fully Variations to the MA were noted as being a major source of administrative costs for industry Several contributors signalled a note of caution around digitalisation: there is substantial work in hand already by EMA and others; and there is a need for a wide-ranging and holistic approach to digitalisation that goes far beyond the regulation. Digitalisations also needs to be properly planned, funded and overseen	No quantitative data identified The incremental improvement to the submission of applications and variations may be relatively low cost and could possibly be done without impeding wider ambitions There would be some limited one-off costs involved with digitalisation of submissions (-) The ongoing costs would be recharged as fees to applicants / MAHs, increasing charges by a small fraction (-)	No quantitative data identified Improved portals for submissions and variations would provide efficiency gains / savings for applicants and MAHs (+++) … and for regulators (+)
Electronic submission of applications or registrations by companies. This would cover not only applications for marketing authorisation and variations, but also possibly for manufacturing or wholesale distribution authorisation as well as registrations of manufacturers/importers of active substance and of brokers.	Eval: industry and regulators argue that the regulatory system had fallen behind on digital IA: all stakeholders are strongly supportive of further digitalisation to improve	All stakeholders were supportive of the need for the regulatory system to more fully exploit digitalisation Variations to the MA were noted as being a major source of administrative costs for industry	No quantitative data identified The incremental improvement to the submission of applications and variations may be relatively low cost and could possibly be done without	No quantitative data identified Improved portals for submissions and variations would provide efficiency gains / savings for applicants and MAHs (++) … and for regulators (+)

[115] https://www.ema.europa.eu/en/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf

[116] https://www.ema.europa.eu/en/documents/report/final-programming-document-2022-2024_en.pdf

Streamlining proposals	Consultation	IA workshop (BG4)	Costs	Benefits
	timeliness, efficiency and consistency	Several contributors signalled a note of caution around digitalisation: there is substantial work in hand already by EMA and others; and there is a need for a wide-ranging and holistic approach to digitalisation that goes far beyond the regulation. Digitalisations also needs to be properly planned, funded and overseen	impeding wider ambitions There would be some limited one-off costs involved with digitalisation of submissions (-) The ongoing costs would be recharged as fees to applicants / MAHs, increasing charges by a small fraction (-)	
Legal basis for Electronic Product Information (i.e. electronic labelling and package leaflet to replace the paper one for hospital administered products and products administered by healthcare professionals).	Eval: no feedback IA: all stakeholders support the move to ePI	All stakeholders support the move to ePI, while noting it may take time and there are issues of digital access / literacy People noted there is substantial activity in this space already, that needs to be learned from.[117] The move to digital also creates opportunities for a more diverse / effective means by which to communicate stator information such that patients are more likely to see this information and understand it It was suggested that the legislation should facilitate this trend by considering ePI equivalent to paper leaflets	No quantitative data identified The numerous pilot initiatives being run at EU, member state and international levels suggest that while the electronic solution may be relatively simple to put in place, the creation of an integrated / safe system is likely to be costly / challenging (--)	No quantitative data identified Electronic product information would provide numerous advantages in terms of the ease of access for the majority of patients with opportunities to improve readability and assistive technologies and to ensure information is kept up to date and in line with the SmPC(++)
Streamline procedures to facilitate efficient interaction and synergies between different but related regulatory frameworks e.g. Medical Device (for certain	Eval: No feedback IA: Strongly positive feedback from	Delegates flagged the presentations by regulators at the DIA 2022 conference openly calling for reform of	No quantitative data identified Devising and implementing new structures	No quantitative data identified Improved interaction may reduce occasional

[117] https://www.eahp.eu/practice-and-policy/ehealth-and-mhealth/ePIsurvey

Streamlining proposals	Consultation	IA workshop (BG4)	Costs	Benefits
type of products) and Health Technology Assessments.	industry and regulators on this aspect	structures and processes both within the core medicines regulators (EMA) and between EMA and others	to facilitate improved interaction would bring one-off costs and ongoing costs for regulators seeking to ensure that all actions / decisions are fully joined up with other affected regulators (-)	delays and duplication of effort (+)
Closing potential gaps in Benefits/Risk of combination products where medicinal products have the primary role	Eval: no feedback IA: not asked directly Stakeholders were strongly positive about the potential benefits of the introduction of coordination and advisory mechanisms to facilitate the timely / consistent assessment of the growing number of combination products	Delegates were supportive of the need for a regulatory ecosystem that didn't have gaps and was well-integrated (e.g. combinations with medical devices) and future proof (e.g. AI)	No quantitative data identified The new mechanisms would bring additional costs for the EMA and other regulators (-)	No quantitative data identified Closing gaps would help reduce some unnecessary delays in assessments for applicants (+)
Introducing joint scientific advice for developers of combination products	Eval: no feedback IA: not asked	Not discussed	No quantitative data identified The creation of a mechanism for providing joint scientific advice may create some additional costs for regulators with one-off costs to set up protocols and guidelines such that the structure / process can be implemented as necessary and consistently (-)	No quantitative data identified The creation of a mechanism for providing joint scientific advice may reduce occasional difficulties working across committees and regulators, and thereby create some small efficiency gains for regulators and some time savings for applicants (+)
Data sharing for centrally authorised medicines with downstream decision makers in compliance with	Eval: no feedback IA: not asked	Delegates acknowledged the importance of a holistic approach	No quantitative data identified	No quantitative data identified

Streamlining proposals	Consultation	IA workshop (BG4)	Costs	Benefits
GDPR, taking into account commercially confidential information and the EHDS proposal		to ehealth including data sharing	Setting up an EU-wide system to facilitate downstream access to authorised medicines data would be challenging and may be quite costly to implement and operate for EMA (fees charged to HTAs) (--)	Improved access to data by HTAs etc may facilitate their assessment processes and allow occasional queries to be answered by direct interrogation of those data. However, it is not clear how significant such data are to effective / expeditious decision making (+) In the longer term, it may benefit MA holders through an ability to re-use large parts of a dossier for an HTA assessment from their submissions to the assessment agency (+)
Increase collaboration between MS and with trusted strategic partners to ensure a better supervision while saving resources by: developing collaborative inspection programmes and expanding the existing ones on API and sterile product manufacturing sites; increase the reliance on inspection reports from trusted authorities, e.g. US FDA, MHRA (concept paper on this); extra inspection capacity and build more efficient specialised inspector capability (concept paper on this)	Eval: no feedback IA: not asked There is substantial work ongoing, including for example the EMA-coordinated International Collaboration on GMP inspections, the ICMRA (International Coalition of Medicines Regulatory Authorities), and through the EMA's ad hoc work with non-EU regulators through its thematic topics or 'clusters.'[118]	International cooperation was not discussed at length during the workshop, however, there was an acknowledgement of the potential for reducing burden through greater cooperation internationally	No quantitative data identified (the EMA has published several reviews of its international programmes, but none has sought to quantify the costs and benefits)[119] The EU pharma legislation may need to explicitly approve the legitimacy of this global collaborative approach. Beyond providing the necessary permission, most of the relevant activities would	No quantitative data identified The EMA's international collaboration on inspections states that there are important gains from increased cooperation and collaboration that derive from pooled resources, reduced duplication, greater consistency, and greater scope / reach of inspections. There is an expectation that the revisions to the legislation will seek to extend the scope of EU interests in the performance of global supply chains and that the need for

[118] https://www.ema.europa.eu/en/partners-networks/international-activities/cluster-activities

[119] https://www.ema.europa.eu/en/documents/other/programme-rationalise-international-good-manufacturing-practice-inspections-active-pharmaceutical/active-substance-manufacturers-terms-reference-procedures-participating-authorities_en.pdf

Streamlining proposals	Consultation	IA workshop (BG4)	Costs	Benefits
			fall outside the legislation. Creating a more substantive international collaboration programme for inspections (etc.) would bring some additional design / set-up costs and would bring costs associated with the EMA's oversight / coordination of EU and EU MS participation in this global programme (-)	collaboration will become more urgent and demand greater reciprocity. This may become more of an international relations issue, however, it should also deliver efficiency and quality benefits for the system overall (+)
Additional leverage of regulators on summary of product characteristics (SmPC) based on evidence on safety and efficacy (i.e. to adapt the product information without full consent of the marketing authorisation holder). This adaptation could be during the assessment of the application for marketing authorisation or during post-authorisation procedures.	Eval: no feedback IA: not asked Our consultation did consider the potential benefits of a more harmonised and regular process for updating SmPC linked with older antimicrobials, which was viewed positively.	Not discussed	No quantitative data identified The intensification / acceleration of the established process for notifying / updating SmPCs would bring additional costs for industry and for regulators (-) The suggestion that regulators – or their agents – would update the product information without the consent of the MAH, even as a last resort, would be resisted by industry (--)	No quantitative data identified With no view on the nature and extent of the problem, it is not possible to determine what benefits such a change would deliver, even qualitatively or directionally (+/-)
Increase or optimise the regulatory support to SMEs, academia and public innovators to bring their innovative products to market more efficiently. Similar measures for academic and public innovators be introduced as for SMEs, e.g. fee reductions, more advice	Eval: the evaluation found a positive view regarding the support provided to SMEs, in terms of both additional advice and fee reductions	Industry delegates underlined their wish for a much more agile and interactive regulatory system. They noted this dynamic approach was especially important for smaller businesses	No quantitative data identified This would have some limited additional cost and resource implications for the EMA and its partner national regulators, in setting up and delivering	No quantitative data identified

Streamlining proposals	Consultation	IA workshop (BG4)	Costs	Benefits
	IA: this question was not asked specifically	On a related matter, industry delegates signalled caution about the possible risks of regulators seeking to encourage engagement by non-commercial actors through the creation of less-rigorous pathways The healthcare and academic communities did not offer a view on the needs / solutions for optimising support	additional, on-demand bespoke advice for SMEs, academics and non-commercial organisations (-) Any further fee reductions would also There may be limited additional demand for such services, so the ongoing costs	
Address availability issues related to radiopharmaceuticals. Better define the scope to avoid overregulation of radiopharmaceuticals as per defined in the evaluation.	Eval: no feedback IA: not asked	Not discussed directly, beyond a short remark about these types of therapies having a potentially high environmental risk and needing to be considered by the pharma legislation based on benefit-risk to patients as well as to the environment	No quantitative data identified	No quantitative data identified

Table 70 Assessment of horizontal measures that may support new regulatory concepts and structures

Empowering new concepts	Consultation	IA workshop (BG4)	Costs	Benefits
Strengthen the environmental risk assessment (ERA), as appropriate, and assess whether it should be part of the risk-benefit assessment; assess whether the introduction of risk mitigation measures, where needed, would be enough to address the environmental concerns; ensure no duplication of testing is carried out; aim at the harmonisation in the way ERAs are carried out in all Member States, while assessing what entails to have a common data basis, accessibility and transparency of environmental information for all products.	Stakeholder feedback revealed broad support for doing more with ERA Public authorities, CSOs and health services believe this is important Industry is slightly positive	Industry is supportive of a strengthened ERA, but suggests the assessment should be risk-based and focus on the APIs rather than product Industry supportive of more harmonisation and more transparency (EPARs) CSOs noted that there is less work done – and more gaps on older APIs – on pharma substances than in other sectors	No quantitative data identified A strengthened ERA would bring additional limited costs for all MA applicants (-) A more careful assessment of an expanded ERA and a fuller record of that assessment may bring limited additional costs for regulators (-)	No quantitative data identified Greater transparency and reuse would avoid duplication of effort and bring some limited savings for industry and regulatory bodies (+) Given the thicket of other applicable EU legislation, this initiative would not add much value from an environmental perspective (+/-)

Empowering new concepts	Consultation	IA workshop (BG4)	Costs	Benefits
		Industry noted that EU-based manufacturers are responsible for a fraction of all releases (2%); perhaps not the case globally Industry noted that there is substantial other legislation that address these issues (inclusion in the pharma legislation is less relevant)		
Empower regulatory authorities to access raw data, e.g. in cases where a regulatory submission include only aggregated data or to monitor the effectiveness following post-marketing authorisation. Competent authorities for medicines authorisation to access raw data of applicants or marketing authorisation holders to review/analyse this data themselves.	Eval: no feedback IA: not asked	Not discussed directly There was general support by industry and regulators and CSOs for the regulatory system to improve its management, re-use and access to regulatory data overall Given the likely costs and risks to privacy / confidentiality, industry may object to the proposal that regulators should have the authority to insist on having routine access to raw data to support their own assessment work	No quantitative data identified Some limited additional costs for industry that would follow a need to curate / archive 'raw data' securely enough to grant regulators managed access (-) Some additional costs associated with regulators having to resource these occasional and ad hoc deep dives (-)	No quantitative data identified The need to make raw data open to regulators may have a small positive impact on the curation of data and the consistency of the underpinning work processes (+) There may be some limited gain for applicants if regulators can clarify at least some technical questions that arise during assessments from direct access to micro-data. However, there is a risk that such open and unguided access to data would be likely to generate more queries rather than fewer. (+) There may be a timing benefit if queries can be resolved more easily and quickly through direct access. (+)
Use under certain conditions experts outside national competent authorities to ensure capacity and expertise for assessment	Eval: no feedback IA: not asked directly EMA / NCA resourcing pressures were	Not discussed directly Delegates suggested that the EU regulatory model is under pressure and that	No quantitative data identified Regulators would have to fund the creation and management of a large pool of	No quantitative data identified A standing college of experts would help to reduce delays in assessments

Empowering new concepts	Consultation	IA workshop (BG4)	Costs	Benefits
	raised in the consultation	resourcing issues are causing many delays and disadvantaging EU businesses	appropriately qualified experts and pay their fees (cf DG RTD's pool of expert evaluators that support the review of calls for proposals (-)	relating to capacity bottlenecks. It is unknown how often capacity is the root cause of significant delays (+) External experts would help to reduce the unevenness of workloads across NCAs, with several EU member states providing a disproportionate share of capacity for scientific assessments (+)
Opening certain procedures for third country participation to strengthen global attractiveness	Eval: no feedback IA: not asked	Not raised as an issue	No quantitative data identified The scope or purpose is unclear, however, there would be additional costs to the regulators if this expands enquiries / applications overall (and that expansion tracks back to organisations with limited prior knowledge of the EU regulatory context (-)	No quantitative data identified The scope or purpose is unclear, so benefits cannot be understood beyond the general notion of increased global attractiveness (+/-)
Adapt where necessary the regulatory system to support the use of new concepts including real world evidence, health data while keeping the standards of Q/S/E	Eval: no feedback IA: RWE was raised in the consultation as being an important trend that will benefit regulatory systems in future The EFPIA study on real-world data and real-world evidence found that companies are making use of RWD (84%) albeit less than half had used these data in	Industry delegates made clear they are advocates of regulators being open to new concepts including RWE Regulators / CSOs did not offer a view on this question	No quantitative data identified Regulators may incur some limited one-off costs associated with the development of new guidelines (-) There may be some inefficiencies / delays initially as committees build experience of using these new concepts and calibrate the value of novel data sources. (-)	No quantitative data identified Some timing and efficiency gains for MA applicants and MA holders, but impacts may be quite limited in the medium term as these data types are generally used as complements to other data Should result in regulators being able to take more confident / speedier decisions on applications Should improve quality / efficiency of post marketing

Empowering new concepts	Consultation	IA workshop (BG4)	Costs	Benefits
	regulatory documents[120]			authorisation activities (+)
Information from application dossiers, including for nationally authorised products, as regards the manufacturing sites for finished products and APIs, available to authorities and make data held by regulatory agencies and manufacturers available using the EHDS framework.	Eval: no feedback IA: not asked	Not raised as an issue directly, but as noted above there was general support across stakeholders for enhancing the use of digital solutions to facilitate increased data sharing and re-use There was strong support for developing structures / platforms to facilitate increased worksharing	No quantitative data identified There would be costs associated with such a system for industry, in ensuring its data are held and curated in a manner that would facilitate this more open approach (-) There would be costs associated with the design and implementation of such a system for EMA and NCAs, even if it were inked with the existing EHDS infrastructure (-)	No quantitative data identified This data sharing would be beneficial to post authorisation activities, providing improvements in speed / convenience of access, reuse and supporting collaborative working (+)
Introduce an EU-wide centrally coordinated process for early dialogue and more coordination among clinical trial, marketing authorisation, health technology assessment bodies, pricing and reimbursement authorities and payers for integrated medicines development and post-authorisation monitoring, pricing and reimbursement. When providing scientific advice to developers, at its scientific discretion EMA can take into account this early dialogue and coordination.	Eval: no feedback IA: not asked	Industry delegates underlined their wish for a much more agile and interactive regulatory system. They noted this dynamic, interactive approach was especially important for smaller businesses A delegate suggested that academia and SMEs should have access to early agile and maybe more informal advice (price is prohibitive for academia). They noted that the INTERACT meeting with the FDA is quite efficient for early discussion: a phone call with a simple briefing package allows for early brainstorming	No quantitative data identified Early dialogue may place additional pressures on EMA finances and resourcing (and the regulatory network) Doing this EU-wide would bring substantial additional costs (--)	No quantitative data identified Early dialogue is seen by industry as a major opportunity to improve developers' abilities to deliver mature / comprehensive applications that are more likely to be assessed quickly (and positively). Doing it EU wide would be a strongly positive approach (++) A more coordinated approach should result in some savings for national authorities (+)

[120] https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.2103

Empowering new concepts	Consultation	IA workshop (BG4)	Costs	Benefits
		and then early directions in regard to potential classification and regulatory considerations		
Create an expert group to give advice/guidance on UMN – cross-sector involving health technology assessment bodies (via the Coordination Group of HTA bodies set up under the new HTA Regulation), pricing and reimbursement bodies, patients, and academic representatives.	Eval: no feedback IA: not asked directly	Not discussed	No quantitative data identified Introducing a regulatory incentive specifically for UMNs will require the creation of an agreed set of definitional criteria or lists of UMNs. This will require additional guidance and possibly additional advice for assessment bodies. A cross-sector working group may reduce the operational effectiveness and timeliness of such a body, from the perspective of medicines regulators specifically (-)	No quantitative data identified The creation of a standing group to give advice on UMNs to multiple regulators and pubic bodies may produce some efficiency gains and support a more consistent implementation, with a potential for cost sharing across stakeholders (+)
Creation of an emergency use authorisation (EUA) at EU level as an additional tool to support faster use of medicines without a marketing authorisation during pandemic situation	Eval: no feedback IA: not asked directly	Not discussed	No quantitative data identified	No quantitative data identified

A.8. Cost benefit analysis for the horizontal measures

A.8.1. Qualitative assessment of costs and benefits relating to the pivotal horizontal measures

Table 71 presents an overview of the 10 pivotal measures and our qualitative assessment of the costs and benefits for each proposal, which we have analysed in Table 72 below.

Table 71 Overview of the pivotal horizontal measures and their expected costs and benefits

Description	Qualitative assessment of costs and benefits
1. **Streamlining of procedures**, including avoiding duplicative processes (including GMO requirements, prioritisation of	Benefits: the various streamlining procedures proposed would deliver direct cost savings to both industry and regulators. Abolition of risk management plans may be the

applications, better coordination within the regulatory network; renewal of marketing authorisation, PhV requirements – RMPs for generics + black symbol): – Abolish the sunset clause for all medicinal products – Abolish requirement for renewal of marketing authorisation for all medicinal products – Abolish the additional monitoring requirement and accompanying black symbol. – Abolish risk management plans for generics, biosimilars, hybrid and informed consent products, unless the reference medicinal product has requirement for additional risk minimisation measure in its risk management plan or unless specifically requested for generics etc. – Certification of active substance master file – an independent procedure prior to application for marketing authorisation for generics	most beneficial to generics companies and national regulators. These various procedures bring occasional costs for most companies at some point in time (++) Costs: the proposed abolition of various duplicative procedures should not result in any meaningful additional costs for any stakeholders. The creation of a certification system for the ASMF would bring one-off costs for the design and implementation of the enhanced procedure, falling on regulators
2. Enable an **accelerated mutual recognition procedure** (MRP) within the EU, Enable a (more) efficient Repeat Use Procedure, For EU authorities to reduce the administrative and cost burden submission of post approval changes – Shorter timeline for MRP and DCP – what is the impact bearing in mind the market protection period? – Repeat use procedure (RUP) – legal basis for administrative zero-day MRP/RUP to prevent of address shortages	Benefits: as accelerated procedure would benefit the generics industry directly and possibly health payers indirectly, with generic competition being brought forward by a month or so in a proportion of cases. A legal basis for a zero-day MRP may help to address critical shortages to the benefit of patients, where there is an alternative medicine(s) authorised in another MS but not in the MS in question. (++) Costs: the accelerated MRP should be achieved through streamlining and harmonisation of procedures (and various improvements to digital infrastructure, worksharing and pan-EU data services), so should bring few if any additional costs for regulators. The zero-day RUP would require some limited one-off costs for the network / regulators to prepare a detail design and associated procedures that all member states would support. (--)
3. Efficient governance of European Medicines Regulatory Network: (not for assessment) formalize the structure of the network including role and tasks of Heads of Medicines Agencies; efficient cooperation of EMA committees – simplify processes of EMA committees when several are involved. Strengthen system of inspections to better use resources – Increase collaboration between MS and with trusted strategic partners to ensure a better supervision while saving resources by : – develop collaborative inspection programmes and expand the existing ones on API and sterile product manufacturing sites – increase the reliance on inspection reports from trusted authorities, e.g. US FDA, MHRA (concept paper on this) – support extra inspection capacity and build more efficient specialized inspector capability (concept paper on this)	Efficient governance Benefits: more efficient governance of the regulatory network should reduce the average elapsed time between initial application and a recommendation, which will benefit developers by creating the potential for earlier market launch and patients indirectly. It should also bring efficiency gains for regulators. Better coordinated cross-border and international inspections should provide efficiency gains for regulators (+++) Costs: Strengthened governance may bring some small additional costs for regulators associated with an expanded coordination function (-)

4. Streamline procedures to facilitate **efficient interaction and synergies between different but related regulatory frameworks** e.g. Medical Device (for certain type of products) and Health Technology Assessments. – Closing potential gaps in B/R of combination products where medicinal products have the primary role – Introducing joint scientific advice for developers of combination products – BTC framework could be added as well.	Efficient interaction between related regulatory frameworks Benefits: more efficient interaction across regulatory frameworks should reduce the average elapsed time between initial application and a recommendation for a proportion of applications (e.g. combination products), which will benefit developers by creating the potential for earlier market launch. It should also bring efficiency gains for regulators. (++) Costs: Devising and implementing new structures to facilitate improved interaction among regulators would bring one-off costs associated with the design / implementation of those new structures and ongoing costs for regulators of running those coordination mechanisms seeking to ensure that all actions / decisions are fully joined up with other affected regulators (-)
5. Legal basis for the network to analyse real world evidence, **create computing capacity, store and manage large data sets and to share the data** with the HTA Coordination Group as set out in Regulation 2021/2282 and Pricing and reimbursement authorities, in compliance with GDPR, taking into account commercially confidentially information and the EHDS proposal.	Real world evidence and a pan-EU data service Benefits: a more inclusive view of allowable data should help regulators with both the assessment of applications and various post-authorisation activities. The creation of an integrated online data service accessible by various types of health regulators should bring major efficiency gains for the system overall. (+++) Costs: The EU and regulators may incur significant one-off costs associated with the creation of a new integrated data infrastructure for the regulatory system overall. There will be additional recurrent costs associated with the operation and maintenance of what would be a large and growing data set. (---)
6. Legal basis for **Electronic Product Information** (i.e. electronic labelling and package leaflet to replace the paper one for hospital administered products and products administered by healthcare professionals).	ePIL Benefits: having a legal basis for ePIL would anticipate and reinforce a trend. Electronic product information would make it easier for healthcare professionals to access comprehensive and up-to-date information on products within different settings. There would be some small environmental benefit in terms of reduced use of paper and less waste, albeit manufacturers would need to run paper and electronic systems in parallel) (++) Costs: manufacturers would incur one-off costs associated with the upgrading of their electronic publishing capabilities. But should otherwise be well placed to expand ePIL provision. Regulators and healthcare systems would incur one-off costs when negotiating the creation of a 'common' EU-wide infrastructure for ePIL and recurrent costs associated with its operation and maintenance. (---)
7. Electronic submission of applications or registrations by companies – This would cover not only applications for marketing authorisation and variations, but also possibly for manufacturing or wholesale distribution authorisation as well as registrations of manufacturers/importers of active substance and of brokers.	Electronic submission Benefits: manufacturers would see efficiency gains from the introduction of a fully digital submission platform. Regulators would similarly see efficiency gains from a move to digital submissions supporting the re-use of data across functions and committees and for example eliminating the need for committee members to work with large paper files. There would be an environmental benefit too from the reduction in the use of paper. This would provide a small but lasting benefit to the whole industry and to all regulators (++) Costs: manufacturers may incur some very limited one-off costs associated with harmonisation of their data systems with any new templates. The regulators would incur one off costs in creating the new submission system and recurrent costs associated with its operation and maintenance. There

	is already substantial use of online submissions and digital solutions, so while there would be costs for all actors these should be relatively modest (-)
8. Increase or **optimise the regulatory support** to SMEs, academia and public innovators to bring their innovative products to market more efficiently	Optimise regulatory support SMEs and non-commercial Benefits: SMEs would benefit from additional support / scientific advice tailored to smaller developers, which may help them to develop applications with more confidence and with a greater likelihood of a successful opinion. Non-commercial organisations would also benefit from tailored support, as they are likely to have even less experience and internal support when it comes to regulatory matters. Given the growing importance of small biopharma, this expansion in regulatory support could be highly beneficial to startups and innovative therapies. (++) According to the latest EMA annual report, requests for scientific advice has been increasing at 5-10% year over the past five years (787 requests in 2020). In 2020, 25% of all requests for scientific advice came from SMEs. The EMA's review of SME support (2020) obtained feedback from 553 SMEs and found the very great majority (80%) judged themselves to be well appraised of the support on offer (fees and advice) and more than 90% judged the support / services to be relevant. The primary requests for improvements related to additional financial discounts and simplified applications Costs: the EMA would incur additional costs associated with this expanded and tailored support. The numbers of users may not be especially high, which would contain costs, however, the amount of support required for an average request may be proportionately much greater than would be the case for most developers (-)
9. Adapt where necessary the regulatory system to **support the use of new concepts** including real world evidence, health data while keeping the standards of Q/S/E	Adapting the system to use new concepts Benefits: this would deliver greater regulatory alignment with important developments, improving the speed of decision making and reducing regulatory costs. It would reward developers for using new and emerging types of data within their applications (++) Costs: the EMA would incur additional one-off costs associated with the creation of new or expanded guidelines and working methods to tackle new concepts with confidence and consistently. (--)
10. Introduce an **EU-wide centrally coordinated process for early dialogue** and more coordination among clinical trial, marketing authorisation, health technology assessment bodies, pricing and reimbursement authorities and payers for integrated medicines development and post-authorisation monitoring, pricing and reimbursement. When providing scientific advice to developers, at its scientific discretion EMA can take into account this early dialogue and coordination.	Early dialogue with developers and across regulators Benefits: early, iterative regulatory advice and dynamic assessment came out as the top two items on an industry poll (DIA Europe 2022 conference) as regards the areas where they would like to see improvements in regulatory performance. Early dialogue and more coordination should deliver efficiency gains for industry and regulators as well as faster decision making overall (+++) Costs: the EMA may incur substantial additional one-off and recurrent costs associated with the move to a more centrally coordinated and dynamic assessment system, covering both the CP and distributed procedures and leading on coordination with other agencies (---)

Lastly, in Table 72, we have summarised this preceding tabular presentation in a more visual, qualitative assessment of the benefits of each of the 10 pivotal horizontal measures, by key stakeholder group. From this perspective, the most promising horizontal measures – overall, for

all stakeholder groups – are the proposals to improve the governance of the European medicines regulatory network, the development of an integrated, pan-EU data architecture for the regulatory system and an EU-wide, centrally coordinated process for early dialogue.

Table 72 Qualitative assessment of the benefits of pivotal horizontal measures, by key stakeholder group

	Business	EMA	NCAs	SMEs	Health Systems	Environmental
Streamlining and de-duplication						
#1 Streamlining of procedures	H	M	M	H	L	L
#2 Accelerated MRP and more efficient RUP	H	L	H	L	M	L
#3 Efficient governance of the European Medicines Regulatory Network	H	H	H	H	M	L
#4 Facilitate more efficient interaction across regulatory frameworks	M	H	M	M	M	L
Digitalisation						
#5 Legal basis to allow network to create an integrated, pan-EU health regulatory data service	M	M	H	H	H	M
#6 Legal basis for setting up ePIL system for healthcare professionals	L	M	M	L	M	M
#7 Electronic submission of applications	H	H	M	H	L	M
Enhanced support and regulatory flexibility						
#8 Optimise regulatory support to SMEs and non-commercial organisation	L	M	L	H	H	L
#9 Adaptation of the regulatory system to support the use of new concepts	H	M	M	H	M	L
#10 EU-wide centrally coordinated process for early dialogue	H	M	H	H	M	L

A.8.2. Overview of costs and benefits

Table 73 presents an overview of the costs and benefits associated with the three major categories of horizontal measures identified through the impact assessment. This has been prepared in line with the better regulation guidelines, with the costs presented in line with the standard cost model.

It shows estimated total costs for the pivotal streamlining measures combined fall in the range €1.1bn to €2.5bn. We estimate the total benefits will fall somewhere in the range €2.8bn-€5.8bn. The benefits significantly outweigh the costs for both the lower and upper bound estimates.

The analysis suggests that the proposed streamlining measures are likely to deliver the greatest quantum of benefits, falling in the range €1.5bn-€3.1bn. By contrast the digitalisation measures are likely to be the costliest to implement, albeit with substantial benefits to the efficiency of the regulatory system overall. The analysis suggests the enhanced support measures are likely to be the most affordable (€72m-€108m), and while they will yield a lower overall benefit (€214m-€428m), it is the highest rate of return proportionately.

Table 73 Overview of the costs and benefits associated with the horizontal measures

	Businesses	**Businesses**	**EMA**	**EMA**	**NCAs**	**NCAs**	**Totals**	**Totals**	**Totals**
	one-off	**recurrent**	**one-off**	**recurrent**	**one-off**	**recurrent**	**one-off**	**recurrent**	**15 years**
Streamlining costs									
Direct									
Enforcement			€1.8m - €3.6m	€3.5m-€7.5m	€15m-€30m	€30m-€60m	€16.8m - €33.6m	€33.5m-€67.5m	
Indirect									
Totals							**€16.8m - €33.6m**	**€33.5m-€67.5m**	**€519.3m-€1,046.1m**
Streamlining benefits									
Direct		€15m-€30m		€3.5m-€7m		€30m-€60m		€48.5m-€97m	
Indirect		€55m-€110m						€55m-€110m	
Totals								**€103.5m -€207m**	**€1,552.5m -€3,105m**

	Businesses	Businesses	EMA	EMA	NCAs	NCAs	Totals	Totals	Totals
	one-off	**recurrent**	**one-off**	**recurrent**	**one-off**	**recurrent**	**one-off**	**recurrent**	**15 years**
Digitalisation costs									
Direct									
Enforcement			€20m-€50m	€4m-€10m	€100m - €300m	€20m-€60m	€120m-€350m	€24m-€70m	
Indirect									
Totals							€120m-€350m	€24m-€70m	**€480m-€1,400m**
Digitalisation benefits									
Direct		€7.5m-€15m		€7m-€14m		€60m-€120m		€75m-€149m	
Indirect									
Totals									**€1,117.5m -€2,235m**
Enhanced support costs									
Direct		€1.6m-€2.4m						€1.6m-€2.4m	
Enforcement				€4.8m-€7.2m				€4.8m-€7.2m	
Indirect									
Totals									**€72m-€108m**
Enhanced support benefits									
Direct		€7.5m-€15m		€1.75m-€3.5m				€9.25m-€18.5m	

	Businesses	Businesses	EMA	EMA	NCAs	NCAs	Totals	Totals	Totals
	one-off	recurrent	one-off	recurrent	one-off	recurrent	one-off	recurrent	15 years
Indirect		€5m-€10m						€5m-€10m	
Totals									**€214m-€428m**

Our overall estimates are likely to be understated slightly, as there are likely to be further indirect benefits associated with these measures, and in particular the likelihood of shortening average times for the assessment of applications, which should flow through to marginally earlier access to new medicines and generic competitors for large numbers of EU citizens and patients. We were unable to push these estimates to the point where we were able to quantify the likely benefits to patients, which are likely to be relatively limited in depth but wide-ranging.

Given the scope and diversity of the proposed initiatives and the large numbers of actors that would be involved, we have had to rely on assumptions drawn from the wider literature, to make our monetary estimates. Given the many uncertainties involved with this process, we have used ranges throughout. Our logic and assumptions are detailed in Table 74.

Table 74 Descriptive overview of the costs and benefits and assumptions associated with the horizontal measures

	Description of types of costs and benefits	Assumptions made in quantification	Notes on sources
Streamlining costs			
Direct	There should be few if any direct costs associated with the various streamlining measures, which would deliver efficiency gains to businesses		
Enforcement	There should be few if any enforcement costs associated with the various streamlining measures, as the principal regulatory measures relate to the abolition of procedures that are duplicated elsewhere in the system	We have assumed the one-off indirect costs might amount to 0.5-1% of EMA annual expenditure (€365m in 2020) and NCA annual expenditure (€3bn), spread over 2-3 years. We have assumed recurrent annual costs would be slightly higher, 1-2%.	We have found no quantitative estimates of the likely costs of these proposed measures through our consultations or literature reviews, and have had to make assumptions about likely level of effort and multiplied this by EMA / NCA budgets
Indirect	There will be no substantive indirect costs from the proposed streamlining measures		

	Description of types of costs and benefits	Assumptions made in quantification	Notes on sources
Streamlining benefits			
Direct	There should be direct cost savings to businesses and regulators from the streamlining measures	We have assumed that these refinements may save businesses 1-2% of their regulatory costs annually (15m-30m: c. €1.5bn based on McKinsey estimate of Regulatory Costs being c. 4.1% of BERD); EMA 1-2% and NCAs 1-2%	We have found no quantitative estimates of the likely benefits of these proposed measures through our consultations or literature reviews, and have had to make assumptions based on estimates of overall regulatory costs.
Indirect	There may be some limited indirect benefits in terms of accelerated procedures meaning applications are authorised several weeks earlier (CP / DCP), which may facilitate at least some new medicines being approved for sale earlier and some generics entering the market earlier.	We assume the average period taken to assess applications may be reduced by 2-4 weeks, albeit the bigger impact may be on outliers and enabling a greater proportion of all assessments to be carried out closer to the median time taken. We based this 10-20 day improvement on the fact that the EMA part of the assessment process is taking around 200 days on average (EMA annual report 2020) and the accelerated assessment takes around 140 days. If we assume 50% of the EMA positive opinions are approved and manage to come to market 2-4 weeks early, and we assume an average annual EU income for a medicine at 50m (c. €1m a week), that would amount to income of around €100m-€200m being brought forward. The market would be competed away 2-4 weeks earlier, so the total income may not change. But there could be first mover advantages as well as the time value of money, and so we might suggest that businesses will benefit by 5% of the value of this earlier cashflow (5m-10m). This accelerated process would apply to generics also, and given the relative scale of assessments (CP v DCP), the benefits for this group of businesses may be an order of magnitude higher (50m-100m)	We have found no quantitative estimates of the likely impact of these proposed measures, and have no good basis for approximating the nature and extent of the possible indirect benefits. We have therefore used a large range for our assumptions.
Digitalisation costs			
Direct	There should be few if any direct costs associated with		

	Description of types of costs and benefits	Assumptions made in quantification	Notes on sources
	the various digitisation measures, which would deliver efficiency gains to businesses		
Enforcement	There will be additional one-off costs for the EMA and other regulators in designing and implementing these various enhanced digitalisation measures	We have assumed the proposed online application system may cost a few millions to implement (c. €2m-€3m, the ePIL system may cost an order of magnitude more (c. €10m-€30m) and the integrated regulatory data system will be the most demanding and costly to design and implement and could cost several hundred millions across all regulators (€100m-€300m), perhaps €120m-€350m in total. We have assumed a split between the EMA (€20m-€50m) and NCAs (€100m-€300m). We have assumed these will be one-off costs - spread over several years - and may be associated with recurrent costs (operation, maintenance, depreciation) on the order of 25% of the one-off costs	We have no quantitative data on costs of benefits relating to the proposed digital measures, so have had to look at past activities for guidance. According to the EMA final-programming-document-2022-2024, the EMA Digital Business Transformation Task Force will have access to 17 staff to deliver its various digital projects, working across 7 areas, including ePIFs and electronic submissions. Annex 19 to the EMA annual report 2020 shows that the agency invested around €7m in Business-Related IT in 2019 and will spend around €20m in 2020. Annual IT spend has fluctuated substantially however, in line with various business development programmes.
Indirect	There will be no substantive indirect costs from the proposed digitalisation measures, as they will retain some aspects of paper-based systems (product leaflets) to minimise risks of digital exclusion (not all citizens have or wish to use digital platforms)		
Digitalisation benefits			
Direct	The various digital initiatives proposed will save time and cost for both businesses and regulators	We have assumed that these refinements may deliver efficiency gains to industry equivalent to 0.5-1% of their regulatory costs. We have assumed an annual efficiency gain of 1-2% for both the EMA and the NCAs	We have found no quantitative estimates of the likely benefits of these proposed measures through our consultations or literature reviews, and have had to make assumptions based on the wider literature on digitalisation and productivity. An OECD review suggests that productivity gains for businesses from digitalisation range from 1-4% on average. Greater use of e-government - as proposed here - is seen to deliver benefits on the order of 1%. The OECD is careful to point

	Description of types of costs and benefits	Assumptions made in quantification	Notes on sources
			out that these figures can differ markedly across sectors and countries, we have therefore used a range of 0.5-1%. These digitalisation proposals will impact to a greater extent on the efficiency of the regulatory system.
Indirect	There may be some limited indirect benefits in terms of accelerated procedures meaning applications are authorised several weeks earlier, which may facilitate at least some new medicines being approved for sale earlier and some generics entering the market earlier.		We have found no quantitative estimates of the likely impact of these proposed measures, and have no good basis for approximating the nature and extent of the possible indirect benefits
Enhanced support costs			
Direct	There may be some limited additional costs to businesses from greater use of advice or increased dialogue more generally	We assume this might cost business an additional €1.6m-€2.4m. The EMA is currently receiving around 800 requests for scientific advice and protocol-assistance. We have no data on the intensity of work involved in preparing the request or answering it, but no doubt a proportion will be formulated in hours while others may take several staff days to respond to. We have assumed an average of 1 staff day to prepare a request and 3 staff days to process the request (with a market value of c. €1k / staff day). We have further assumed that a more interactive approach to dialogue - and greater support for SMEs non-commercial organisations - may double of treble this level of activity, for industry and regulators. For business: 1.6m=800*1*1000*2 or 2.4m = 800*1*1000*2; For EMA: €4.8m=800*3*1000*2 or €7.2m=800*3*1000*3	We have found no quantitative estimates of the likely costs of these proposed measures through our consultations or literature reviews, and have had to make assumptions about the likely level of effort based on EMA activity statistics.
Enforcement	There will be additional costs for regulators associated with the enhanced and extended support measures	We assume this might cost the EMA an additional €4.8m-€7.2m. The EMA is currently receiving around 800 requests for scientific advice and	We have found no quantitative estimates of the likely costs of these proposed measures through our consultations or

	Description of types of costs and benefits	Assumptions made in quantification	Notes on sources
		protocol-assistance. We have no data on the intensity of work involved in preparing the request or answering it, but no doubt a proportion will be formulated in hours while others may take several staff days to respond to. We have assumed an average of 1 staff day to prepare a request and 3 staff days to process the request (with a market value of c. €1k / staff day). We have further assumed that a more interactive approach to dialogue - and greater support for SMEs non-commercial organisations - may double of treble this level of activity, for industry and regulators. For business: 1.6m=800*1*1000*2 or 2.4m = 800*1*1000*2; For EMA: €4.8m=800*3*1000*2 or €7.2m=800*3*1000*3	literature reviews, and have had to make assumptions about the likely level of effort based on EMA activity statistics.
Indirect	There will be no substantive indirect costs of these enhanced support measures		
Enhanced support benefits			
Direct	Industry - and SMEs in particular - should benefit from better and more dynamic advice avoiding queries on applications (delay) and rework to the same (cost); regulators should benefit from more mature applications that can be assessed more easily and quickly	We have assumed that these refinements may save businesses 0.5-1% of their regulatory costs annually (7.5m-15m: c. €1.5bn based on McKinsey estimate of Regulatory Costs being c. 4.1% of BERD); EMA 0.5-1%. We have assumed these measures will be of less benefit to NCAs than the more general streamlining and digitalisation measures, and so have not included a value for a benefit.	We have found no quantitative estimates of the likely direct benefits of these proposed measures
Indirect	There may be some limited indirect benefits, whereby faster assessments, on average, may facilitate at least some new medicines being approved for sale earlier and some generics entering the market earlier.	We assume the average period taken to assess applications may be reduced by 2-4 weeks. We based this 10-20 day improvement on the fact that the industry part of the assessment process is taking around 160 days on average (EMA annual report 2020) and 200 days for SMEs. If we assume 50% of the EMA positive opinions are approved and manage to come to market 2-4 weeks early, and we assume	We have found no quantitative estimates of the likely indirect benefits of these proposed measures

	Description of types of costs and benefits	Assumptions made in quantification	Notes on sources
		an average annual EU income for a medicine at 50m (c. €1m a week), that will amount to income of around €100m-€200m being brought forward. The market would be competed away 2-4 weeks earlier, so the total income may not change. But there could be first mover advantages as well as the time value of money, and so we suggest that businesses will benefit by 5% of the value of this earlier cashflow (5m-10m).	

A.8.3. Overview of costs and benefits relating to simplification and burden reduction

This annex deals with horizontal measures, which are primarily designed to simplify the regulatory system and reduce burden on industry and regulators alike. This is done for reasons of good governance but also in part to create the financial headroom to introduce new legislative actions and procedures that will bring additional costs, in line with the one in one out principle. As such, the preceding sub-sections deal extensively with simplification and burden reduction.

Table 75 represents these data for the wo horizontal measures that relate most directly to simplification and burden reduction, specifically streamlining and digitalisation measures. The table summarises the balance of costs and benefits, and suggests that the measures as proposed may deliver a reduction in compliance costs and burden in the range of €1.2bn-€2.4bn for industry. More specifically:

- The proposed streamlining procedures will yield useful cost savings for European pharmaceutical businesses, with estimated cost savings falling in the range of €1bn-2.1bn over the next 15-years
- The streamlining procedures are estimated to be cost neutral for the EMA, with investments in additional coordination structures and the development of new protocols and procedures being mirrored by broadly equivalent savings, with the balance of costs and benefits estimated to fall in the range €-4m to €2m over the next 15 years
- The streamlining procedures are estimated to be slightly positive in efficiency / monetary terms, for the national competent authorities, with investments in additional coordination and new procedures being outweighed by savings, with the balance of costs and benefits estimated to fall in the range €15m to €30m over the next 15 years
- The proposed digitalisation measures will provide relatively modest financial savings to industry, given the primary focus is on the integration of regulatory systems and platforms across the EU and support for the re-use of data (e.g. the 'Once Only' principle of the EU digital strategy). Electronic submission will deliver industry cost savings. These are estimated at €112m-€225m over 15 years

- The proposed digitalisation measures will provide similarly modest financial savings to the EMA, given the substantial costs involved in the design and development of the new systems. The savings are estimated at €65m-€70m over 15 years
- The proposed digitalisation measures will provide relatively greater financial savings for NCAs, with the EMA shouldering more of the substantial costs involved in the design and development of the new systems. The savings across the whole EU regulatory network are estimated at €700m-€1,200m over 15 years

Table 75 Overview of the costs and benefits associated with the horizontal measures related to simplification and burden reduction

	Businesses	**Businesses**	**EMA**	**EMA**	**NCAs**	**NCAs**
	one-off	**recurrent**	**one-off**	**recurrent**	**one-off**	**recurrent**
Streamlining costs						
Enforcement			€1.8m-€3.6m	€3.5m-€7.5m	€15m-€30m	€30m-€60m
Indirect						
Streamlining benefits						
Direct		€15m-€30m		€3.5m-€7m		€30m-€60m
Indirect		€55m-€110m				
Total savings		€1,050m-€2,100m		€-3.9m to €1.8m		€15m-€30m
Digitalisation costs						
Direct						
Enforcement			€20m-€50m	€4m-€10m	€100m-€300m	€20m-€60m
Indirect						
Digitalisation benefits						
Direct		€7.5m-€15m		€7m-€14m		€60m-€120m
Indirect						
Total savings		€112m-€225m		€65m-€70m		€700m-€1,200m