EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring

PHARM 780

PHARMACEUTICAL COMMITTEE
7 November 2019

Subject: **Duplicate marketing authorisations for biological medicinal products**[1]

Agenda item 5

This point was presented in the Pharmaceutical Committee meeting of October 2018. The purpose of this document is to inform Member States of the results of the targeted Stakeholder consultation[2] which took place from 18 May to 10 September 2018 and to exchange views on the possible revision of the Commission note[3] on the handling of duplicate marketing authorisation applications.

1. Background

In the framework of the centralised procedure, only one marketing authorisation may be granted to an applicant for a specific medicinal product[4]. In view of the unique nature and EU dimension of marketing authorisations granted under the centralised procedure, Regulation (EC) 726/2004 limits the ability of applicants/holders to obtain more than one marketing authorisation per medicinal product.

In particular, Article 82(1) 2nd subparagraph of Regulation (EC) 726/2004 provides that:

> *"the Commission shall authorise the same applicant to submit more than one application to the Agency for that medicinal product when there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients, or for co-marketing reasons."*

[1] This document has not been adopted by the European Commission and, therefore, it does not reflect an official position of the European Commission. It is only meant to be a tool for discussion and the views expressed therein do not necessarily reflect those of the Commission and its services.
[2] https://ec.europa.eu/health/human-use/consultations/20180518_biologicalmedicinalproducts_en
[3] https://ec.europa.eu/health/sites/health/files/files/latest_news/2011_09_duplicates_note_upd_01.pdf
[4] Article 82 (1) first subparagraph of Regulation (EC) 726/2004.

In such cases, the Commission assesses whether the conditions of Article 82(1) are met on a case-by-case, taking into account the overall objectives of preserving public health and the harmonisation of centrally authorised products[5]. In cases where the Commission agrees to the submission of a further application for the same medicinal product ("duplicate marketing authorisation"), the choice of the legal basis remains the sole responsibility of the applicant.

To be noted: Article 82 (1) concerns marketing authorisation applications under the centralised procedure. There are no corresponding provisions in Directive 2001/83/EC that apply to nationally authorised products.

2. The specific case of duplicate marketing authorisation applications (MAA) of biological medicinal products

Under Article 82(1), the Commission shall agree to the application for a duplicate if there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients. According to Annex I.1 of the 2011 Commission note on the Handling of Duplicate Marketing Authorisation Applications, "*The first introduction of a generic product by the holder of the reference medicinal product can also improve the availability of a medicinal product. This is because the first entry of a generic to the market has an impact on availability as it usually increases accessibility*".

The 2011 note did not include specific considerations with regard to biological products and/or biosimilar medicines. Granting of duplicate marketing authorisations as generics in the case of biological medicinal products has raised concerns from the generic industry. They underlined the impact this may have on the biosimilar market at national level, as only originator companies can request a duplicate of their own biological medicinal product as a generic. As national pricing, reimbursement and substitution rules in the European Union are generally linked to the regulatory status of the medicinal product, they consider that this would affect choice and competition, and also undermine the EU concept of biosimilar medicines, and ultimately may limit the range of options available to patients.

3. Results of the consultation

The Commission received feedback from 9 Member State Competent Authorities and 10 representatives of generic and innovative industries, healthcare professionals and patients organisations.

The results of the consultation are presented in a summary report which is annexed to this working document.

4. Possible revisions to the Commission note

In light of the results of the targeted consultation on the specific case of duplicate MAA explained under 2 above the Commission services are considering amending the Annex I.1. of the Commission note on duplicates relating to public health reasons along the following approach:

A duplicate marketing authorisation is an exceptional process. For duplicates (chemical or biologics) requested on the basis of public health reasons the

[5] For further details, see the Commission services note on the handling of Duplicate Marketing Authorisation Application fn. 3 (supra)

applicant should provide specific evidence with regards to the product in question to allow the Commission to verify a **positive effect on availability.** Taking into account the experience gained with market realities, the first entry of a generic on the market is not automatically considered to increase availability.

The applicant should justify why a duplicate is needed and demonstrate how a second marketing authorisation would increase availability and patient access, based on objective and verifiable reasons, as required in Article 82 (1) of Regulation 726/2004. In this regard, one possibility is to ask the applicant, as part of their justification for increased availability and patient access, to list the Member States where the "first" medicinal product is *actually* marketed and indicate where the duplicate will be made available. If the market intention does not cover the entire EU, justification should be provided and the Member States in which the product is not to be placed on the market should be listed.

5. Exchange of views

Member States are invited to:

- Comment on the proposed approach under point 4 above;
- Indicate whether they have had any further experience with duplicates of centrally authorised biological products on their markets since the public consultation ended.

Annex to the working document

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Medicines: policy, authorisation and monitoring

SUMMARY REPORT

Subject: **Synopsis of contributions received following the targeted stakeholder & Competent Authority consultations on duplicate marketing authorisations for biological medicinal products**

The arguments presented in this document are a summary of those presented by the relevant stakeholders during the targeted consultations. They do not represent the European Commission's official position and do not prejudge any decision of the Commission on the matter.

1. Objective of the consultation

From 18 May to 10 September 2018 the Commission launched a targeted consultation directed to stakeholders. The objective was to ***seek their views on the issue of granting duplicate marketing authorisations for biological medicinal products (MPs) on the grounds that they would be a "first generic".*** More specifically, it aimed to seek their views on ***the impact that such authorisations would have on the availability of biosimilars to healthcare professionals and patients***. One possible consideration was that such authorisations could have anticompetitive effects and undermine other treatment options available to patients. On this basis, the Commission presented an indicative alternative wording of Annex I (part 1) of the Commission note on handling duplicate marketing authorisation applications[6].

On 23 October 2018, the Commission circulated the above consultation document to Member State Competent Authorities in the framework of the Pharmaceutical Committee[7]. In addition, it submitted a series of questions requesting their comments and possible experience on the issue. The questions focused, among others; on the ***effect*** that duplicate marketing authorisations of generics of biological medicinal products have ***on the availability of relevant medicinal products to healthcare professionals and patients*** given the possible alternative of biosimilars.

[6] https://ec.europa.eu/health/sites/health/files/files/latest_news/2011_09_duplicates_note_upd_01.pdf

[7] https://ec.europa.eu/health/sites/health/files/files/committee/81meeting/pharm759_4iv_duplicates_en.pdf

2. Responders

The Commission received feedback from **9 Member State Competent Authorities and 10 representatives of generic and innovative industries, healthcare professionals and patients organisations.** Specifically, these are broken down to: 1 patient organisation, 1 healthcare professional organisation, 4 entities belonging to the generics industry and 4 entities representing originator companies. For more detailed information on the identity of the responders please refer to the table annexed to this note.

3. Main arguments put forward in the consultation

According to Article 82(1) of Regulation (EC) 726/2004 (the Regulation), a MP of the same applicant can only receive a duplicate marketing authorisation "[…] *if there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients, or for co-marketing reasons"*.

The current Commission note[8], in Annex I, accepts that the first introduction of a generic by the holder of the reference MP can improve the availability of the MP because such a first entry of a generic on the market usually increases accessibility.

a. Arguments that are generally in favour of a stricter scrutiny for generics of biological MPs

The arguments under this section were drawn from the input of the majority of Member State Competent Authorities participating in the consultation and stakeholders representing the generics industry, a patients organisation and a healthcare professionals organisation.

Contrary to their chemical counterparts, only originator companies can produce *generics of biologic* MPs (hereafter autobiologicals) following the procedure of Art. 10(1) of Directive 2001/83 EC (the Directive). This is because of manufacturing/technological reasons due to which only autobiologicals comply with the definition laid down in Art. 10(2)(b) of the Directive, whereas any "competing" biologic MPs can only be characterised as "biosimilars" and receive authorisations following Art. 10(4) of the Directive. This difference is the reason why autobiologicals and their biosimilar counterparts may have a *de facto* uneven position on the national market. As a result, differences among Member State health systems can influence market access for certain competing products which, in time, potentially results to an negative effect on availability of the MP to patients and healthcare professionals.

The impossibility to characterise biosimilars as "generics" has repercussions on a series of factors that influence market access. The most important factors reported are the following:

- **Differences in the investment/development and authorisation phases**
  Contrary to generics of biological products, which may benefit from the Art. 10(1) derogations relating to pre-clinical tests and clinical trials, biosimilars have to invest time and money for pre-clinical tests and clinical studies demonstrating biosimilarity to the reference MP. As such, they are subject to additional costs

[8] Cf. footnote 1

and time losses in the investment/development and authorisation phases, which also has an impact on their marketing value and market penetration capabilities.

- **Eligibility for pharmacy substitution**
  The vast majority of EU MSs either do not allow pharmacy substitution for biosimilar medicines or such substitution is not practiced.· Whereas when a MP is characterised as a "generic", substitution is in principle automatically allowed as generics benefit from the premise that they are exact copies of the innovative product. The result is that when it comes to substitution practices, autobiologicals are placed on a privileged position compared to biosimilar MPs.[9]

- **Clinical medical supervision**
  Placing autobiologicals on the market with a generic "status" can reportedly affect the decision making of physicians and clinical decision makers in treatment monitoring. This is partly because it opens the way for misconceptions by medical practitioners (and patients) as to the differences of therapeutic properties between autobiologicals and their bioequivalent MPs. In effect, the bioequivalent alternative can erroneously be regarded as a less effective treatment compared to the original and its generic (true) copy.

- **Pricing policies**
  An autobiological MP will almost certainly be marketed at a lower price than its reference product. It is common for generic medicines to have a mandatory price decrease compared to that of the originator medicine ("price linkage" markets). Biosimilars may also be subject to price linkage, but the originator price list decrease applied for generic medicines is typically much bigger than that observed for biosimilars[10]. The resulting situation would allow originator companies to severely undercut the price of potential biosimilar competitors while allowing the reference originator product to maintain a high price. Such practices could be a tool for the originator company to capture the market more effectively.[11]

- **Tendering/procurement procedures**
  The tendering systems in MSs can be multi winner or single winner tender systems; INN-based or not. In single winner/INN-based systems autobiologicals and biosimilars compete for the tender regardless of their regulatory pathway. In this context, concerns may arise when autobiologicals are used as a tool to influence pricing dynamics to drastically reduce the market value for the first biosimilar medicine. In another example, in multi winner systems (e.g. Italy) both the originator MP and its autobiological can theoretically participate in and win the tender process. In such a case, the originator company would essentially be competing against itself with two of its own MPs, possibly even produced in the same manufacturing plant. Such practices can be unfavourable to competitors and may also lead to supply disruptions.[12]

[9] In 5 EU MSs there is a clear or potential competitive disadvantage for biosimilars.

[10] N.B: this reference refers to price reductions observed in *chemical* MPs. Steep price differences are not necessarily observed in the case of autobiologicals given the high production costs for those molecules.

[11] In 17 EU MSs there is a clear or potential competitive disadvantage for biosimilars according to one submission.

[12] In 12 EU MSs there is a clear or potential competitive disadvantage for biosimilars according to the generics industry.

- **General remarks made by stakeholders and certain member states**

Even though the introduction of autobiologicals in the market can *initially* have a positive effect on availability, *in the long term* they may have a negative effect on the availability of biosimilars. This also opens up the possibility of undercutting competing MPs through anticompetitive pricing practices such as price dumping in tendering processes.

Two stakeholders expressed the view that the Commission should take measures to level the playing field. Duplicate requests should not be accepted solely on the basis that the product is a first generic of the reference MP. It was also mentioned by one stakeholder that a duplicate authorisation should lose its validity once it is proven that biosimilar alternatives exist at a sufficient quantity to adequately meet demand. The same respondent also contended that to solve the problem at hand, the Commission should go even further, questioning whether biological MPs should be allowed to receive generic status at all. A similar argument expressed advocates that duplicate authorisations for biologics shouldn't be based at all on Article 10(1) of Directive 2001/83/EC. The dichotomy **reference medical product vs generic** (for chemical MPs) can only be mirrored by **reference medicinal product vs biosimilar** (for their biological counterparts). An introduction of a third category of autobiologicals would in essence be contrary to the system created by Articles 10 and 82(1) of the Directive and Regulation respectively.

b. Arguments that are generally against a stricter scrutiny for generics of biological MPs

The arguments under this section mostly reflect the views of originator companies.

- **Generics of biological MPs inherently improve availability and should be treated in the same way as their chemical counterparts**

Article 82(1) of the Regulation allows for the provision of Duplicate MAs for medicinal products under certain circumstances, this includes generics of biological MPs. Public health reasons, in particular regarding the availability of medicinal products to healthcare professionals and patients justify such practice.

The first introduction of an autobiological will inherently increase availability of the said medicinal substance on the market, as it will be marketed *in addition to* the reference biological product as well as any other possible competing products. Such an addition will have a positive effect on availability for patients and healthcare professionals.

Furthermore, any duplicate authorisation for a first generic can be granted with a full label, without carving out any indications that may be covered by patent protection for the innovative product. This may lead to an increase in availability and accessibility for a larger section of the patient population.

It follows that when it comes to duplicate Marketing Authorisations, from a legal standpoint; generics of biologicals medicinal products should not be treated any differently from their chemical counterparts and should be subject to the exact same authorisation criteria. This is because generics of biological medicinal products are not

any different from their chemical counterparts in terms of the effect they have on availability. There is, therefore, no reason to exclude biological products from the application of the duplicate guidance, or require any additional evidence over and above what is provided for small molecule products. Proper substantiation and provision of sound evidence should support all duplicate applications when concerning generics (biologicals or other).

- **The practical difficulty of providing evidence and substantiation – demand for clarity**

The change the Commission proposes in the body text of Annex I is as follows: "*Requests for duplicate marketing authorisations need to be properly substantiated and based on sound evidence*". The standard applied under this wording is quite high. This creates a practical problem for the applicants as well as potentially the Commission as it is hard to apply such a standard in practice.

It is not clear how a marketing authorisation holder (whether for a small molecule or a biological product) will be able to provide reasoning that is "properly substantiated and based on sound evidence". Especially when such reasoning relates to the launch of a product that has, by definition, not yet been authorised, and where the pricing negotiations that follow vary from one Member State to another and are unpredictable in outcome. The outcome will often affect the decision whether to launch the MP in a particular Member State. As such, the marketing authorisation holder will not be able to provide "sound evidence" of the extent to which the authorisation will increase availability. If the Commission applies the proposed wording, it needs to clarify what "*properly substantiated*" and "*sound evidence*" actually entail.

- **Issues created by changing the established practice**

The current logic has been the guiding force in the application of Article 82(1) and has been followed by the Commission for years. It is currently reflected in its 2011 guidance, which was issued at a time when biological medicinal products were well known and were already available on the market.

The proposed revision of Annex I to the Commission note on Handling of Duplicate Marketing Authorisation Applications will change the established practice used to apply the legal provision of Article 82(1). Any change to such practice needs to be properly justified, clearly stating the reasons why the introduction of a first generic of a chemical medicinal product is considered to improve the availability of the product and why, either in general or under specific circumstances, the introduction of a "first generic" of a biological medicinal product is not. Such a substantiated approach is also required if the Commission is to respect the principles of equal treatment and protection of legitimate expectations of applicants.

Finally, a procedural point made by one stakeholder pertains to the scope of the Commission consultation. The targeted consultation asks stakeholders to comment on a specific provision of the Commission note and a proposed change to how the Commission makes the public health assessment when examining applications for duplicate marketing authorisations relating to biological medicinal products. Any outcome of the consultation should be restricted in affecting this specific issue and

cannot entail changes to other items included in the document unless proper consultation takes place.

c. Member State Competent Authorities' experience and specific comments

The specific consultation launched towards National Competent Authorities focused in particular on the following issues:

- Their views on the impact of duplicate marketing authorisations of biological medicinal products on the availability of biosimilars to healthcare professionals and patients.
- Their experience on the first introduction of generic MPs in terms of availability of the MP to patients.
- Their experience in terms of increase of availability when it comes to autobiologicals.
- Their opinion on whether the Guidance should address the specificities of biosimilars.

The feedback received from National Competent Authorities (NCAs) showed that there is no experience on the actual effect duplicate authorisations for autobiologicals have on availability. At least in the framework of this consultation no such actual/practical cases were mentioned.

Even though, in principle, the first introduction of a generic MP (chemical or biological) improves availability and reduces prices. The first introduction of a generic (chemical or biological) medicinal product *per se* improves availability to patients as there is usually a mandatory price reduction on generic products. The originator however does not have an interest to keep prices low permanently. A duplicate could be used as a vehicle to deter competing biosimilars from entering or staying on the market. Therefore, the introduction of an autobiological on the market can have (theoretically at least) negative effects on availability in the long term as biosimilars have a proven record in improving availability.

With the exception of Hungary, all Member State NCAs that participated in the consultation agree that the Commission guidance needs to be revised. One Member Statre argued that any revision of the note should also aim to clarify the scope of Article 82(1) with reference to all the potential inclusion and exclusion criteria. If necessary, the guidance should include in what scenarios such criteria would be applicable. Another Member State puts in question whether a duplicate MA should be provided on the basis of Art. 10(1) in cases where the request is made near or after the end of the patent term/exclusivity period, or even whether biological MPs can be given "generic" status at all unless the applicant is able to show that the manufacturing method is also identical to the reference product.

Almost all respondents agreed that more clarity is needed on what "*properly substantiated*" and "*sound evidence*" actually entail. Terminology on this issue also needs clarification. There are many emerging terms used by relevant actors which are not seen in the legislation and can be confusing. Such terms include "autobiologicals", "biosimilars", "biogenerics", "autobiosimilars", "autogeneric", "bioidentical", "biosimilar generics" etc. A discussion among NCAs and the Commission would be opportune and would help to increase transparency and respond to these questions.

4. Conclusion

Representatives from the generics industry, healthcare/patients organisations and the majority of the Member State Competent Authorities that participated in the consultation consider, in principle, that duplicate authorisations for generics of biological MPs have a potential negative effect on availability, especially in relation to the availability of biosimilar alternatives on the market. According to this logic, the introduction of an autobiological cannot be assumed to have an automatic positive effect on availability and it would be for the applicant to demonstrate that this is the case.

Representatives of originator companies consider that the current long-standing practice accepts that duplicate MAs for a first generic will generally have a positive effect on availability and that there are no objective reasons to treat biological generics differently than their chemical counterparts. Consequently, the first introduction of an autobiological should be regarded as having the same positive effect on availability as it is currently assumed for generics of chemical products and that proper substantiation and evidence should be a requirement for both chemical and biological generic MPs authorised under article 82(1).

Specifically regarding the experience gained on the subject, it seems that a majority of Member State Competent authorities that responded to the consultation recognise that autobiologicals have a potential to adversely affect availability in the long run. Most arguments however are made on a theoretical basis, as there is still not enough experience to draw practical conclusions on the issue.

Finally, the vast majority of stakeholders consulted are of the opinion that more clarity is required as to how the legal provision of Article 82(1) is to be applied and specifically what will “properly substantiated” and “sound evidence” actually entail.

Annex (1): Table of contributions received

Annex

Synopsis of contributions received following the targeted stakeholder & Competent Authority consultations on duplicate marketing authorisations for biological medicinal products

Company	Category	SME	Transparency register ID Nr.
European Association of Hospital Pharmacists (EAHP)	Healthcare professional organisation	N/A	82950919755-02
European Cancer Patient Coalition (ECPC)	Patient organisation	N/A	-
KERN Pharma S.L.	Generic industry	NO	-
Medicines for Europe	Generic industry	N/A	48325781850-28
ProGenerica e.V.	Generic industry	-	-
WinMedica	Generic industry company	YES	-
European Biopharmaceutical Enterprises	Originator companies	N/A	768792210017-73
European Federation of Pharmaceutical Industries and Associations	Originator companies	N/A	38526121292-88
Pfizer N.V.	Originator company	NO	4263301811-33
Sanofi	Originator company	NO	61291462764-77

Member State Competent Authorities that replied to the consultation:

Belgium, Denmark, Spain, Finland, France, Hungary, the Netherlands, Portugal, Sweden