The present document summarises the responses to the questionnaire circulated in December 2016 to STAMP, EUneHTA and CAPR members

Individual responses to the questions are in attachment.

Prescription control to the initially licensed population

One of the points raised in the Adaptive pathways discussions at STAMP was whether control to the initially licensed population was feasible, and whether there would be a substantial risk of off-label use.

Factors that may influence prescription and its control are: frequency of disease, precision of diagnosis, availability of therapeutic alternatives, price and reimbursement, point of dispensing (hospital, specialised doctor), societal pressure and expectations.

Prescription control is considered generally not achievable for private prescription

In many countries, once the drug is approved, any physician can prescribe it under their own responsibility; in others it is considered that a restricted medical prescription is an adequate way to ensure control.
Some MS feel that the adaptive pathways approach would not pose a problem in this respect, while others feel that in practice the prescription controls have been shown difficult to implement and their effectiveness hard to monitor.

Reimbursement restrictions can have a steering effect, but there are doubts whether they are adequate to ensure *full* control. This is easier in MS where a single public fund with a single informatic system has been set up. In an extreme case (DE), even off-label use (under prescriber's responsibility) can be covered by the health insurance if no alternative treatment is available.

Setting up a registry is a way to control prescription, and the Italian experience is significant in this respect, even allowing distinction between different indications for the same product. It was also suggested that a less resource-intensive scheme could be modelled on the traceability schedules in place for medicinal blood products (e.g. coagulation factors

Certain therapeutic areas (e.g. oncology, Hepatitis C) are more viable for effective prescription control, as there is a need to strike a balance between the resources required to achieve the control and the cost of the drugs. For high cost drugs, or specialised healthcare areas, registers and electronic prescription methods are more likely to have been set up in the MSs (see also electronic prescriptions below).

In Italy, under certain circumstances an "authorised" off label use can take place under a managed entry agreement set up for data collection.

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Importance of the SmPC wording, and communication to prescribers

To achieve prescription control to the initially licensed population the specific conditions for drugs approved under adaptive pathways must be appropriately communicated to both healthcare professionals and patients.

Further efforts to improve sections 4.2 and 5.1 of the SmPC would be auspicable, so that the indicated population is unequivocal. Important elements to clarify are the kind of pre-treatment, the combination with other medicines, treatment duration or number of cycles, the investigated population and transferability to other populations.

Electronic prescription and electronic data capture

This is a vital element to implement prescription control and efficient observational data capture, which are resource intensive activities. It is also important for monitoring the effectiveness of the prescription control measures. However, in countries where prescriptions are mostly manually generated, there is little or no facility for point-of dispensing arbitration or approval.

Electronic prescriptions should contain details of the treatment indication, which is imperative to restricting medicinal products to licensed indications for the purpose of reimbursement. In some cases only indirect, *a posteriori* analysis of registries can give the information whether the intended indication restriction was respected.

For products with multiple indications, these should be distinguishable, and the Italian experience on registry has shown that this is possible.

The investment in infrastructure and administration should be considered, together with a clear methodology and harmonisation/interoperability of systems. These systems should also be interlinkable to registries so that the data for the prescription can be utilised for effectiveness analyses

Registry data and their ownership

Drug-product Registries that systematically collect data on all eligible patients are a tremendous resource for capturing important information on safety. Patients treated in real life and tracked by Registries differ, on average, from those enrolled in RCTs with regards to complexity of their underlying disease, comorbidities, and concomitant medications. Drug product Registries, by definition, focus on patients treated with a given medicinal product.

The Italian experience of using standardized eligibility criteria within treatments with different drugs for the same therapeutic indication allowsnot only to analyse the real life outcome for a given drug, but also to compare the different treatment options (e.g. with the use of match paired analysis). Furthermore it is also possible to describe the various treatment pathways used in clinic practice for specific therapeutic indication and measure their respective outcome.

AIFA Registries are also used to increase awareness of prescribers on safety concern and Risk Minimisation Measures in order to optimize the safe and effective use of drugs.

Data quality was mentioned by several responders as a major challenge, and an analysis of some examples is ongoing in the EMA registries pilot. Insufficient data, no comparator data, no quality of life data, incomplete patient records are all important for quality data.

At present in many cases when a company finances the data collection, they own the data and the government receives only coded data. Transparency is considered important in all

cases, and in particular if there is public funding the data should be accessible by the public bodies. In Italy the data collection is financed by the MAH, but the data owned by the government. It was considered important that this access is granted for decision-making in other areas (cost effectiveness, pharmacovigilance, etc).

Even academic groups are sometimes an obstacle to data access, being unwilling to release data before a publication has been made.

Disease registries are more frequently publicly accessible. An example of positive experience is the registry of all pregnancy-related medications in Finland. It is publicly funded and administered, and from the registry data can be released against a fee (even to industry for MAA purposes).

The issue of data protection and anonymization of data must be considered, and is particularly important in case of very rare diseases where patient identification may be easier. The possibility to link different sources via, e.g., national personal identification numbers however allows more complex outcome data analysis on disease characteristics, comorbidity, treatment, adherence etc

How to ensure RWD are gathered after the initial authorisation

- The existence of a legal framework for registries greatly facilitates data collection (Italy)
- The plausibility and feasibility of the registry, with consideration to the health care system burden and deviation from clinical practice are important.
- Do not directly put the new pharmaceuticals within the reimbursed system, but link link funding to research for a limited period.
- substantially decrease the price for the initially licensed population so that there is a clear incentive for the market authorisation holder to provide additional research data.

Registries linked to Pay-per-performance, risk sharing

Eleven MS responded that they had experience with such schemes, while seven responders said that these are not yet in place, but they are reflecting on the issue or implementation has just started.

In general, the collection of real world effectiveness data is considered important, particularly in the case of Adaptive pathways where early clinical data could be the basis for approval.

Managed Entry agreements (MEA) can be based on different models of reimbursement:

1. Cost sharing (CS) - provides a discount on price of first courses of therapy for all patients eligible for treatment, as identified by the Summary of Product Characteristics
2. Risk sharing (RS) - compared to the previous, the discount applies only to non-responders
3. Payment by result (PbR) - extends the terms of the RS, providing for full refund from the pharmaceutical company on all "non-responders" (100% of treatment failures).

Pay-per performance usually requires clinicians to provide additional clinical details and this has proved difficult to date. Where the performance measure can be collected without placing additional administrative burden on clinicians (or independent of clinicians) it is somewhat easier to collect the indicators e.g. Sustained Virologic Response Weeks 12’s for hepatitis C, or survival rates for certain cancers. The success of a post-authorisation data

collection measure depends strongly on the buy-in from physicians and patients: it should not deviate too much from current clinical practice.

Both resource investment and the choice of agreed, clear-cut and actionable performance measures are important considerations when setting up such schemes. This would facilitate subsequent decision-making by regulators and HTAs. When the scheme comes to an end, payers often experience difficulties in getting partial reimbursement from the pharmaceutical companies in the cases where such payments are required by the terms of the scheme.

Risk sharing schemes are where budget caps or price reductions are negotiated before the introduction of the technology, and are the simplest to implement. They are less open to argument since, invariably with pay-per performance, issues will arise around sharing of sufficient data to assure pharmaceutical companies that any non-pay due to poor performance is robustly supported by evidence. They normally do not affect the actual practice of treatment in the hospitals and do not add the burden of additional data collection, however, these schemes miss the opportunity of RWD collection.

In some countries performance based schemes do not fit within the current way of funding, for instance in hospital care. Experience in the Netherlands has shown that although this is technically possible, the additional burden for the different stakeholders like physicians, hospital pharmacists and hospital administrators is substantial. To make these schemes work, they would need to fit in the funding mechanisms within hospitals.

There seems to be little or no experience on collection of data from compassionate use programs, and this could be an area worth of further exploration.

From the answers to Q2, the impression is that that in many cases there is a division of competencies within a MS and that there are instances of performance data collection required by HTAs and payers where the information would not be fed back to the EU regulatory authorities for consideration in the labelling, but be used mainly for reimbursement decisions. Also, the relative ease to implement a price cap/reduction as compared to a pay-per-performance scheme may make them an easier to negotiate solution for drugs with marginal benefit, where instead the data collection on real life effectiveness would be of interest to EMA. This could be a missed opportunity and STAMP may wish to discuss.

Critical stakeholder engagement

To engage all critical stakeholders is important to clearly identify those are really relevant in the process (as few as possible, as much as needed); and to allow them to participate in the process from the very beginning.

For productive engagement, all stakeholders, including patients and healthcare professionals, must perceive a benefit. The views of patients and their risk perception are very important, as well as their understanding that if the product does not fulfil its promise, it may be withdrawn from reimbursement or from the market.

In addition, alignment of different stakeholder’s processes needs to be explored. There may be barriers in terms of balancing opportunities for stakeholders to participate with providing timely outcomes, and managing issues around sharing of information, especially where manufacturers regard some information as being commercially sensitive.

Another concern is the AP procedures would add complexity and cause extra work load and new expertise requirements for regulators (especially regarding PhV monitoring), HTA bodies, and payers, in light of repeat cycles of assessment and negotiations with sponsors.

It is essential that public organisations continue to ensure they have sufficient resources to be able to participate in meeting in an advisory capacity. Funding options for patient, HTA, and payer participation in Adaptive Pathways needs to be addressed.

HEALTH TECHNOLOGY ASSESSMENT (HTA) COMPETENCE AND CAPACITY

Overall, the feedback in relation to existing HTA competence and capacity has been positive. Germany for example has well-established and highly experienced HTA bodies, considering the high and reliable standard of the EU marketing authorisation concerning drug quality, clinical evidence and safety as an important achievement and as the basis of their work. In ES patients associations, scientific and professional societies and the holder of the marketing authorization participate in different stages of compiling the final report as well, which can be considered an example of work sharing in the HTA field. The availability of these reports facilitates not only the pricing and reimbursement decisions but also the incorporation of the medicinal product into clinical practice. Finland on the other hand would prefer taking part to AP on a case-by-case basis.
French HTA and AIFA have the competence to participate in AP procedures, as they have already been involved in the EMA AP and EMA-HTA parallel scientific advice pilot. In addition, NICE has recently established an Office for Market Access that offers a broader range of services and support to companies and through which NICE engages and facilitates contact with different stakeholders. NICE therefore has the necessary competence and capacity to participate in adaptive pathways procedures. Hungary aims to increase capacity of HTA department.

EXPERIENCE AND CAPACITY OF NCA's IN EARLY SCIENTIFIC ADVICE/ADAPTIVE PATHWAYS

For countries such as Austria and Spain who are represented in the Scientific Advice Working Party of EMA, most of these members have significant experience and contribute very actively to the working party and some are directly involved in the adaptive pathways pilot project. Teams of assessors are working together with the representatives in the SAWP to cover all parts of drug development (quality, nonclinical, clinical, statistics, pharmacovigilance – new chemical entities/generics, biologicals/biosimilars, orphans, paediatrics, advanced therapies, herbals). NCA's also support scientific advice and the independent clinical research units, HTA activity, and actively collaborate with the units responsible for the availability of medicinal products under special situations (compassionate use and foreign medication- off label and not authorized products) .

On the other hand some of the smaller NCA's do not have the experience at the national level to take on early scientific advice connected to adaptive pathways and UK for example being one of the larger NCA's currently cannot be certain what can be achieved in respect of understanding efficacy through observational research and the scenarios in which pre-licensing uncertainties might be accepted with the promise of enhanced post-authorisation data. Hungary believes that colleagues should be trained on adaptive pathways and additional human resource should be dedicated to this approach.

Challenges linked to the Adaptive approach, particularly from small NCA perspective.

It was found that one of the biggest challenges especially amongst small NCAs is the required flexibility in timing of individual procedures and the difficulties in allocating resources. Delay in submission is an issue for several types of procedures in the regulatory system and happens on an almost regular basis for centralised marketing authorisation applications, less often for scientific advice submissions. This challenge may also be an issue in the adaptive pathways approach, where multiple and flexible scientific advice meetings are foreseen and various stakeholders need to be aligned for each individual target date. The

major hurdle for SMEs (and spin-offs in the academic field) will be to access information on adaptive pathways. Many of those SMEs do not regularly follow EMA communication and publications. This might be an important role for national activities.

Another reported potential challenge, especially for small NCAs could be the capacity to actively participate in all the steps and also in the capacity to give advice on post-marketing studies/registries, which is something relatively new and peculiar to adaptive pathways. As a small NCA has limited experience and resources, the proposed adaptive pathways procedure will rely largely on NCAs.

One of the major challenges would be cross ministerial work and liaison with other national bodies which are currently either involved in the reimbursement decision process (Ministry of Health) or which have never yet been involved in such a decision. A revised system of the process of the decision making involving a number of stakeholders would be required.

Another challenge for small NCAs would be the lack of technical expertise for the assessment of some types of products:

•An adaptive approach requires exploring all available options in order to map out a bespoke route to a marketing authorisation. This will necessarily be more resource intensive than the traditional way of working, not only for NCAs but also for HTAs and payers. It must be carefully guarded that this increased effort does lead to timelier patient access and more reasonable prices.

•International collaboration is a key for smaller countries. For HTA in a smaller country such as the Netherlands, issues like resources, competence, and sufficient patient data are crucial to bring adaptive pathways forward. This is only possible in collaboration with other involved Member States

•The issue of the consequences if the "real-life" data, e.g. from registries, are unfavourable for the medicine:

- Will these data be acceptable for the company to accept delisting, or will they argue that the quality of "real-life data" is not adequate?
-There is always the issue of the effects of delisting on patients.

The possibility for a small single nation to influence the global general development plan may be perceived to be very limited. Small NCAs, in countries representing smaller markets, may from that perspective have a special challenge. In order to overcome these challenges it was suggested that offering the support of adaptive pathways to small and medium enterprises (SMEs) early (after proof of principle) is expected to bring significant benefit.

According to Hungary, additional human and ICT resources are needed for NCA including HTA department-no previous experience regarding establishment and maintenance of registries.

PROVISION OF SCIENTIFIC ADIVCE FROM NCA's TO SME's AND ACADEMIA IN HOME COUNTRY

The majority of countries with experience and capacity in scientific advice/adaptive pathways will offer national scientific advice to applicants including large pharmaceutical companies as well as SMEs and academia. The advice given is provided on demand, and focused specifically on the academy, university, hospitals and other non-profit organizations that may require additional support for research and development of innovative projects. Some NCAs may offer this SA free of charge (e.g. France and Portugal) in order to major

therapeutic innovations, unmet medical need in severe conditions, rare diseases, and paediatric developments. Other NCAs on the other hand (e.g. AIFA) may provide a fee reduction (-25%) for SMEs and Public Institutions and some may not provide a fee reduction or waiver for either SMEs or academia (e.g. UK).

Smaller NCAs are not in a position to provide formal scientific advice e.g. Latvia and Romania.

Other comments

HTA-Bodies have proposed that regulators may/should share assessment reports in draft status (e.g. day 120, possibly day 80). This might speed up and facilitate assessment by HTA-Bodies. Vice versa, HTA-Bodies could be invited to comment DURING the regulatory assessment, e.g. based on day 120 for day 180 ("late dialogue" as supplement to early dialogue in adaptive design). Some of the concerns relate to the HTA involvement and centralised collection of data for reimbursement purposes, as it remains unclear whether such data would meet all the needs of the national reimbursement and pricing authorities

There is currently no formal process for linking expensive high technology and hospital drugs with real world patient outcome data and analysing it, with the exception of a number of specific research databases. In many cases, existing databases were not originally set up for this purpose and therefore not all required data is currently collected. Therefore, it would be useful to determine how other Member States have, or propose to, resolve such difficulties in order to make adaptive approaches more feasible.

Some other aspects that should be investigated at MS level:

1. Regional involvement
2. Health manager involvement (at hospital and territory level)
3. Data collection: drug-based or disease (therapeutic indication)-based
4. IT system & web platform
5. MEAs application
6. Pricing & reimbursement aspects
7. Innovation criteria (PRIME scheme)
8. Analysis of data collection: timing and updating (pricing & reimbursement re-negotiation).
9. liaise with academic institutions that organise translational research.