Adaptive Licensing – A new approach in medicinal product authorisation

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Meiner Familie

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List of abbreviations

AL	Adaptive Licensing
BPWP	Blood Products Working Party
CHMP	Committee for Medicinal Products for Human Use
CMA	Conditional Marketing Authorisation
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
HTA	Health Technology Assessment
IMA	Initial Marketing Authorisation
MA	Marketing Authorisation
MIT	Massachusetts Institute of Technology
MP	Medicinal Product
NEWDIGS	New Drug Development Paradigms
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
PK	Pharmacokinetic
PL	Package Leaflet
PAM	Post-Authorisation Measure
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
R&D	Research and Development
RCMA	Renewed Conditional Marketing Authorisation
RMP	Risk Management Plan
RMS	Risk Management System
SEED	Shaping European Early Dialogues for Health Technology
SMA	Subsequent Marketing Authorisation
SmPC	Summary of Product Characteristics
US	United States
USD	United States Dollar

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1. Introduction

1.1. Trends in pharmaceutical Research and Development

Over the last decades, a variety of scientific and technological advances providing the basis for successful and efficient efforts for developing innovative medicinal products (MPs) have been achieved. These improvements include, for example (1):

- Utilisation of combinatorial chemistry
- Acceleration of DNA sequencing techniques
- Development of high-throughput screening

These achievements have substantially facilitated the expansion of chemical libraries, identification of drug targets, testing of compound libraries against protein targets, etc. Moreover, the scientific knowledge on mechanisms underlying various diseases and new MP targets has dramatically increased during the last years (1).

However, in parallel the number of new chemical and biological entities brought to the market has leveled off in the past (Figure 1), even though pharmaceutical Research and Development (R&D) expenditure has continuously increased (Figure 2) (2).

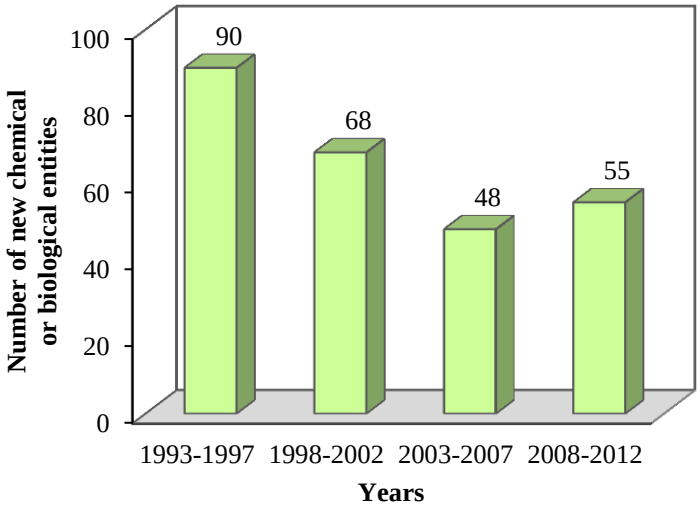


Figure 1: New chemical or biological entities brought to the market
Number of new chemical or biological entities brought to the market in Europe within the time period from 1993 to 2012. Source of data: EFPIA – The Pharmaceutical Industry in Figures – Key Data 2013 (2).

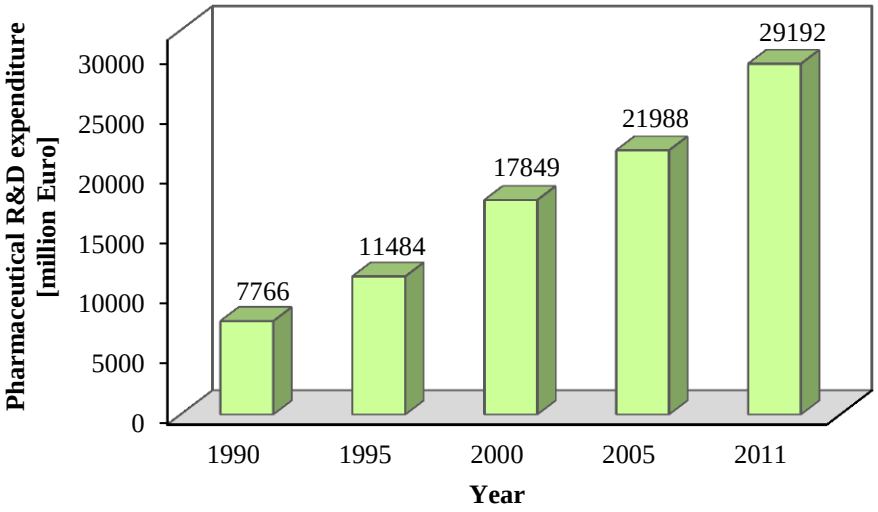


Figure 2: Pharmaceutical R&D expenditure
Pharmaceutical R&D expenditure in Europe within the time period from 1990 to 2011. Source of data: EFPIA – The Pharmaceutical Industry in Figures – Key Data 2013 (2).

Correspondingly, the financial investment required in order to bring a new MP to the market has steadily increased over the past three decades (Figure 3). In 2012, the cost of developing a new chemical or biological entity was estimated at €1.172 billion ($1.506 billion) by the Office of Health Economics in London (2). Even higher numbers have been proposed by the InnoThink Center for Research In Biomedical Innovation that calculated the costs for developing an average MP by a major pharmaceutical company amounting to at least $4 billion, but it could be as much as nearly $12 billion (3). By implication, the number of new MPs approved per billion euro or US dollar (USD) spent on R&D has substantially decreased during the last years. This development represents a considerable decline in pharmaceutical R&D efficiency.

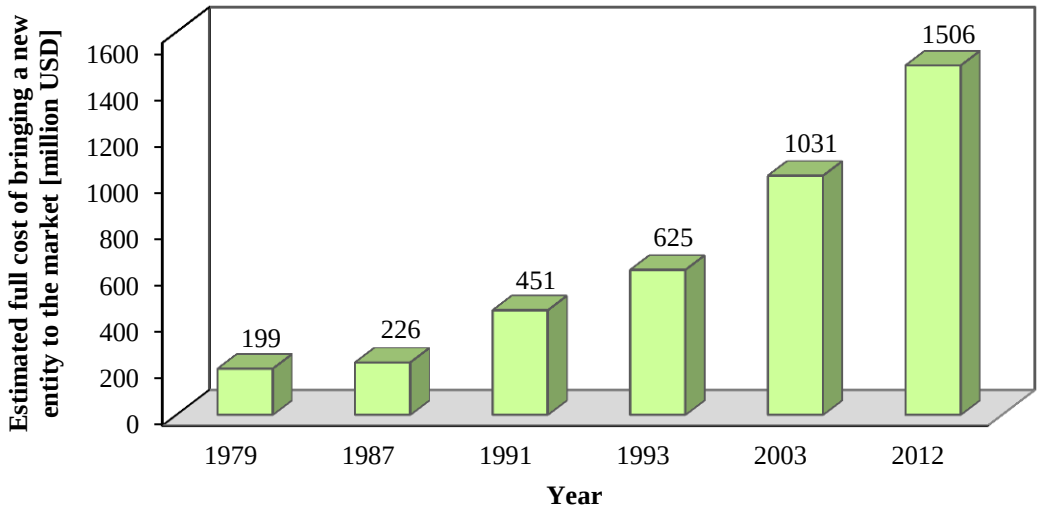


Figure 3: Estimated full cost of bringing a new entity to the market
Estimated full cost of bringing a new chemical or biological entity to market within the time period from 1979 to 2012. Source of data: EFPIA – The Pharmaceutical Industry in Figures – Key Data 2013 (2).

1.2. Initiative for Adaptive Licensing in the European Union – the European Medicines Agency Road Map 2015

The mission of the European Medicines Agency (EMA) is "to foster scientific excellence in the evaluation and supervision of medicines for the benefit of public and animal health". This results in a variety of guiding principles including a strong commitment to public and animal health as well as the support of research and innovation to stimulate the development of better medicines (4). However, this places regulators in a dilemma between providing patients with timely access to new MPs and the requirement of a data package that is as complete as possible prior to MP licensing.

In order to comply with its mission, the EMA developed a longer term strategy in 2005 focusing on the protection of public health, improvement of the regulatory environment for MPs and facilitation of innovation, research and development in the European Union (EU). In continuation of this strategy "The European Medicines Agency Road Map 2015: The Agency's Contribution to Science, Medicines, Health" was published in 2010 (5). Within this document the Agency has identified three strategic areas that represent the focus of the EMA's main initiatives and activities from 2010 to 2015 (5):

- Addressing public health needs
- Facilitating access to medicines
- Optimising the safe and rational use of medicines

For each of these three strategic pillars, various activities and tasks have been provided that serve to achieve the targeted objectives. Interestingly, within the strategic area of facilitating access to medicines – among other proposals – in-depth reflections about a more "staggered approval" of MPs are listed. According to the Road Map 2015, this approach would be characterised by an approval for a better defined / more restricted population of good responders followed by the broadening of the approved target population in the post-authorisation period, when more "real-life data are available" (5). This concept of adaptive licensing is further described in the EMA's document "From Vision to Reality", which was created for the purpose of facilitating the implementation of the EMA's Road Map 2015 (6). According to this document, the "balance between early approval with limited data and later approval with a more extensive data package" should be explored. For this purpose, the following targeted activities have been defined (6):

- Consideration of the advantages and ways of functioning of early authorisations of MPs in restricted populations
- Investigation of the broader applicability of the "staggered approval" concept and preparation of guidance on this issue

1.3. The concept of Adaptive Licensing

During the last years, a variety of proposals for potential adaptive approaches to future MP licensing have been put forward. These concepts of Adaptive Licensing (AL) have been published under various labels, including the EMA's "staggered approval" approach. An exemplary list of different labels for AL proposals is presented in table 1. Though deviating in detail, all proposals provided below are based on the fundamental idea that knowledge about new MPs evolves continuously over time rather than representing a binary process (7).

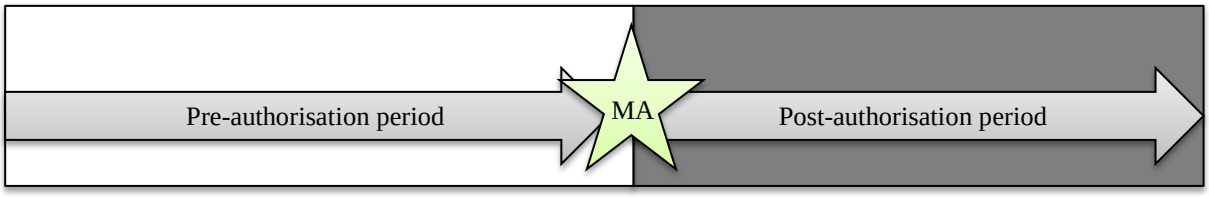
Source	Name of the proposed concept
European Medicines Agency (EMA)	Staggered approval
US Food and Drug Administration (FDA)	Progressive reduction of uncertainty
Health Canada	Progressive authorisation
Health Technology Assessment International	Managed entry
MIT / NEWDIGS	Adaptive Licensing

Table 1: Examples of international proposals for AL approaches
Proposals for adaptive approaches to MP licensing from various sources all over the world (modified from Eichler et al., 2012 (7)). MIT / NEWDIGS, Massachusetts Institute of Technology / New Drug Development Paradigms.

Under the traditional, binary regulatory approach, the life cycle of a MP is divided into two distinct phases – the pre- and the post-authorisation period – separated by the "magic moment" of the granting of a marketing authorisation (MA) (Figure 4). At this particular time, the status of a new pharmacological therapy is raised from "experimental" to "safe and efficacious" and the exposure to the new MP is expanded from a relatively small number of clinical trial subjects to millions of real-life patients. While clinical trial subjects are required to give informed consent, meet specific, predetermined inclusion criteria and fail to meet defined exclusion criteria, the situation changes immediately upon regulatory approval (the "magic moment") (7).

In contrast to this traditional approach, AL is based on the concept of replacing the key event of receiving a single MA by a progressive management / reduction of uncertainty as well as iterative periods of data collection and regulatory assessment resulting in the adaptation of the MA. Thus, the basic principle of AL is the idea that evidence generation in MP development is a continuum and, consequently, MP licensing should follow a stepwise approach characterised by continuous learning about a MP (Figure 4) (7). However, this approach is accompanied by an acknowledged level of uncertainty. Therefore, AL aims at balancing timely access of patients to new MPs with the need for adequately evolving risk-benefit data ("access versus evidence") in order to facilitate reasonable patient care decisions for the benefit of public health.

Traditional, binary approach



AL

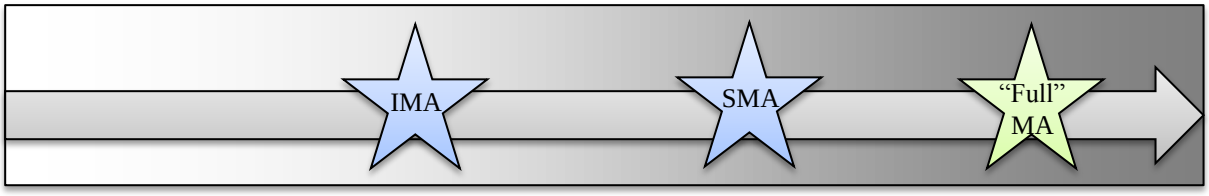


Figure 4: Comparison of the traditional, binary MP licensing approach and the AL concept
Depictive representation of the binary MP licensing approach versus AL, which constitutes a staggered approach of MP licensing characterised by the granting of an initial MA (IMA) followed by a single or various subsequent assessment and authorisation steps (SMA, subsequent MA), ultimately resulting in a "full" MA.

1.4. Aim of the Master's Thesis

Pharmaceutical R&D has been confronted with a considerable efficiency crisis during the last years. Obviously, significant countervailing forces have outweighed the scientific and technological progress over the past decades (1). Arising at least in part from this situation, calls for regulatory changes to support pharmaceutical innovation have been put forward. One concept that has been proposed as a potential approach to solve the problem of a declining R&D productivity is AL (8). This concept is based on the idea that evidence generation in MP development is a continuum and, thus, licensing of MPs would have to follow a stepwise approach. Initially, administration of a new MP to patients would be restricted in accordance with the current level of knowledge about the MP and would be extended during subsequent authorisation steps on the basis of continuous generation of evidence (7).

The aim of this master's thesis is to analyse the feasibility of AL under the current legal and regulatory framework and with regard to the present conditions in the field of MP development, approval and utilisation. For this purpose, the master's thesis aims at providing responses to the following questions:

- Which general requirements would be associated with a successful implementation of the AL concept?
- Which existing legislative provisions and regulatory mechanisms could facilitate the implementation of AL?
- Which outstanding issues and gaps exist in the current legal and regulatory framework for the implementation of AL?

In the context of these questions, the feasibility and required conditions for the implementation of the AL concept, potential approaches to overcome the obstacles to such attempts and, finally, the potential of AL to solve the broadly acknowledged problems of an unmet medical need in various therapeutic areas and a decline in pharmaceutical R&D efficiency are discussed.

2. Analysis of the feasibility of Adaptive Licensing

2.1. Prerequisites for the implementation of Adaptive Licensing

2.1.1. Potential scenarios of Adaptive Licensing

A variety of proposals for the implementation of AL have been put forward in the recent past. Many potential scenarios comprise a continuous extension of the label population, as the knowledge about the MP evolves. Thus, the initial MA could be based on demonstrating a favourable benefit-risk balance in a restricted, clearly defined patient population characterised, for example, by a high medical need, high probability to benefit from the MP (high expected responsiveness), low predicted susceptibility to adverse reactions or high treatment concordance, under tightly controlled conditions including, for example, restricted prescription and compliance-enhancing measures (see sections 2.2.3 and 2.2.9). Consequently, clinical trials that are required to demonstrate a positive benefit-risk balance for this restricted target population would likely cause reduced expenditures – in terms of time and cost – due to an increased signal-to-noise ratio (7).

However, the initial MA granted under this scenario would have to reflect the clinical trial conditions more closely than under the current, traditional licensing approach. Moreover, adherence to the label would have to be ensured (see section 2.1.3) and knowledge about the MP would have to be generated continuously following the granting of the initial MA (see section 2.1.5). This knowledge would have to be generated based on treatment experience in the restricted label population as well as randomised, controlled clinical trials conducted in parallel in a wider (less restricted) patient population. In case of favourable results, the MA would be broadened and the criteria for eligibility of patients to the respective treatment would be relaxed (7).

Another potential scenario for AL would be the granting of an initial MA based on convincing effects on surrogate endpoints rather than clinical endpoints, whereas subsequent authorisation steps would be premised on the relevant clinical outcome. However, variable predictability of clinical benefit on the basis of surrogate endpoints represents a major issue associated with this scenario (7). Therefore, this option would require an agreement on surrogate endpoints for various therapeutic indications that are suitable to predict a clinical benefit for patients and, thus, are considered to be acceptable to regulators and payers.

Apart from that, a variety of additional proposals for AL have been put forward recently. According to these suggestions, different authorisation steps could focus not only on different patient populations or endpoints, but also on different comparator treatments, e.g. placebo-controlled studies for initial licensing and active comparator-controlled studies for subsequent authorisation steps (7).

2.1.2. Graduated applicability

The EMA's AL approach aims at balancing timely access of patients to new MPs with the requirement of adequate risk-benefit data (5). Consequently, the concept of AL would provide pharmaceutical companies with the opportunity of an earlier market access for new MPs compared to the traditional, binary regulatory approach. However, the EMA is strongly committed to the protection of public health (4). Thus, the extent of applicability of AL would likely vary for different MPs and would probably have to be decided on a case-by-case basis. Therefore, it seems reasonable that the specifics of an AL approach would probably depend on the following crucial factors:

- Severity of the disease
- Prevalence of the disease
- Availability of alternative treatment options
- Availability of preventive interventions
- Target patient population
- Characteristics of the MP, e.g. mode of action, significant benefit over existing treatment options in terms of safety or efficacy
- Experience gained with MPs of the same pharmacological class
- Availability of preclinical data and conclusions drawn from this data

For example, in case of serious or life-threatening diseases, the amount of data required for an initial MA might be reduced compared to the amount of clinical data required for a MP intended for the treatment of a less serious condition. The same might be true for MPs developed for patients suffering from rare diseases or in case of a lack of safe and efficacious alternative treatment options. Moreover, there might be restrictions to the extent of applicability of AL for MPs exhibiting a certain mode of action (e.g. biological MPs) or in case of concerns originating, for example, from previous experience with MPs of the same pharmacological class or from available preclinical data indicating potential safety issues associated with the MP.

2.1.3. Prevention of off-label use

MPs are authorised for well-defined "label-scenarios" including clear and precise therapeutic indications (7). These indications define the target disease or condition (while distinguishing between treatment, prevention and diagnostic indications) as well as the target patient population including any restrictions to this population (e.g. age limits) or the therapeutic setting (e.g. add-on treatment, second-line treatment).

Nevertheless, MPs are frequently prescribed and administered to patients off-label, i.e. under conditions, which do not match with the label (7), for example, in cancer treatment or treatment of paediatric patients – therapeutic areas that are characterised by a particularly high rate of off-label use.

However, off-label use would substantially counteract the concept of AL (7), particularly after the granting of the initial MA for a restricted patient population with the most urgent medical need for the MP, thus, potentially willing to accept a higher level of uncertainty about the MP (see section 2.1.4), because the initial MA would be based on a limited amount of available data. Therefore, ensuring adherence to the label would constitute a major prerequisite for the success of AL (7). Consequently, any distribution of an initially authorised MP would have to prevent off-label use. This might, for example, mean that prescribers would have to be specifically qualified or educated in order to guarantee compliance with the predefined treatment conditions as laid down in the label of the MP.

Currently, there is a variety of regulatory mechanisms in place that could be utilised for the purpose of preventing off-label use (e.g. additional risk minimisation measures that represent conditions to the MA; see section 2.2). A well-known example for a MP being subject to such precautionary measures is thalidomide. Thalidomide won notoriety in the context of the Contergan scandal, in which consequence the product was withdrawn from the market in the early 1960s due to its pronounced teratogenicity. However, Thalidomide Celgene was authorised and re-introduced to the EU market in 2008 for the treatment of multiple myelomas (9). As additional risk minimisation measures, the MP has to be prescribed and dispensed according to a special programme to prevent exposure of unborn children, i.e. off-label use, for example, in pregnant women. The MA holder was required to set up a controlled distribution and pregnancy prevention programme, including Dear Healthcare Professional Letters, Educational Healthcare Professional's Kits, etc., and to collect information on the use of the MP outside its approved indication (10) (see also section 2.2.3).

2.1.4. Acceptability of uncertainty

In general, the feasibility of AL would always depend on the willingness of all parties involved to accept an increased level of uncertainty associated with MPs authorised via the AL pathway (7). This would include patients, pharmaceutical companies, health care providers, regulators as well as Health Technology Assessment (HTA) bodies. The level of uncertainty would be particularly high during the initial licensing stages and would be expected to decrease with additional data becoming available through continuous knowledge generation (see section 2.1.5). Importantly, the willingness to accept a given level of uncertainty might vary depending on the factors provided in section 2.1.2. However, an increased acceptability of uncertainty should not be interpreted as a general lowering of scientific standards. Instead, AL aims at balancing the regulators' need for comprehensive clinical data with the patients' need for timely access to new MPs (further details: see section 2.3.8).

Importantly, an increased level of uncertainty would be associated with the need for a rigorous and explicit communication to the public, patients and health care providers in order to explicitly point to the limited base of evidence. This would most likely involve established ways of communication and patient / prescriber information including, for example (11):

- Dear Healthcare Professional Letters
- Educational Healthcare Professional's Kits

as well as new ways of communication, e.g. (7):

- Post-initial MA informed-consent forms
- Labelling of MPs as "initially authorised" – potentially accompanied a new symbol in the product information for ease of identification of these MPs

2.1.5. Continuous knowledge generation

Under the conventional regulatory approach, post-approval experience with a MP in patients outside of clinical trials contributes only marginally to evidence generation. In contrast, AL would have to exploit this source of information to a greater extent in order to provide a sound basis for regulatory and patient-care decisions in the post-initial-MA period (7). Thus, in order to be a successful pathway for future MP licensing, AL would have to ensure a managed data generation covering also later stages of the MP's life cycle. High quality data would have to be generated continuously for the purpose of facilitating multiple rounds of well-informed assessment, the adaptation of the regulatory status of a MP and the continuous reduction of uncertainty.

Data might be generated through additional clinical studies as well as active and passive surveillance in the post-initial-MA period in order to guarantee a continuous evaluation of the risks and benefits of a new MP (7). Active surveillance would have to comprise both, close monitoring for safety and adverse events as well as for efficacy (including unexpected benefits). Thus, evidence generation methodology might encompass, for example:

- Interventional studies (conventional randomised, controlled clinical trials as well as pragmatic clinical trials)
- Non-interventional studies (observational studies based on electronic medical records)
- Registries, which represent organised systems that use observational methods to collect uniform data on specified outcomes in a certain population defined by a particular disease (disease registries) or prescription of a MP (exposure registries) (12)

Moreover, the success of AL would depend on precise prospective concepts for generating high-quality data following the granting of the initial MA (7). These development plans for the systematic generation of knowledge about a new MP would have to include all proposed measures as well as the respective timelines, for example, the timing of interim analyses in ongoing clinical trials in order to facilitate decision making during the planned authorisation steps.

Importantly, the holder of an initial MA would have to enter into a commitment to conduct all studies and measures that have been agreed upon in advance (7). However, the requirements for data generation could vary depending on the stage of authorisation, i.e. the level of uncertainty. For example, later stages might be characterised by less frequent assessment rounds and a reduced spectrum of different sources of information (e.g. clinical trials for other indications and observational data).

2.1.6. Intensive collaboration between applicants, competent authorities and Health Technology Assessment bodies

AL would be based on a continuous knowledge generation and the respective adaptation of the MA. Thus, this licensing approach would require an early communication and close collaboration between sponsors, competent authorities and HTA bodies. All parties involved would have to agree on a predefined development programme and, consequently, a predefined authorisation plan early in MP development (7). This agreement would have to specify the evidence required at each stage of the development in order to pass the next authorisation step and to ensure reimbursement. However, these development and authorisation plans would still have to possess a certain level of flexibility to allow for an interim adjustment on the basis of

new relevant information becoming available during MP development (see section 2.3.3). Moreover, it would likely be necessary to agree on the terms of reimbursement, i.e. the price of a MP, in advance (7). It seems to be realistic that the amount of money paid for the product might vary between different stages of authorisation, i.e. after the granting of the initial and subsequent MAs or the full MA. The price could potentially reflect the level of available information about the MP. However, under an AL approach data from comparative clinical studies that might prove an additional benefit of the new MP over existing therapies (appropriate comparators), which mainly influence the price of a new MP, will most likely not be available in early licensing stages (see also section 2.3.8). Moreover, additional factors would have to be taken into account regarding reimbursement considerations, e.g. the limited number of patients, who will be treated with the MP after the granting of the initial MA, thus, the limited generation of revenues (see also section 2.3.6).

2.2. Current regulatory mechanisms facilitating Adaptive Licensing

2.2.1. Conditional marketing authorisation

The conditional MA concept represents a regulatory mechanism for an early entry into the market for a certain subset of MPs despite the lack of comprehensive clinical data in terms of safety and efficacy. This subset of MPs is defined within Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004, which constitutes the legal basis for conditional approval (13). MPs that fall within the scope of this Regulation are specified in Article 2. According to this article, Regulation (EC) No 507/2006 covers products for human use that fall under Article 3(1) and 3(2) of Regulation (EC) No 726/2004 and belong to one of the following categories (13):

(1) MPs for the treatment, prevention or diagnosis of seriously debilitating or life-threatening diseases
(2) MPs to be used in emergency situations (specified by the World Health Organization or in the framework of Decision No 2119/98/EC)
(3) Designated orphan MPs (in accordance with Article 3 of Regulation (EC) No 141/2000)

Moreover, all the following requirements have to be met (Regulation (EC) No 507/2006, Article 4) in order to qualify for a conditional MA (13):

(1) Positive risk-benefit balance (according to article 1(28a) of Directive 2001/83/EC)
(2) Comprehensive clinical data can likely be provided by the applicant at some future date
(3) Fulfillment of unmet medical needs (i.e. if there exists no satisfactory method or if there is a major therapeutic advantage over existing methods)
(4) Benefit to public health outweighs the risk due to the lack of comprehensive clinical data

Therefore, the conditional MA concept is applicable only to a small subset of MPs – mainly MPs for serious, life-threatening or rare conditions with few therapeutic alternatives.

However, this approach possesses some considerable analogies with the AL concept, as it substantially diverges from the traditional, binary licensing approach (Table 2) and represents a more staggered path of MP licensing (Figure 5). For example, specific obligations with predetermined timelines are imposed on the holder of a conditional MA including the completion of ongoing studies and conduct of new studies to provide additionally required data as well as the collection of pharmacovigilance data (Regulation (EC) No 507/2006, Article 5). Moreover, a conditional MA is subject to an annual renewal due to a validity of only one year (Regulation (EC) No 507/2006, Article 6) allowing for various rounds of reassessment and can ultimately be converted into a full MA in accordance with Article 14(1) of Regulation (EC) No 726/2004 (Regulation (EC) No 507/2006, Article 7). Importantly, the granting of a conditional MA – by analogy with potential consequences of the granting of an initial MA under an AL approach – needs to be reflected in the product information including the Summary of Product Characteristics (SmPC) and the package leaflet (PL) (Regulation (EC) No 507/2006, Article 8) (13).

Taken together, the conditional MA route – similarly to AL – allows for a stepwise licensing approach, but only for a certain subset of MPs, whereby allowing these MPs to reach patients with an unmet medical need earlier than it might be the case under the traditional, binary approach. In parallel, the conditional MA concept ensures the generation of additional data on the MP following the granting of the initial, conditional MA and the submission of this data for regulatory assessment, which would be a major requirement for AL.

	Full MA ("traditional approach")	Conditional MA
Comprehensive clinical data	Available	Demonstration of a positive benefit-risk balance; confirmation pending
Validity	5 years	1 year
Renewal	Once after 5 years (standard case; see section 2.2.8)	Annually
Long-range objective	-	Conversion into a full MA upon fulfillment of the specific obligations

Table 2: Comparison of the full MA and conditional MA concepts
Comparison of the main characteristics of the full MA concept (traditional, binary licensing approach) and the conditional MA approach.

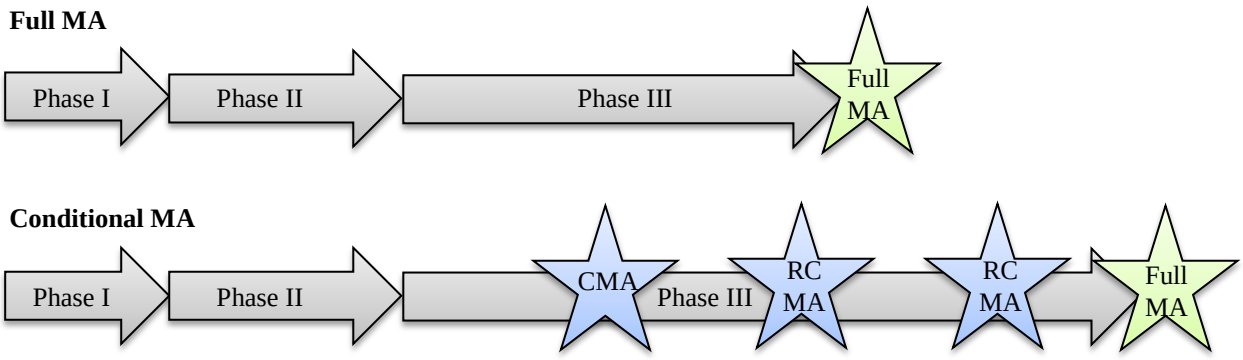


Figure 5: Comparison of the fundamental setup of common clinical development programmes aiming at a full or conditional MA
Depictive representation of the full MA vs. the conditional MA approach indicating the more staggered character of the approval process associated with a conditional MA (CMA), which has to be renewed annually (RCMA, renewed CMA) and is ultimately converted into a full MA.

2.2.2. Marketing authorisation subject to certain conditions

In 2010 a new pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU – amending Regulation (EC) No 726/2004 and Directive 2001/83/EC – in conjunction with Commission Implementing Regulation (EU) No 520/2012), which has had a significant impact on MA applicants and MA holders in a variety of areas, was adopted in the EU (14).

The new pharmacovigilance legislation brought into MP legislation the concept of a MA granted to a MP subject to certain conditions. These conditions can include, for example:

- Any conditions or restrictions to ensure the safe and effective use of the MP (see section 2.2.3)
- Conduct of post-marketing studies: PASS, PAES (see section 2.2.4)
- Compliance with stricter obligations in terms of recording and reporting of suspected adverse reactions, etc.

Such obligations can be imposed on MA holders as conditions for the granting of the MA and the deadlines for the fulfillment of these conditions are determined in the MA (Directive 2001/83/EC, Article 21a) (15). Importantly, non-compliance with these obligations can result in the suspension or revocation of the MA or the refusal of the renewal of the MA (see sections 2.2.5 and 2.2.8).

In principle, the concept of a MA subject to certain conditions could be utilised under an AL approach, as it addresses several prerequisites for the implementation of AL (e.g. communication of uncertainty about a MP, prevention of off-label use, continuous knowledge generation; see section 2.1) as described in the following sections.

2.2.3. Risk management system and risk management plan

The new pharmacovigilance legislation introduced the requirement of a Risk Management System (RMS) for all newly authorised MPs as part of the applicant's pharmacovigilance system (Directive 2001/83/EC, Article 104(3)) (15, 16). A RMS is a set of pharmacovigilance activities intended to identify, characterise, prevent or minimise risks associated with a MP (including the assessment of effectiveness) (Directive 2001/83/EC, Article 1(28b)). Moreover, each MA application has to be accompanied by a Risk Management Plan (RMP), which represents a detailed description of the RMS (Directive 2001/83/EC, Article 8(3(iaa))) (15).

A RMP should include as key elements the following information / descriptions (17):

- Safety profile of the MP
- Further / future characterisation of the safety profile
- Risk minimisation measures including an assessment of the effectiveness of these measures
- Post-authorisation obligations imposed as a condition of the MA (see sections 2.2.2 and 2.2.5)

Importantly, the RMP discusses three types of risks – identified and potential risks as well as any missing information in terms of risks (12, 16).

Risk minimisation activities may consist of (12):

- Routine risk minimisation activities (activities, which apply to every MP, e.g. measures associated with the SmPC, labelling, PL, pack size or legal status of the MP (see also section 2.2.9)) or
- Additional risk minimisation activities (e.g. Dear Healthcare Professional Letters, educational materials, controlled distribution systems)

The SmPC and PL are important routine risk minimisation tools, as they represent a controlled and standardised format to provide health care professionals and patients with information about a MP. The legal status of a MP (e.g. "MP subject to medical prescription") complements these measures, as it is a tool to control the conditions, under which a MP becomes available to the public (see section 2.2.9). Moreover, controlling the pack size can ensure that a patient treated with a MP subject to medical prescription will need to see a health care professional at defined intervals. Thus, prescribing can be linked to the need for review of the patient (12).

Under the traditional, binary licensing approach, the majority of safety concerns may be adequately addressed by these routine activities. However, in some cases, i.e. for some risks, additional risk minimisation activities might be necessary in order to ensure the safe and effective use of a MP.

Many of these additional measures are based on enhanced communication complementing the information in the SmPC and PL (e.g. Dear Healthcare Professional Letters, educational material). Importantly, additional risk minimisation activities are conditions of the MA and the key elements are detailed in annex II of the product information (Annex II - D. Conditions or restrictions with regard to the safe and effective use of the medicinal product) (12).

Extensive guidance on additional risk minimisation measures has recently been provided by the Guideline on good pharmacovigilance practices (GVP) - Module XVI - Risk minimisation measures: selection of tools and effectiveness indicators. This guideline refers to the following additional risk minimisation measures (18):

- Educational programmes
- Controlled access programmes
- Other risk minimisation measures including pregnancy prevention programmes and direct healthcare professional communication

Educational programmes are based on targeted communication with the purpose to supplement the information in the SmPC and PL and positively influence the actions of healthcare professionals and patients. Educational materials, for example, could provide healthcare professionals with guidance on prescribing – including patient selection – and treatment monitoring. Moreover, educational tools could aim at enhancing the awareness of patients and healthcare professionals on the risks associated with a certain MP (18).

Controlled access programmes consist of interventions that aim at controlling access to a MP (beyond the level ensured by routine risk minimisation measures like the legal status of the MP). In the context of these programmes, access to / prescription of a MP could depend on various requirements, for example (18):

- Specific testing / examination of patients to ensure compliance with strictly defined clinical criteria / the indication (for example, to prevent off-label use)
- Documentation of receipt and understanding of information on the risks of a MP by healthcare professionals and patients
- Enrolment in specific data collection systems (e.g. patient registries) to ensure a systematic patient follow-up
- Dispension of the MP in registered and approved pharmacies

Taken together, the RMP serves as an important tool to minimise the risks associated with a MP. Moreover, the RMP has to be updated continuously throughout the MP's life cycle upon availability of relevant, new information (Implementing Regulation (EU) No 520/2012, Article 32) (19), as knowledge grows over time and uncertainty (potential risks, missing information) decreases. Thus, the RMP can be adapted to the level of uncertainty about a MP. Furthermore, a summary of the RMP will be made publicly available (Implementing Regulation (EU) No 520/2012, Article 31(1)) (19). This means that the level of uncertainty associated with a new MP is being communicated to the public and could potentially serve as an additional source of information (along with the product information) to enable physicians and patients to make informed decisions about the acceptability of the level of uncertainty and, ultimately, the administration of a certain MP.

However, the RMP does not only cover safety issues, but also refers to the collection of efficacy data in the post-authorisation period as outlined in the RMP section "Plans for post-authorisation efficacy studies" (Implementing Regulation (EU) No 520/2012, Annex I) (19) (see section 2.2.4).

In sum, the RMP, which must continuously be adapted to the level of knowledge about a MP throughout the MP's life cycle, represents an important tool to facilitate the following activities:

- Elaboration of the safety profile characterisation of a MP and the collection of safety as well as efficacy data and in the post-authorisation period
- Prospective planning of the implementation of risk minimisation measures

This could be utilised for the implementation of the AL concept, which would require the implementation of certain risk minimisation activities, for example, for the purpose of preventing off-label use, as well as a systematic and continuous generation of knowledge about a MP. Therefore, the various routine and additional risk minimisation measures (conditions to the MA) described above could be used under an AL approach to inform patients and healthcare professionals about the uncertainties associated with a MP, ensure adherence to the label / the indication and facilitate data generation in the post-authorisation period (e.g. via patient registries).

2.2.4. Post-authorisation safety studies and post-authorisation efficacy studies

The new pharmacovigilance legislation adopted in 2010 significantly strengthened the legal basis for requesting post-authorisation safety and efficacy studies (PASSs / PAESs) by competent authorities (20). A PASS is a study relating to an authorised MP that aims at obtaining further information on the safety of a MP (identification, characterisation or quantification of a safety hazard or confirmation of a safety profile) or measuring the effectiveness of risk management measures (Directive 2001/83/EC, Article 1(15)) (15, 21). Thus, a PASS might be a clinical trial, a non-interventional study or a non-clinical safety study (22). In contrast, a PAES is conducted in order to obtain information on the benefit of a MP, i.e. to verify the efficacy of an authorised MP, including efficacy under "real-life" conditions (20).

A PASS or PAES can either voluntarily be initiated by a MA holder or be imposed on a MA holder by a competent authority (21). The obligation to conduct these post-authorisation studies can be imposed on MA applicants or MA holders at the time of the granting of a MA subject to certain conditions (Directive 2001/83/EC, Article 21a; Regulation (EC) No 726/2004, Article 9(4)) or after the granting of a MA (Directive 2001/83/EC, Article 22a; Regulation (EC) No 726/2004, Article 10a) (15, 23).

The purpose of these post-authorisation studies is to provide additional information on the benefit-risk balance of a MP in order to facilitate decision-making on the MP and, ultimately, to ensure its safe and effective use. Therefore, PASSs and PAESs – also in view of a potential implementation of AL – can serve as tools for the continuous and managed generation of knowledge about a MP in spite of the fact that a MA will or has already been granted.

2.2.5. Post-authorisation measures and their enforcement

As described above, it might be necessary for MA applicants to agree to the generation of additional data in terms of the safety and efficacy of a MP in the post-authorisation period in order to receive a MA (see sections 2.2.1 – 2.2.4).

Post-authorisation measures (PAMs) that can be imposed on applicants are classified into their appropriate legal framework, under which they will be enforced, and are categorised as follows (24):

- Specific obligations
- Annex-II conditions
- Additional pharmacovigilance activity in the RMP
- Legally binding measures
- Recommendations

Specific obligations are binding conditions to the MA and can only be imposed on MAs granted under exceptional circumstances or conditional MAs. They provide the basis for the annual reassessment and renewal of the MA (24). Thus, the renewal of a conditional MA is critically influenced by the MA holder's compliance with the specific obligations. PAMs that do not belong to the category of specific obligations can be required for any type of MA (see section 2.2.2).

Annex-II conditions – while not precluding the granting of a MA – are PAMs that are considered to be crucial to the benefit-risk balance of the MP. Thus, they are binding conditions to the MA. Examples for annex-II conditions might be post-authorisation studies on safety and efficacy (PASS, PAES) (24).

Additional pharmacovigilance activities could be all measures to investigate a safety concern of a MP, i.e. identify and characterise risks or assess the effectiveness of risk minimisation activities, and are listed in the RMP. Additional pharmacovigilance activities can be imposed as either specific obligations, annex-II conditions or required post-authorisation activities in the RMP, all of which are enforceable. Thus, there is an obligation to provide the requested data within the specified timeframe (24).

Legally binding measures are PAMs that are defined as statutory in the MP legislation and, thus, have to be provided by MA holders. These measures may include, for example, requests for provision of data that is not yet linked to a safety concern identified in the RMP as well as updates of the product information (Directive 2001/83/EC, Article 23; Regulation (EC) No 726/2004, Article 16) (15, 23, 24).

In contrast, recommendations are not binding to the MA. They might represent suggestions for further development of the MP, for example, regarding the patient population, and should be viewed as important considerations (24).

Ultimately, non-fulfillment of PAMs that are binding (e.g. annex-II conditions) can lead to the following scenarios:

- Reiteration of the PAM with a clarified scope and adjusted timelines
- Initiation of regulatory actions

Regulatory actions might finally result in the initiation of a referral procedure with the aim of varying, suspending or revoking the MA (24). According to Article 116 of Directive 2001/83/EC, the MA can be suspended, revoked, withdrawn or varied for various reasons (e.g. if the MP is harmful, lacks therapeutic efficacy or has a non-favourable benefit-risk balance) including the situation that conditions binding to the MA have not been fulfilled (15).

Thus, PAMs serve as important and enforceable tools for competent authorities to ensure the implementation of certain risk minimisation measures and to request the generation of additional safety and efficacy data in the post-authorisation period complementing available data on a MP at the time of the granting of the MA. Therefore, they could be utilised for the implementation of AL to ensure a continuous knowledge generation following the granting of an initial MA, adherence to the label and communication / awareness of the uncertainties associated with a MP authorised under an AL approach.

2.2.6. Additional monitoring

The concept of additional monitoring has been introduced by the new pharmacovigilance legislation adopted in 2010. This concept applies to MPs, which require enhanced data collection in the post-authorisation period in order to mitigate safety risks, i.e. to ensure a prompt identification of safety issues as well as a quick initiation of an adequate action (25).

The additional monitoring status can be assigned to a MP in the context of the granting of the MA or at any time in the post-approval period. Although any information that becomes available about a MP and might have an impact on the benefit-risk balance of the product is monitored by competent authorities in the EU, some MPs require enhanced data collection. This includes the following MPs (26):

- MPs containing a new active substance
- Biological MPs
- MPs given conditional approval or authorised under exceptional circumstances
- MPs with a MA subject to certain obligations (e.g. PASS), conditions or restrictions in terms of safety in order to ensure a safe and effective use of the MP (see section 2.2.2)

Moreover, MPs can be included in the list of medicines under additional monitoring upon recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC). MPs under additional monitoring are labelled with a black symbol – a inverted triangle – in the product information (SmPC, PL) accompanied by a statement encouraging healthcare professionals and patients to report suspected adverse reactions (26). A list of MPs subject to additional monitoring is publicly available at the EMA website (27).

However, it should be mentioned that additional monitoring – even though strengthening the monitoring of certain MPs – does not lead to an earlier granting of a MA. Moreover, additional monitoring – although aiming at an enhanced collection of safety data – does not cover a potential need for enhanced collection of efficacy data, which would be required for AL.

2.2.7. Periodic safety update reports

Periodic safety update reports (PSURs) have to be provided by MA holders of MPs (except for some types of MAs, e.g. MAs for generic and homeopathic MPs) to the competent authorities at regular intervals specified in the MA (28). PSURs need to contain the following information (Directive 2001/83/EC, Article 107b; Regulation (EC) No 726/2004, Article 28(2)) (15, 23):

- Summaries of data relevant to the benefits and risks of a MP (including all study results)
- Scientific evaluation of the benefit-risk balance of the MP (including data from clinical trials in unauthorised indications)
- All available data regarding the volumes of sales and prescriptions of the MP as well as an estimate of the population exposed to the MP

Thus, PSURs are important tools for monitoring the development of a MP's safety profile in the post-authorisation period. However, they summarise not only data on the risks of a MP but also on the benefits of a MP and serve to re-evaluated a MP's benefit-risk balance in due consideration of all available data. Consequently, PSURs do not exclusively contain safety data. These reports also incorporate and provide an update on efficacy data (28). Importantly, based on the evaluation of the cumulative safety and risk-benefit analysis, MA holders need to include conclusions in terms of required changes or actions in the PSUR, e.g. changes to the SmPC (Implementing Regulation (EU) No 520/2012, Article 30(5)) (19). Therefore, PSURs that have to be submitted periodically can serve as a regulatory tool to reveal required changes to the MA, i.e. to adjust a MA to the current level of knowledge about the benefit-risk balance of a MP, and could facilitate the implementation of AL.

2.2.8. Renewal of a marketing authorisation

In accordance with Article 24 of Directive 2001/83/EC and Article 14 of Regulation (EC) No 726/2004, a MA is valid for 5 years – except in case of a conditional MA, which is valid for 1 year (13) – and can be renewed after 5 years (15, 23). In general, this provides competent authorities with the opportunity to re-evaluate the benefit-risk balance of a MP after a significantly increased number of more diverse patients have been treated with the product under "real-life" conditions. The outcome of a renewal procedure can be the following:

- Renewal of the MA with unlimited validity
- Renewal of the MA for additional five years requiring a second renewal
- Renewal of the MA bound to certain conditions
- Refusal of the renewal of the MA

Grounds for refusal are conclusively listed in Article 116 of Directive 2001/83/EC and include, for example, the situation that conditions binding to the MA have not been fulfilled (15).

Thus, the requirement of the renewal of a MA might be considered as a first step towards multiple rounds of MP assessment and authorisation – as proposed for AL – thereby ensuring the fulfillment of PAMs. However, current legislation stipulates that once renewed, the MA will be valid for an unlimited period, unless there are justified grounds relating to pharmacovigilance including exposure of an insufficient number of patients. In the latter case, one additional five-year renewal could be imposed on the MA holder (Directive 2001/83/EC, Article 24(3); Regulation (EC) No 726/2004, Article 14(3)) (15, 23). This may allow for a third assessment and authorisation round (after the granting of the initial MA and the first

renewal) – particularly in case of a limited number of patients, which would be the case following the granting of the initial MA under an AL approach. However, according to the current MP legislation the timing of the re-evaluation process is fixed to the five-year-rhythm and usually takes place only once – or twice at a maximum.

2.2.9. Legal status of medicinal products

Upon granting of a MA for a MP, the conditions and restrictions, under which the MP should be made available to patients – the so called legal status or classification of the MP – must be specified by the competent authority (Directive 2001/83/EC, Article 70; Regulation (EC) No 726/2004, Article 9(4)(b)) (15, 23). Accordingly, MPs are classified into the following categories:

- MPs subject to medical prescription
- MPs not subject to medical prescription

MPs should be subject to medical prescription, if they could potentially represent a danger, if utilised without medical supervision, if they are frequently or extensively used incorrectly, if they contain substances or preparations, which activity and / or adverse reactions require further investigation or if they are intended to be administered parenterally (Directive 2001/83/EC, Article 71(1)) (15, 29). Thus, the third criterion (activity / adverse reactions require further investigation) would allow for a classification of MPs authorised under AL as "subject to medical prescription" following initial / early authorisation steps due to the limited experience or use of the MP.

Moreover, MPs subject to medical prescription can be further differentiated into the following subcategories:

- MPs on medical prescription for renewable or non-renewable delivery
- MPs subject to special medical prescription
- MPs on restricted medical prescription, reserved for use in certain specialised areas

MPs shall be subject to special medical prescription, if they contain narcotic or psychotropic substances in a non-exempt quantity or if there is a substantial risk of medical abuse, addiction or misuse for illegal purposes given that the MP is used incorrectly – even if this would only be a precautionary measure based on the novelty and properties of the substance (Directive 2001/83/EC, Article 71(2)) (15, 29).

A MP shall be subject to restricted medical prescription, if it is reserved for administration in a hospital environment (based on its pharmaceutical characteristics, novelty or in the interest of public health), if the MP is intended to treat conditions, which must be diagnosed in a

hospital environment or institutions with adequate diagnostic facilities, or if the MP may cause very serious adverse reactions requiring prescription by a specialist or special supervision throughout the treatment (Directive 2001/83/EC, Article 71(3)). MPs that meet the criteria for both subcategories mentioned above are subject to special and restricted medical prescription (15, 29).

Thus, the legal status of a MP, according to the current MP legislation, allows for certain restrictions on the prescription of the MP. In view of a potential implementation of AL, MPs in the early licensing stages could be classified as "MPs subject to restricted medical prescription" due to the risks / the level of uncertainty associated with these products and additional risk minimisation measures – representing conditions to the MA – could be detailed in the RMP in order to facilitate adherence to the label, i.e. to prevent off-label use (see section 2.2.3).

2.2.10. Scientific Advice and parallel Scientific Advice with Health Technology Assessment bodies

One prerequisite for the success of the AL concept would be an early communication and intensive collaboration between sponsors, competent authorities and HTA bodies in order to agree on a development programme as well as an authorisation and reimbursement plan in an early stage of MP development (7) and to adjust these plans – as necessary – throughout the life cycle of the MP on the basis of new relevant information becoming available during MP development (see section 2.1.6).

In this context, Scientific Advice represents an existing regulatory mechanism and valuable opportunity for communication and close collaboration between sponsors and regulators (30). Scientific Advice is provided by the EMA as well as national competent authorities in order to give advice on the appropriateness of tests and studies in the development of a MP (Regulation (EC) No 726/2004, Article 57(1)(n)) (23). It can be requested at any stage of MP development and serves to facilitate the development and availability of high-quality, efficacious and acceptably safe MPs for the benefit of public health. Importantly, Scientific Advice from the EMA can be requested independently of the eligibility of the MP for the centralised procedure. However, Scientific Advice is not legally binding either on the EMA or national competent authorities or on the sponsor with regard to any future MA application for the MP concerned (30). Nevertheless, Scientific Advice is a well-established and frequently utilised tool in MP development (Figure 6).

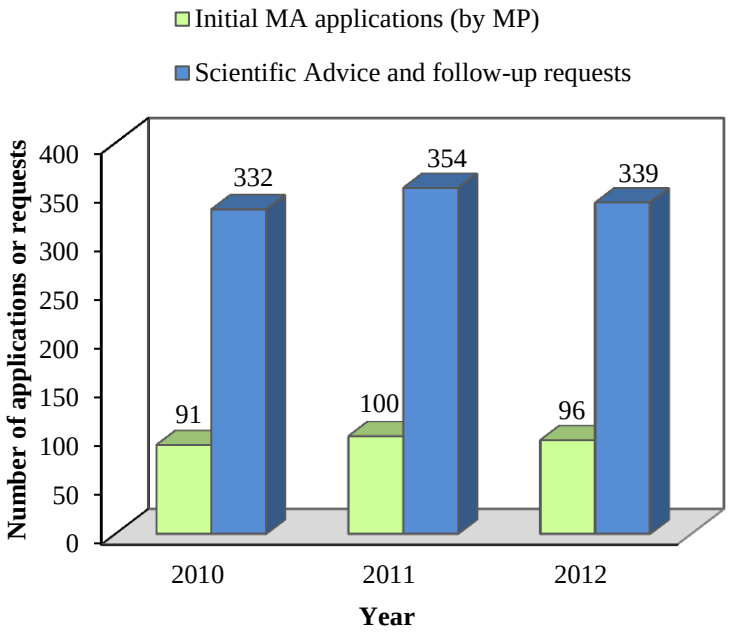


Figure 6: Initial-evaluation applications and Scientific Advice requests
Number of initial MA applications (by MP) as well as Scientific Advice and follow-up requests submitted to the EMA within the time period from 2010 to 2012. Source of data: Annual Report 2012, EMA (31).

Importantly, as published by Regnstrom et al. in 2010 (32), seeking Scientific Advice and complying with it has been associated with a greater chance of receiving a positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP). While the success rate of companies requesting and following Scientific Advice is 90%, the success rate for obtaining a MA for companies that do not request Scientific Advice is 30% (32). Thus, this tool facilitates and improves the availability of MPs for patients and, therefore, in parallel promotes pharmaceutical R&D.

However, while the possibility of obtaining agreement from regulators on a proposed MP development plan has commonly been used in the past, to date HTA bodies are usually not involved in these discussions. In order to address this issue, the EMA has launched a pilot project of parallel Scientific Advice with HTA bodies in 2010 for the purpose of providing sponsors with simultaneous feedback from both, competent authorities and HTA bodies, on their development programmes. This might help sponsors to establish the evidence required by both parties in order to assess the benefit-risk balance and determine the value of a new MP (33).

By the end of 2013, 25 parallel Scientific Advice procedures have been conducted by the EMA and several HTA bodies taking part in the pilot project. Moreover, guidance for EMA-HTA parallel Scientific Advice will be developed and published for public consultation in early 2014. This guidance might represent an important tool in MP development for the

purpose of facilitating a tripartite communication and collaboration between sponsors, regulators and HTA bodies, which will ultimately facilitate the fulfillment of both, regulatory and reimbursement requirements, by pharmaceutical companies (34).

Additionally, HTA bodies have initiated the Shaping European Early Dialogues for Health Technology (SEED) consortium, which consists of 14 national and regional HTA bodies. The aim of this consortium is to explore various scenarios for conducting early dialogues. The EMA is associated with the SEED consortium and will take part in these dialogues (34).

In conclusion, it is increasingly recognised that a close collaboration between sponsors, regulators and HTA bodies is a crucial process for enabling new MPs to reach the market, facilitating public health and supporting pharmaceutical R&D. However, the concept of a tripartite collaboration is still in the early stages of establishment given the fact that only a few parallel Scientific Advice procedures involving both the EMA and HTA bodies have been conducted as part of the pilot project to date and the development of guidance documents for these procedures is still in progress. Thus, considerable progress will be required in order to establish a tripartite dialogue as a standard path in MP development and to facilitate the implementation of AL.

2.3. Outstanding issues and gaps of the regulatory and legal framework

2.3.1. Restricted applicability of the conditional marketing authorisation concept

Despite the possibility of an early market access for new MPs in the absence of comprehensive clinical data via the conditional MA path, the most commonly taken route to the market is still the traditional, binary approach (Figure 7). This can be illustrated by an analysis of the utilisation of the conditional MA option. In 2013, for example, the CHMP issued 81 positive opinions on the granting of a MA for new MPs, among which only five ones represented opinions recommending the granting of a conditional MA (35). Overall, the proportion of positive opinions recommending conditional approval was well below 10 % from 2010 to 2013 (Figure 7) (31, 35, 36, 37).

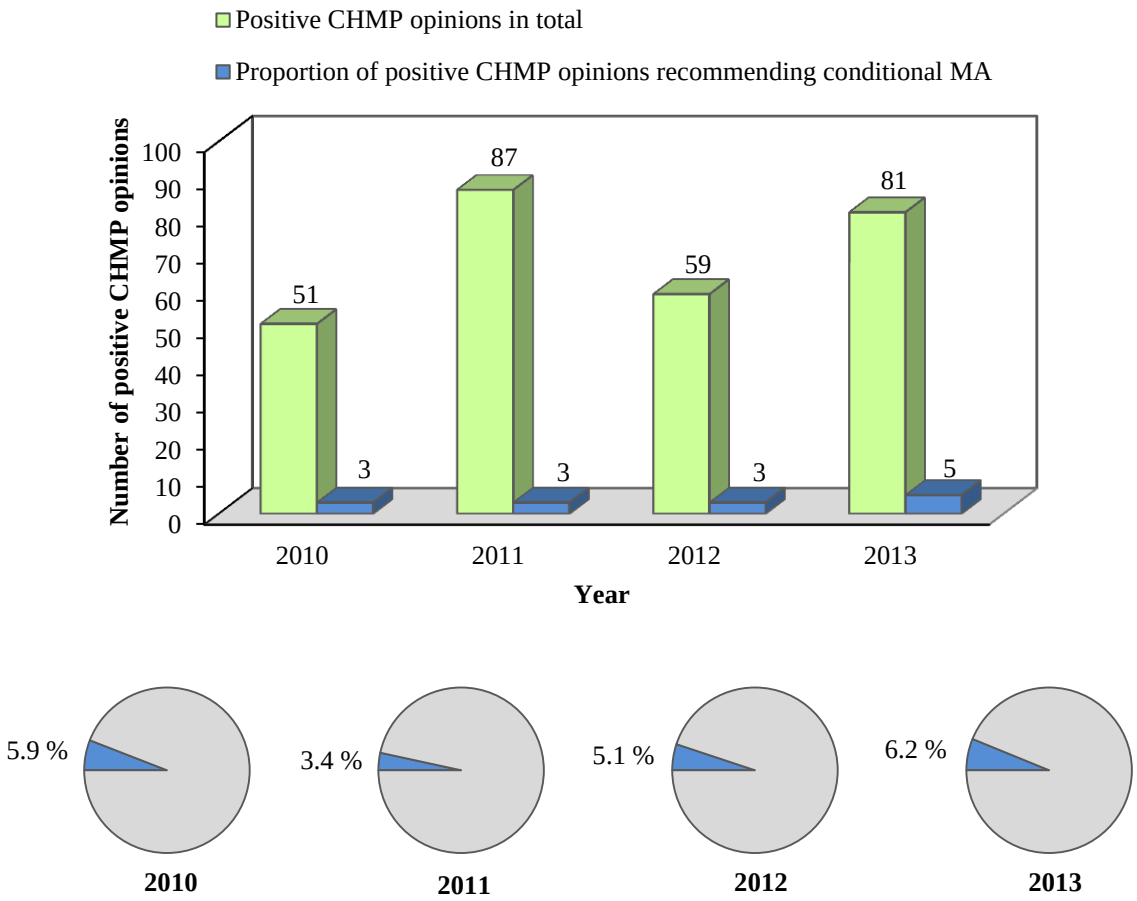


Figure 7: Proportion of positive CHMP opinions recommending conditional MA
Total number of positive CHMP opinions issued from 2010 to 2013 (green) including the proportion of opinions recommending conditional MA (blue) (upper panel). Relative frequencies of positive CHMP opinions recommending conditional MA (in blue) per year (lower panel). Source of data: Number of positive CHMP opinions in 2010 and 2011: Annual Report 2011, EMA (36); number of positive CHMP opinions in 2012: Annual Report 2012, EMA (31); number of positive CHMP opinions in 2013: News and press release archive, EMA website (35); number of positive opinions recommending conditional MA: Register of Human MPs, EMA website (37).

One main reason for this moderate utilisation of the conditional MA concept might be the fact that only a small subset of MPs – mainly MPs for serious, life-threatening or rare conditions with no or few therapeutic alternatives – fall within the scope of Regulation (EC) No 507/2006 and, therefore, qualify for a conditional MA (13) (see section 2.2.1).

In contrast to the conditional MA concept, which is applicable only to certain subsets of MPs, AL would aim at a more comprehensive approach for MP approval. Thus, AL would have to be applied more broadly, i.e. to most new MPs. However, this is not feasible with due consideration of the current legal framework for conditional MAs, which stipulates a variety of requirements that have to be met in order to qualify for this type of MA (Regulation (EC) No 507/2006, Article 2 and 4) (13) (see section 2.2.1).

2.3.2. Limited flexibility of existing medicinal product licensing schemes

According to the current MP legislation, once a MA is granted, this MA is valid for 5 years – except in case of a conditional MA, which is valid for one year (13) (see section 2.2.1) – and can be renewed after five years. The basic idea associated with the renewal of a MA is a re-evaluation of the benefit-risk balance of a MP on the basis of the current scientific knowledge, whilst taking into account the experience made with the MP administered to a significantly increased number of patients under "real-life" conditions. Even though a renewed MA, in general, is valid for an unlimited period of time, the current legal framework allows for a second renewal after additional five years based on justified grounds relating to pharmacovigilance (15, 23) (see section 2.2.8).

In principle, this provides a statutory basis for up to three consecutive assessment and authorisation rounds – particularly in case of a limited number of patients treated with the MP (which would apply to the period following the granting of the initial MA under an AL approach). However, this scenario of three authorisation steps represents the absolute maximum exploitation of the current legal framework for non-conditional MAs – rather than a standard approach – and the timing of the reevaluation and authorisation steps is fixed to the five-year-rhythm (see section 2.2.8).

In contrast, AL would require a more flexible approach of MP licensing with several authorisation steps at variable intervals. These requirements would partially be covered by the conditional MA concept, which represents a more staggered path of MP licensing due to a MA validity of only one year and, consequently, the need for an annual renewal of the MA (unless the conditional MA is converted into a full MA) (13) (see section 2.2.1). However, even the conditional authorisation approach – though allowing for various assessment rounds – is still linked to a fixed schedule for the re-evaluation and authorisation / renewal steps in one-year-intervals rather than representing a truly flexible approach.

Thus, more comprehensive AL approaches would require an adjustment of the current MP legislation in order to facilitate a highly flexible approach of staggered MP approval that meets the requirements of different MPs, patient populations and diseases as well as different stages in the MP's life cycle characterised by varying levels of knowledge about the MP.

2.3.3. Issues regarding a tripartite communication and collaboration between sponsors, regulators and Health Technology Assessment bodies

Most critical to the concept of AL is the establishment of a detailed MP development plan including the requirements for the repeated steps of assessment and authorisation as well as for reimbursement tailored to the respective MP and agreed upon in advance by all stakeholders – sponsors, regulators and HTA bodies (7).

As described in section 2.2.10, the concept of obtaining agreement from competent authorities on a proposed MP development programme (Scientific Advice) is well established and a commonly taken route by a variety of sponsors (30). Moreover, there are initial attempts to establish a tripartite dialogue, which also involves HTA bodies (33, 34). However, AL would require a well-attuned communication and close collaboration between these three parties in all stages of MP development – especially during early stages – in order to agree on a development programme as well as on an authorisation and reimbursement plan in advance (7).

Although the concept of obtaining regulators' agreement on MP development strategies is well established, this does not apply to the proposed approach of parallel Scientific Advice with HTA bodies (34) (see section 2.2.10.). This type of interaction is still in a pilot phase and characterised by limited experience and guidance. Thus, in the past substantial problems have arisen due to a lack of alignment of requirements from regulatory and reimbursement perspective. Some new MPs authorised by the European Commission on the basis of a positive outcome of the assessment of these MPs by the EMA's scientific committees failed to be reimbursed, because they failed to fulfill the requirements of HTA bodies (34). Therefore, substantial efforts are still required to bridge these two areas and harmonise the respective requirements in order to establish a basis for a successful implementation of AL. As a first step, the EMA plans to develop and publish guidance for EMA-HTA parallel Scientific Advice in 2014 (34).

Additionally, the situation is further complicated by the fact that even though requirements for the authorisation of MPs are harmonised across the EU, the field of HTA is considerably less harmonised, i.e. European HTA is more diverse and segmented due to the fact that reimbursement for MPs is a national rather than a European responsibility (34).

Moreover, to date the vast majority of Scientific Advice procedures has related to Phase III of the clinical development (36) (Figure 8), while AL would require an early communication between all stakeholders.

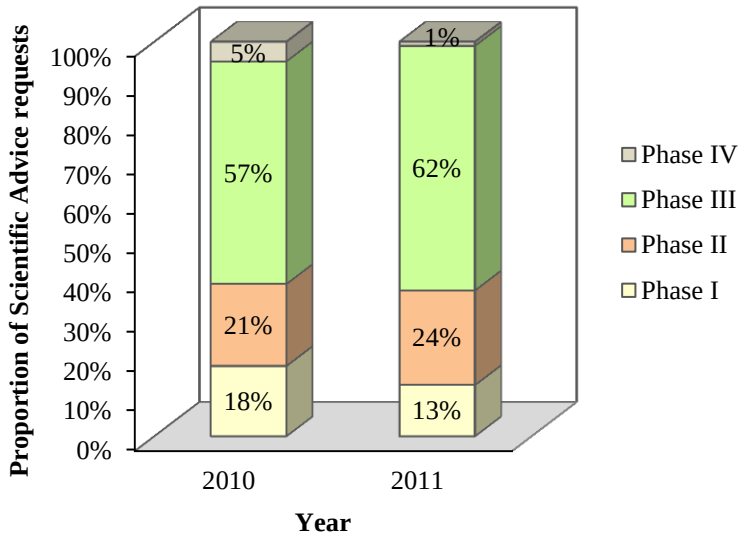


Figure 8: Clinical trial phases of Scientific Advice requests
Proportion of Scientific Advice requests submitted to the EMA in 2010 and 2011 relating to different phases (Phase I - IV) of clinical development. Source of data: Annual Report 2011, EMA (36).

Apart from that, the legal status of the Scientific Advice provided by competent authorities might pose an additional problem. At the moment Scientific Advice is not legally binding on the competent authority or on the sponsor with regard to any future MA application (30). The same holds true for consultations with HTA bodies. Thus, AL would require a new level of collaboration between sponsors, regulators and HTA bodies with a new level of bindingness and commitment, as the AL concept relies on the agreement on a detailed development, licensing and reimbursement plan in advance and adherence to this programme by all stakeholders (7). Nevertheless, it might be necessary to adjust these agreed plans during MP development – as necessary – when new relevant information becomes available. However, this adaptation would have to occur by mutual agreement, which might represent a considerable challenge.

2.3.4. Necessity of increased personnel expenditure

The concept of AL is based on multiple steps of MP authorisation (7). However, these repeated steps of regulatory assessment as well as a close collaboration between sponsors, regulators and HTA bodies in order to elaborate a detailed development / authorisation / reimbursement plan for a new MP in advance would result in a substantially increased expenditure of human labour for all stakeholders. Thus, the implementation of AL would most likely lead to considerably increased staff requirements on all sides. Therefore, in order to implement such a highly labour-intensive concept, appropriate resources would have to be provided.

However, it seems feasible that at least part of the elaboration of a detailed development plan for some MPs could be realised by developing new guidelines or revising existing guidance documents, which would reduce the extent of required interactions between sponsors and competent authorities regarding a specific MP. Nevertheless, appropriate resources would also have to be provided in order to support these activities. Moreover, guidance documents could certainly not completely substitute for a close collaboration between all stakeholders in order to successfully implement an AL approach, for example, because HTA bodies would have to be involved and guidelines are unlikely to cover all specific particularities of MPs developed for a certain indication.

2.3.5. Limitations of data generation following initial licensing

As described in section 2.1.5, an AL approach would require a continuous generation of high-quality data about a MP throughout the product's life cycle in order to facilitate multiple authorisation steps. Knowledge generation might occur through additional clinical studies as well as active and passive surveillance (7). However, this entails several potential issues.

For example, data generation after the granting of an initial MA might be challenging due to ethical reasons. Once a MP has passed regulatory assessment and received an initial MA, it seems to be unethical to perform placebo-controlled studies and assign patients to placebo treatment (7). However, placebo-controlled trials initiated before the granting of the initial MA would still be possible and active comparator-controlled trials might still be feasible in the post-approval period provided that there are existing treatment alternatives. Apart from that, clinical trials in the EU need to be approved by the competent authority of the member state, where the trial is conducted, as well as the responsible ethics committee. As opinions about the ethical acceptability of a clinical trial following the granting of an initial MA might vary, obtaining an approval could be challenging in some cases and / or countries.

Moreover, patients might be reluctant to enrol in randomised controlled trials – even in case of active comparator-controlled trials – once the MP is authorised and potentially available to the patient, as the MA – in current public perception – would imply a certain level of guarantee on the safety and efficacy of a MP. In this case knowledge generation would have to rely on observational data. However, patients' compliance might pose a potential issue here due to the fact that poor compliance could critically influence the benefit-risk assessment. This might ultimately lead to false-negative results during subsequent regulatory approval rounds. Thus, it seems to be questionable whether observational data could be sufficiently robust to substitute for evidence generated by randomised controlled trials. Therefore, a key

goal under the AL concept would be to ensure the availability of high-quality information by establishing measures to enhance patients' compliance (7).

Taken together, under an AL approach initial licensing might render randomised placebo-controlled trials impossible while the generation of high-quality data via observational studies could be difficult.

2.3.6. Limited generation of revenues during early licensing stages

As described above, AL would enable at least some patients to have timely access to new MPs (7). This would be associated with an earlier return of investments for pharmaceutical companies. However, due to the fact that an initial MA would only allow for the treatment of a restricted rather than a broad patient population, the extent of revenues generated – particularly during the initial / early licensing stages – would be limited. Nevertheless, due to less expensive clinical trials, the overall financial balance of innovative pharmaceutical R&D – at first sight – might be favourable under an AL approach. However, in order to evaluate the attractiveness of AL from business perspective for the pharmaceutical industry, additional aspects would have to be taken into account.

According to the current MP legislation, MA holders benefit from a data exclusivity period of eight years for newly authorised innovative products, during which applicants of generic MPs cannot rely on the dossier of reference MPs. Additionally, these generic products cannot be placed on the market until ten years have elapsed from the granting of the MA of the reference MP (market protection period). This period may be extended to eleven years in case of an authorisation of one or more new therapeutic indications of significant clinical benefit compared to existing therapies within the first eight years of the ten years market protection period (Directive 2001/83/EC, Article 10(1); Regulation (EC) No 726/2004, Article 14(11)) (15, 23). Thus, both periods – data exclusivity as well as market protection – would elapse following the granting of an initial MA under an AL approach and these periods would expire after 8 or 10 (+1) years, even though sales are expected to be limited in the initial licensing stage due to the fact that only a restricted population of patients may be treated with the MP. Therefore, savings achieved by less expensive clinical trials might likely be compensated by losses in sales following the granting of an initial MA under an AL approach (compared to the sales following the granting of a full MA under the traditional, binary approach). Ultimately, it remains questionable whether AL, which would reduce the number of patients eligible to be treated with a new MP in the initial licensing stages and, thus, eligible to reimbursement to a relatively small population, would be an attractive route for the pharmaceutical industry.

2.3.7. Challenges to the prevention of off-label use

A satisfactory prevention of off-label use would provide the basis for a successful implementation of AL (7). However, the feasibility of this aim seems to be questionable. In some cases, national health care systems or reimbursement policies may limit permissible use of a MP (8). Moreover, restrictions on MP prescription and distribution can be imposed by competent authorities in the form of the legal status of the MP as well as conditions and restrictions to the MA (see sections 2.2.2., 2.2.3., 2.2.5 and 2.2.9). These restrictions would have to aim at ensuring a tightly managed distribution of the MP including enrollment and education of prescribers as well as registration of patients.

One possible scenario under the current legal framework would encompass that a MP authorised according to the AL concept for the treatment of a restricted patient population would have to be subject to restricted medical prescription, which would need to be reflected in the SmPC in section "4.2 Posology and method of administration" referring to section "4.4 Special warnings and precautions for use". Moreover, the MA holder would have to implement a variety of additional risk minimisation measures as specified in the RMP. These measures would represent conditions to the MA (annex II conditions) and could contain, for example, a controlled distribution / education programme (agreed upon with national competent authorities) in order to ensure that:

- All physicians and pharmacists who intend to prescribe or dispense the MP would receive a Dear Healthcare Professional letter prior to launch
- Prescribers could additionally be provided with an Educational Healthcare Professional's Kit containing, for example, healthcare professional booklets, patient booklets and cards, etc.

Moreover, MA holders could be obliged to implement controlled access programmes in order to prevent but also monitor potential off-label use. These programmes could include, for example:

- Documentation of receipt and understanding of information on the risks of a MP by healthcare professionals and patients
- Enrolment of patients in specific data collection systems, e.g. patient registries collecting at least patient demographics and indications to ensure a systematic patient follow-up
- Dispension of the MP in registered and approved pharmacies

However, it seems unlikely that all these measures can completely prevent off-label use, which is a frequent phenomenon in medical practice – especially in case of serious diseases and / or if there are no satisfactory treatment alternatives for the patient population that would be excluded from the initially approved indication / patient population.

Thus, a successful implementation of more comprehensive AL approaches would probably have to be accompanied by additional measures to prevent off-label use. These measures could encompass new tools to improve the communication and ensure awareness of the uncertainties about an initially authorised MP, for example:

- Post-initial MA informed-consent forms
- Labelling of MPs as "initially authorised" – potentially illustrated by a new symbol appearing in the product information (SmPC, PL)

However, additional provisions would most likely be required in order to ensure adherence to the label, e.g. legislative changes affecting the liability of MA holders and prescribers in case of a documented violation of the approved treatment conditions (given a documented awareness of these conditions) or changes affecting reimbursement of MPs under such conditions.

2.3.8. Potential lack of acceptance of increased uncertainty by all stakeholders

Basically, it remains questionable, whether all stakeholders would be willing to accept an increased level of uncertainty in relation to a new MP, particularly during the initial licensing stages, as constituted by an AL approach. This would likely represent a considerable issue to the implementation of AL.

For example, an increased acceptability of uncertainty by regulators might easily be misinterpreted by the public, patients and physicians as a general lowering of scientific standards. However, AL does not aim at a general lowering of the regulatory bar. Regulatory decisions about the granting of an initial or subsequent MA would not be made on the basis of insufficient data. Indeed, decisions would be based on restricted data requirements, but this would be due to the fact that the approved indication would be restricted as well, because the MA would only be granted for the treatment of a restricted patient population. Thus, AL does not aim at lowering regulatory requirements in general. It rather aims at the reconciliation of an acceptable level of reduced data requirements and a conditional as well as restricted outcome of the regulatory assessment for the benefit of patients with the highest medical need for a new MP.

However, it is not predictable, whether patients and physicians would be willing to take this risk, as the public (and legislators) seemed to have a clear risk-averse disposition in relation to MPs in the past (38). While the public seems to accept certain (small) risks in daily life due to the perception of being able to control these risks, risks related to MPs obviously cause considerable concerns, probably attributable to the impression that these risks are beyond individuals' control.

Moreover, the granting of an initial MA under conditions of acknowledged uncertainty could easily be misinterpreted by the public as shifting the responsibility for this uncertainty about a MP's efficacy and safety to physicians and patients. Thus, acceptance of increased uncertainty under an AL approach is questionable.

Moreover, according to the current MP legislation, authorisation of a MP does not affect the civil or criminal liability of the manufacturer and MA holder (Directive 2001/83/EC, Article 25) (15). As the initial marketing period under an AL approach would be associated with a certain amount of uncertainty about the MP, it seems questionable, whether AL would be considered being an attractive option for pharmaceutical companies. While MA holders would benefit from an earlier return of investments compared to the traditional, binary licensing approach and reduced R&D expenditures due to shorter and less expensive clinical trials, an increased risk resulting from a substantial uncertainty about the benefits and the risks of the MP during the initial marketing period might prevent companies from taking the route of AL.

Even among regulators the acceptability of uncertainty about a MP might vary. This might lead to divergent positions of the competent authorities in different EU countries. Moreover, in case of the centralised procedure, ultimately, the MA is granted by the European Commission (Regulation (EC) No 726/2004, Article 10(2)) (23). However, to date the European Commission does not seem to be convinced that AL is the best way forward regarding MP licensing and, therefore, might be averse to finally taking responsibility for the AL approach (38).

A similar issue as outlined above for the regulators from different EU member states might arise related to reimbursement. As HTA is under national responsibility (34), the acceptance of uncertainty about a MP might substantially diverge between different HTA bodies, potentially resulting in considerable reimbursement issues in certain countries. In Germany, for example, there is a comparative assessment of the additional benefit of a new MP over an appropriate comparator in the first year following the granting of a MA, which represents the basis for price negotiations. Thus, comparative studies and proof of additional benefit over

appropriate comparators are required (39). Under an AL approach it would most likely not be possible to provide this data after the granting of the initial MA, thus, leaving a considerable gap between HTA assessment and the initial MA evidence basis. Consequently, reimbursement could become a critical issue. Moreover, physicians and patients in principle need to know the relative efficacy of a new MP in relation to available alternatives at the time of (initial) approval in order to make objective and well-informed decisions. This lack of comparability might lead to an additional decrease of the acceptance of MPs authorised via an AL approach.

2.3.9. Complexity of global development programmes

Major pharmaceutical companies nowadays usually aim at simultaneous global launches of new MPs at the earliest time in order to maximise profits and provide patients with innovative MPs in a timely manner. However, this approach requires the alignment of the regulatory strategy across many countries and the generation of a global MP development programme. For this purpose, communication with global regulatory authorities should be initiated early in MP development in order to meet the various national requirements. The final goal is a single global clinical development plan that includes the major markets – usually the US, Europe, Japan and other emerging markets (40).

Even under the current traditional, binary licensing scheme this global development plan faces challenges from individual market environments and diverging regulatory requirements that might result in a separate development for some countries. However, this situation would be further complicated in case of the implementation of AL.

As described in section 1.3, proposals for AL have been published under various labels in various countries including the US, Europe and Canada (see table 1). Even though these AL proposals share the common feature of being based on the fundamental idea that knowledge about MPs evolves continuously over time rather than representing a binary process, the different suggestions for the implementation of AL deviate in detail. Thus, national interpretations and implementations of the AL concept might vary, for example, regarding the acceptable level of uncertainty, the requirements that have to be met for the various authorisation steps or the potential issues in terms of reimbursement.

3. Case study

In 2011, the CHMP adopted a new guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (41). This guideline was developed by the Blood Products Working Party (BPWP) – a temporary working party of the CHMP – that was set up to provide recommendations and expertise on all issues relating to the safety and efficacy of blood products (42). In a recent publication, authored by the current chair and vice-chair of the BPWP (Anneliese Hilger and Bengt Ljungberg) and others, it was stated that the scheme for evaluation of factor VIII products described in the new guideline would be in line with the novel concept of AL based on a stepwise learning about a new MP under conditions of acknowledged uncertainty and repetitive cycles of regulatory assessment (43). Therefore, this staggered approach for the authorisation of factor VIII products presented in the guideline is further examined below.

Factor VIII represents one of the essential proteins involved in blood coagulation (blood clotting). Thus, deficiency of factor VIII results in a severe bleeding disorder called haemophilia A (44). Patients suffering from haemophilia A are more prone to bleeding compared to healthy subjects and show prolonged bleeding after injury or surgery. Currently, the treatment of haemophilia A is mainly based upon replacement of the lacking factor VIII in order to prevent or stop bleeding (45).

In order to harmonise requirements for MA applications for recombinant or plasma-derived factor VIII MPs, the BPWP has developed a staged approach to the licensing of factor VIII products laid down in the guideline mentioned above. This guideline describes in detail a stepwise process for the authorisation of these MPs, thereby covering clinical investigations required in the pre- and post-authorisation period (41).

According to the guideline, efficacy must be demonstrated by results of pre-authorisation clinical trials in conjunction with the commitment to perform post-authorisation investigations and bridge in the long term between clinical trial and routine use outcomes. Importantly, appropriate pharmacokinetic (PK) data are the most relevant surrogate endpoints of efficacy of new factor VIII MPs, whereas clinical efficacy should be assessed during a minimum of 50 exposure days. In terms of safety, immunogenicity must be investigated in the pre-authorisation stage – with previously treated patients (PTPs) being the most suitable candidates for testing, as they are considered to be low-risk-patients – and results need to be substantiated with post-authorisation studies. Due to the fact that haemophilia A is a rare disease, the number of patients required for enrolment into pre-authorisation trials is 100, which is considered to be adequate to provide relevant information on general safety aspects

and demonstrate efficacy. Further information, mainly focusing on safety issues, needs to be generated in the post-authorisation period (Figure 9) (41).

Importantly, the guideline proposes a stepwise approach for the clinical development of factor VIII products with the purpose of having some experience in adults and older children before including younger children. Thus, the initial patient population to be investigated are PTPs ≥ 12 years of age. Afterwards, when PK as well as efficacy and safety data from 20 PTPs ≥ 12 years of age for at least 50 exposure days are available, clinical trials in children aged 0 to < 12 years can be initiated. These children should be allocated to two age cohorts (6 to < 12 years and < 6 years) and studies should be started with the generation of PK data followed by investigation of efficacy and safety in 50 PTPs (children) for at least 50 exposure days. These data are required for the granting of the "initial" MAA (Figure 9) (41).

However, the indication will be restricted as to the exclusion of previously untreated patients (PUPs), who have never been treated with clotting factor products, unless efficacy and safety data from 50 PUPs for at least 50 exposure days are available. These PUP studies need to be conducted for all novel, recombinant factor VIII products. For plasma-derived products the need for PUP studies will be considered on a case-by-case basis. In general, PUP studies should be initiated prior to the granting of the MA, once data (50 exposure days) are available from 20 patients < 12 years of age (Figure 9) (41).

Additionally, MA applicants are obliged to submit the clinical study protocol for post-authorisation studies together with the MA application as part of the RMP. Post-approval investigations should be performed in 200 PTPs of a balanced age distribution and at least 100 PUPs for at least 100 exposure days. Notably, a separate progress study report should be provided to the relevant competent authorities two years after the granting of the MA to allow for the evaluation of the recruitment status, progress and adherence to timelines. Post-authorisation investigations should be completed within four years post-approval (Figure 9) (41).

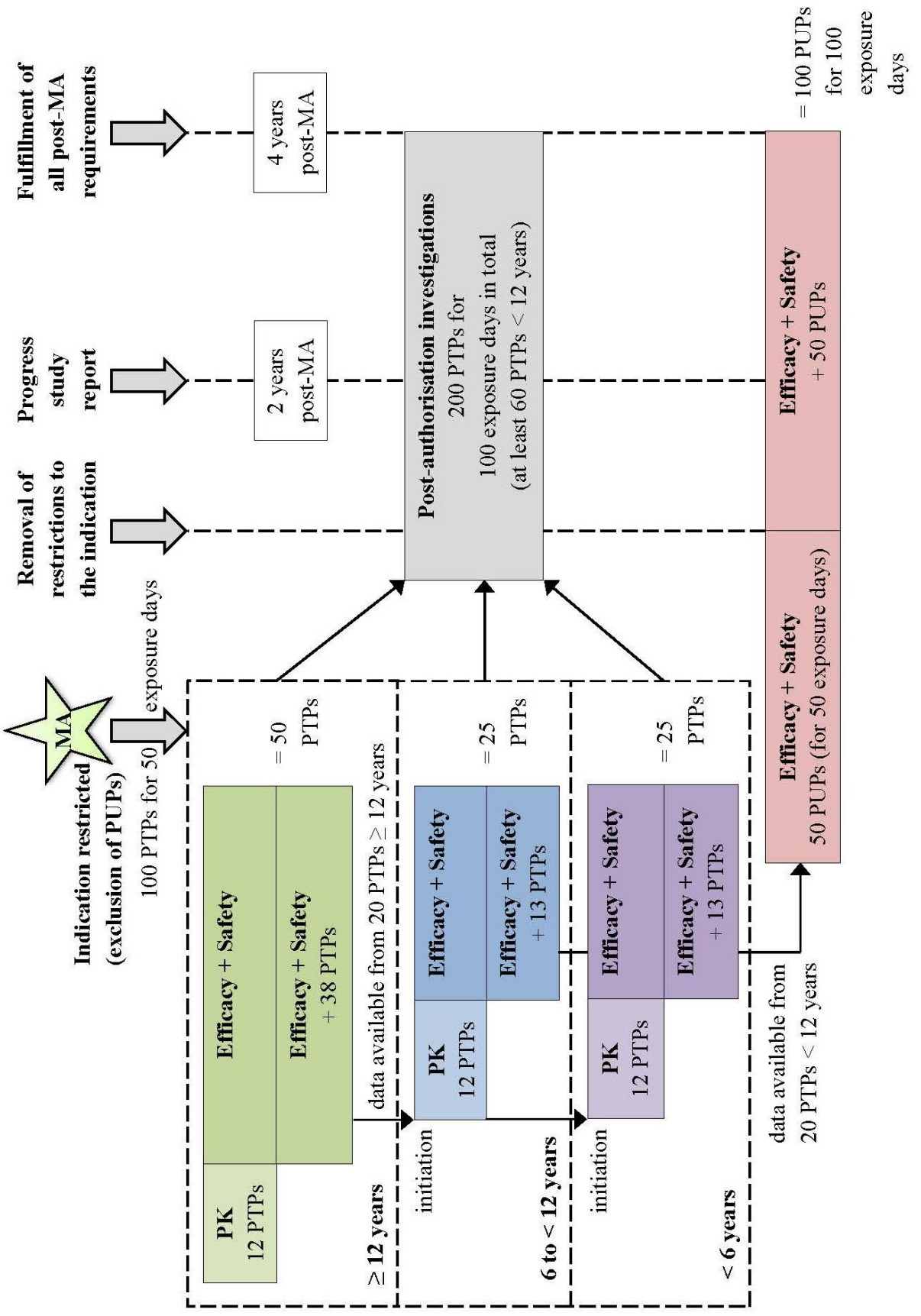


Figure 9: Overview of the clinical trial concept for the investigation of factor VIII products
Overview of the clinical development programme for factor VIII products (modified from the guideline on the clinical investigation of factor VIII products) (41).

Analysis of the staggered approach for the authorisation of factor VIII MPs presented in the guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products has revealed the presence of several elements distinctive of the AL concept in the proposed development and licensing scheme for factor VIII products (41):

1) The (initial) MA is based on data generated in a restricted patient population – in this case PTPs. Consequently, the initial patient population eligible to the MP treatment excludes PUPs. This restriction will be reversed once a predefined amount of data generated in PUPs is available.
2) The development and licensing of factor VIII products follows:
    - A detailed development programme and authorisation plan as specified in the guideline, which defines the requirements for obtaining a MA as well as all necessary post-authorisation activities including the timelines
    - The concept of continuous and stepwise knowledge generation with
        - PK data serving as the most important surrogate endpoints for efficacy
        - Children below the age of 12 being studied only after a predefined amount of data is available from adults and adolescents
        - PUPs being studied only after a specified amount of data is available from PTPs
3) Continuous knowledge generation in the post-authorisation period is associated with iterative rounds of regulatory assessment following the granting of the initial MA:
    - Once efficacy and safety data from 50 PUPs (for at least 50 exposure days) are available → removal of the restrictions to the indication of new factor VIII MPs
    - Two years after the granting of the MA → progress study report to be provided by the MA holder to the relevant competent authorities → evaluation of the recruitment status, progress and adherence to timelines
    - Four years after the granting of the MA (at the latest) → completion of all post-MA investigations → even though not specified in the guideline, this should result in the adaptation of the product information via a variation procedure
    - Five years after the granting of the MA → renewal of the MA

However, there are several elements, which are distinctive of the AL concept, that have not been implemented or addressed in the guideline for factor VIII MPs (41). This includes the following AL aspects:

1) Granting of an initial MA for the treatment of a restricted patient population with the highest medical need followed by subsequent authorisation steps associated with a broadening of the target patient population:
    - Although the initially targeted patient population for new factor VIII products is restricted to PTPs, this population was selected based on safety considerations (PTPs are considered to be low-risk patients in relation to immunogenicity) rather than their medical need for the MP
    - Despite the fact that the guideline for factor VIII products involves iterative rounds of regulatory assessment, the proposed licensing approach still resembles the traditional, binary approach due to the fact that there are actually only two effective / mandatory authorisation steps – the granting of the MA and its renewal after five years
2) Prevention of off-label use: even though the indication of new factor VIII MPs is restricted to PTPs, it remains unclear how treatment of PUPs should be prevented in the early post-authorisation period
3) Intensive communication and collaboration between sponsors, regulators and HTA bodies in early stages and throughout the development of a MP: whereas a close collaboration between sponsors and regulators in order to create a detailed MP development and licensing plan in early stages of MP development has been replaced by a detailed EMA guidance document, the guideline does not indicate an involvement of HTA bodies in the generation of this document and does not address a potential need for alignment of regulatory and reimbursement requirements
4) Acceptability of uncertainty by all stakeholders: the reasons provided under item 3) might result in a lack of acceptance of uncertainty / of the proposed development plan by HTA bodies

Taken together, the guideline for factor VIII products represents a first attempt to implement the concept of AL within the current framework of MP legislation – though revealing that the implementation of a more comprehensive AL approach would most likely require changes of the current MP legislation. The guideline clearly aims at providing patients with timely access to factor VIII products by balancing the extent of clinical data required for a MA against the availability of patients suffering from this rare disease called haemophilia A by proposing a stepwise approach of knowledge generation. However, the guideline for factor VIII products has been strongly criticised for increasing regulatory requirements towards an increased number of patients compared to the previous version of the guidance document, because sponsors are obliged to provide (43):

- Data from 50 children aged < 12 years in order to obtain a MA (previous guideline: 20 children < 6 years, submission in the post-authorisation period acceptable)
- Data from PUP studies as described above (previous guideline: PUP studies not required)
- Post-authorisation data from 200 PTPs as described above (previous guideline: number of patients not specified)

However, these changes are well founded as explained hereafter. The requirement of pre-authorisation data from children below the age of 12 years, for example, is a result of the implementation of the Paediatric Regulation (43) (Regulation (EC) No 1901/2006 amended by Regulation (EC) No 1902/2006), which dramatically changed the regulatory environment for paediatric medicines in the EU as well as the regulatory requirements, especially for new MPs, in terms of paediatric studies (46, 47). In this regard, inclusion of paediatric patients into the pre-authorisation clinical programme ensures the availability of sufficient information on the use of factor VIII products in children and prevents extensive off-label use in this population.

Moreover, the requirement for PUP studies for novel factor VIII MPs reflects the need for reliable data being available for these most vulnerable subjects (43) due to an increased risk of product related immunogenicity in PUPs (41) and, therefore, serves to protect public health. The previous approach of requesting documentation of all PUP treatment has been proven inefficient with extremely limited data finally submitted to the competent authorities (43), which further substantiates the notion that under the traditional, binary regulatory approach, post-approval experience with a MP in patients outside of clinical trials contributes only marginally to evidence generation (7) (see section 2.1.5).

Furthermore, the definition of a fixed number of PTPs for the generation of post-authorisation data reflects the need for a statistically solid basis for the evaluation of the safety and, thus, the benefit-risk balance of new factor VIII products, thereby balancing a potentially low incidence of immunogenicity (generation of antibodies against factor VIII) with the limited number of haemophilia A patients (43).

Therefore, the guideline on the clinical investigation of factor VIII MPs represents an ambitious attempt to balance increased legal requirements (in terms of paediatric studies) and well justified scientific requirements (in terms of data from PUPs and PTPs in the post-authorisation period) with timely access of patients to new factor VIII products by implementing the concept of AL. This approach allows for an early MA for the treatment of both, adults and children, as well as a continuous and proper generation of knowledge in the post-authorisation period.

Notably, MPs for the treatment of haemophilia A authorised in the past can serve as impressive examples for the limited utilisation and / or applicability of the conditional MA approach, even though haemophilia A is well recognised as a debilitating, life-long and maybe even life-threatening disease, because bleeding can occur in various organ systems including, for example, the brain and the gut (44). Thus, factor VIII products – in principle – would fall under the scope of Article 2 of Regulation (EC) No 507/2006 and, consequently, would qualify for the granting of a conditional MA (13) (see section 2.2.1).

Moreover, the prevalence of haemophilia A is approximately 0.7 in 10,000 people in the EU (44), which is below the limit for orphan designation (5 in 10,000 people in the EU) (48). Thus, due to the seriousness and rarity of the condition, MPs intended for the treatment of haemophilia A, in principle, would qualify for orphan medicinal product designation provided that the MP is of significant benefit to those affected by the condition (Regulation (EC) No 141/2000, Article 3) (48). An orphan medicinal product designation would additionally justify the applicability of the conditional MA concept (Regulation (EC) No 507/2006, Article 2) (13). Nevertheless, none of the six MPs approved for the treatment of haemophilia A via the centralised procedure from 1999 to 2013 has been granted a conditional MA (49). However, there are 10 active orphan designations for MPs intended for the treatment of haemophilia A (50) indicating a potential tendency of pharmaceutical companies to aim at applying for orphan medicinal product designation and, consequently, to benefit from the various incentives associated with this status (Protocol Assistance, access to the centralised procedure, ten years of market exclusivity, fee reductions, etc.) (51), thereby not necessarily targeting the granting of a conditional MA.

4. Discussion

Despite the scientific and technological improvements and achievements during the last decades, the pharmaceutical industry is confronted with high attrition rates in MP development and, thus, a substantial decline in R&D productivity (1). This phenomenon might be attributable, for example, to the complexity of biological systems in conjunction with a limited understanding of these complex systems and to increasing regulatory requirements (which have been tightened with each critical incident caused by a new MP in the past (1)), but probably also to suboptimal MP development by pharmaceutical companies.

Facilitating an earlier market access for new MPs via AL has been proposed to be a promising approach in order to counteract this decline in pharmaceutical R&D efficiency (8). However, it remains questionable, whether AL might serve as an appropriate solution for this issue. While AL undoubtedly can reduce the time to get access to a new MP for patients with the most urgent medical need, thus, potentially willing to accept a higher level of uncertainty (7), AL will probably not reduce the time to a full MA in the majority of cases. A delay of the general market access seems to be the more likely scenario for most of the MPs, as the development and authorisation scheme is following a stepwise approach with changing target patient populations and objectives. However, AL may reduce the costs for MP development due to an enhanced communication and collaboration between sponsors, regulators and HTA bodies (7) and, therefore, the facilitation of taking well-informed decisions earlier and continuously throughout MP development. Taken together, AL may not reduce the attrition rate in pharmaceutical R&D, but may decrease the failure rate in late stages of clinical development or post-approval. This would ultimately result in reduced costs for product development and, consequently, counteract the decline in R&D efficiency. However, AL alone can probably not serve as a universal remedy for the productivity crises in pharmaceutical R&D, because AL cannot address all factors that have potentially contributed to the crisis. Recently, Scannell et al. have identified a variety of causes of the decline in R&D efficiency, e.g. (1):

- A constantly improving spectrum of authorised (safe and efficacious) MPs in some therapeutic areas has been setting high standards for newly developed MPs for the same indications in terms of getting authorised and reimbursed. This situation has given rise to a number of secondary, cost-intensive symptoms including, for example, a tendency towards:
    - An increasing size of pivotal clinical trials accompanied by increased levels of noise and heterogeneity in multicentre trials

  - An increasing number of required phase III trials (for example, Invokana containing the active substance canaglifozin, that was authorised in 2013 as mono- and add-on therapy for the treatment of adult patients with type 2 diabetes mellitus for the purpose of improving glycaemic control (control of blood glucose levels) has been studied in 9 main studies involving a total of around 10,000 patients with type 2 diabetes (52))
- Each real or perceived critical event associated with MPs in the past has lowered the risk tolerance of competent authorities and increased regulatory requirements
- R&D spending has considerably increased in the past due to the pharmaceutical industry's tendency – until recent years – to add human and other resources to R&D in response to increasing competition and time pressure
- Overestimation of the ability of advances in basic research and new screening methods has led to the rejection of older, probably more efficient methods to identify MP candidates, resulting in a lack of predictability of clinical success
- Narrow clinical search programmes aim at the identification and verification of precise effects of new molecules designed in view of a single molecular target rather than looking broadly at the therapeutic potential of a new active substance, thus, new and promising therapeutic effects might be overlooked

The factors mentioned above have contributed to an increase in the expenditure of time and money required for the clinical development of new MPs (52), but not all of them can be addressed by AL. However, most of the costs of pharmaceutical R&D are related to the costs of failed projects (8, 52). In this context, AL could reduce late-stage failure rates as outlined above, which represent the major cost driver in pharmaceutical R&D.

Taken together, AL – though probably not being the universal cure for the decline in R&D efficiency – might be a promising attempt to solve at least part of this problem, thereby facilitating timely access of patients to new MPs. However, in order for AL to be a successful approach a variety of requirements would have to be fulfilled.

First, the implementation of the AL concept would require turning away from the current public perception that upon regulatory approval a new pharmacological therapy is raised from "experimental" to absolutely "safe and efficacious" for all patients (7), which is unrealistic even under the traditional, binary licensing approach for the following reasons:

- MP administration is always associated with risks
- There is only partial congruence between the population of patients treated under the strictly controlled conditions of clinical trials and the more diverse population of "real-life" patients (most patients with the disease)
- Some risks are unlikely to be identified in clinical trials, for example, due to the limitation of concomitant diseases or medications in trial subjects, limited number of patients and duration of the trials, rareness of certain risks, etc.

Thus, even under the traditional licensing scheme, a certain degree of uncertainty remains at the time of MP approval and the granting of a MA can only be interpreted as the decision that there is sufficient evidence to prove that for the average patient the benefit of a MP outweighs its risks. Therefore, regulators already need to balance between knowing as much as possible about a new MP, i.e. the need for evidence, and making a product available to non-trial patients as well as facilitating pharmaceutical innovation by providing market access for new MPs.

However, this awareness has probably not sufficiently found wider entrance into public perception yet. As a consequence, increased acceptability of uncertainty would be a crucial factor for the success of the AL concept (7). This would require an unambiguous communication of the aim of the AL approach, which does not target lowering of scientific standards or regulatory requirements in general (7). Instead, AL aims at providing patients with timely access to new MPs in a staggered manner by

1) Granting an initial MA for the treatment of a restricted patient population with the highest medical need followed by
2) Subsequent authorisation steps associated with a broadening of the target population

As the initially approved indication would only allow for the treatment of a restricted patient population that would benefit most from the new MP, the requirements imposed on the net benefit-risk balance for the various authorisation steps would be similar. For the initially approved indication / patient population a higher benefit could outweigh potential risks due to the limited availability of data. However, in order to broaden the target population, knowledge about the MP would have to be generated continuously in the post-initial MA period in order to decrease the level of uncertainty and potential risks. Moreover, in addition to limiting the initially approved patient population, a variety of other risk management measures would have to be implemented. The initial MA status would have to be reflected in the product information. Furthermore, patients and physicians would have to be informed in detail about the knowledge and missing knowledge about the MP and off-label use would have to be

prevented in an effective way (see details below).

In general, the acceptability of uncertainty by all stakeholders will most likely depend on various factors – mainly the severity of the disease and availability of alternative treatment options – as described in detail in section 2.1.2. Thus, it remains questionable, whether a graduated applicability of AL would suffice to successfully implement this concept or if AL would only have to be applicable to a certain pool of MPs or indications – probably still in a graduated way (i.e. applicability of more comprehensive AL approaches in case of life-threatening diseases without or with only limited treatment alternatives). This assumption is due to the fact that it seems to be highly unlikely that an increased uncertainty about a MP would be acceptable, for example, in case of the following situations:

- Benign diseases
- Availability of various and satisfactory treatment alternatives
- Classes of MPs known or predicted to be associated with higher risks, for example, due to the mechanism of action

However, it is worth mentioning that the subset of MPs being subject to the probably highest acceptability of uncertainty, i.e. MPs for serious, life-threatening or rare conditions with few therapeutic alternatives, would – in principle – already qualify for a conditional MA according to the current MP legislation (13). Nevertheless, this possibility has not extensively been exploited in the past, as the most commonly taken route to market is still the traditional, binary licensing scheme (see section 2.3.1). This might have various reasons including the restriction of MPs falling within the scope of conditional approval as well as the fact that a conditional MA is bound to specific obligations and a fixed authorisation schedule with one-year renewal intervals (13) (see section 2.2.1).

Nevertheless, it seems to be questionable, whether a broader applicability of such a staggered licensing scheme like conditional approval, but characterised by more flexibility – like proposed for AL – would encounter broader acceptance by the public, patients and physicians for the reasons outlined above. Moreover, given the fact that under current legislation the granting of a MA does not affect the civil or criminal liability of the manufacturer and MA holder (Directive 2001/83/EC, Article 25) (15) (see section 2.3.8) in conjunction with the uncertainty associated with an initially authorised MP under the AL approach as well as the inadequacy of current data exclusivity / market protection provisions and the limited generation of revenues in early licensing stages (see section 2.3.6), AL might not represent a highly desirable approach for MP licensing from pharmaceutical industry's point of view.

Another prerequisite for the success of AL would be a continuous generation of knowledge about the MP in the post-initial-MA period, as AL aims at obtaining more specific clinical data earlier – to enable regulators to take well-informed decisions on the granting of initial MAs – but throughout the life cycle of the MP. This in turn would require the awareness that the initial MA is conditional and, thus, tied to a strict adherence to post-approval commitments by the MA holder. As demonstrated in sections 2.2.5 and 2.2.8, there are various possibilities to enforce the fulfilment of post-authorisation commitments. However, measures like the suspension or revocation of the MA or refusal of the renewal of the MA might be critical in view of public health, especially in case of withdrawing life-saving MPs from patients lacking alternative treatments. Thus, the success of the AL approach would depend on the reliability of pharmaceutical companies to perform studies agreed upon as well as on an increased collaboration between applicants, regulators and HTA bodies.

Importantly, the new pharmacovigilance legislation adopted in 2010 (Regulation (EU) No 1235/2010 and Directive 2010/84/EU – amending Regulation (EC) No 726/2004 and Directive 2001/83/EC – accompanied by the Commission Implementing Regulation (EU) No 520/2012), introduced a variety of measures in order to facilitate post-authorisation monitoring, risk management and post-approval data generation (14) (see sections 2.2.2 to 2.2.6). Thus, this new legislation – in principle – provides a basis for competent authorities to pursue the AL concept, for example, due to a considerable extension of the regulators' authority to request post-authorisation studies on the safety (PASS) and efficacy (PAES) of a MP. Consequently, the new pharmacovigilance legislation allows for the benefit-risk assessment of a MP being a continuous process. Moreover, the obligation to introduce a RMS and provide a RMP for all new MPs as well as the introduction of the concept of a MA subject to certain conditions constitute a basis for the establishment of various risk management measures supporting the implementation of the AL concept (as described in section 2.2), for example, by facilitating the prevention of off-label use as well as the communication and awareness of uncertainties about new MPs authorised under an AL approach. Furthermore, PSURs can serve as a regulatory tool to provide competent authorities with continuous information on the benefits and risks of an authorised MP at regular intervals as specified in the MA, thus, providing a certain degree of flexibility in terms of data submission intervals depending on the MP under consideration (see section 2.2.7).

However, even though the new pharmacovigilance legislation in general provides a variety of regulatory mechanisms to facilitate the implementation of AL, both Regulation (EU) No 1235/2010 as well as Directive 2010/84/EU specifically state that "it is essential that a strengthened system of pharmacovigilance does not lead to the premature granting of marketing authorisations" (Regulation (EU) No 1235/2010, recital 17; Directive 2010/84/EU, recital 10) (53, 54). This might challenge an exhaustive exploitation of these pharmacovigilance tools for the purpose of granting initial MAs according to the AL concept at an earlier point in MP development compared to the traditional, binary licensing approach.

Moreover, the current MP legislation does not constitute a legal basis for the implementation of more comprehensive AL approaches with multiple steps of iterative regulatory assessment and approval at flexible intervals. At the moment, apart from a MA under exceptional circumstances, which can be granted to MPs, if comprehensive clinical data cannot be provided at all (for example, in case of extremely rare diseases) (55), there are only two potential options for the granting of a MA:

- "Normal" / "full" MA, which would allow for up to three authorisation steps (standard case: two authorisation steps including the initially granted MA and a single renewal) at five-year intervals (see section 2.2.8) (15, 23)
- Conditional MA, which would allow for various authorisation steps, but still at fixed intervals of one year duration and only for a certain subset of MPs falling within the scope of Commission Regulation (EC) No 507/2006 (see section 2.2.1) (13)

Therefore, even the conditional MA concept would not provide sufficient flexibility and, thus, an appropriate legal basis for the implementation of a more comprehensive AL approach for the majority of MPs. However, it might certainly be possible to initiate pilot projects following a less comprehensive AL approach (for example, comparable to the licensing scenario described in the guideline on the clinical investigation of factor VIII products (41)). These pilot projects might include MPs currently being in development and might aim at an evaluation and, finally, authorisation according to the AL concept – most likely on the basis of a conditional MA.

Correspondingly, in the past decade, ideas arose that the AL concept needs to be tested in advance in the form of demonstration projects. In order to address this issue, the Massachusetts Institute of Technology (MIT) along with global regulators (including the EMA), pharmaceutical companies, health care providers, payers and other stakeholders have entered into a collaboration called the New Drug Development Paradigms (NEWDIGS) initiative. This initiative serves to test new ideas and models for MP development in live

demonstration projects using MP pipeline candidates. One module of the NEWDIGS activities focuses on AL and aims at systematically evaluating different pathways of AL through interactive simulations and demonstration projects in a "microenvironment" of agreed policies between all stakeholders (7, 56, 57, 58).

Moreover, the EMA has recently (March 2014) launched an AL pilot project to explore AL with real medicines in development. For this purpose, pharmaceutical companies have been invited to participate in the pilot project by submitting ongoing MP development programmes for consideration as prospective pilot cases (59, 60).

Insights gained from these demonstration and pilot projects might serve as a valuable source of information on the implications of utilising AL as well as the extent of changes in MP legislation required for a successful implementation of AL.

At the moment, the most reasonable scenario for an initial implementation of more comprehensive AL approaches in terms of required changes in MP legislation seems to be the legislative adaptation of the conditional MA concept in that it allows for:

- Regulatory re-assessment and authorisation at flexible intervals, which duration could potentially be further specified in appropriate guidelines → Required revision of the current MP legislation: adjustment of the validity of a conditional MA (Regulation (EC) No 507/2006, Article 6) (13)
- Applicability to a wider range of MPs → Required revision of the current MP legislation: adjustment of the scope (Regulation (EC) No 507/2006, Article 2) as well as the requirements (Regulation (EC) No 507/2006, Article 4) for conditional approval (13)

However, the long-term objective in case of aiming at a broader implementation of AL would probably be a more extensive revision of the current MP legislation, which would, for example, aim at the introduction of the following, additional provisions, tools and regulatory mechanisms:

- New ways of communication to ensure awareness and understanding of a certain level of acknowledged uncertainty, e.g. post-initial MA informed-consent forms, labelling of MPs as "initially authorised" – potentially illustrated by a new symbol appearing in the product information (SmPC, PL)
- A new reward / incentive / exclusivity structure, e.g. extension of the data exclusivity and / or market protection period in the context of a broadening of the approved target patient population; possibility for multiple and / or flexible extensions based on the added value of the broadening for public health

- New / additional mechanisms to prevent off-label use, e.g. shift of liability in case of proven off-label use from MA holders to prescribers, who have a proven record of education regarding the risks and uncertainties as well as the restrictions to the label of a new MP authorised according to the AL concept

Moreover, substantial efforts in terms of the establishment of an early communication and close collaboration between sponsors, regulators and HTA bodies with an enhanced level of bindingness of the advice, provided by regulators and HTA bodies, would still be required. This would include the finalisation of the parallel Scientific Advice guidance documents as well as the extension of this concept beyond the pilot phase (34) towards a more commonly used approach including the provision of required financial and human resources (see sections 2.3.3 and 2.3.4). Furthermore, an attempt to harmonise European HTA / reimbursement requirements (comparable to the regulatory requirements) for MPs would be desirable in order to bridge potential gaps or discrepancies between both areas. This harmonisation could be initiated and further developed by the European Commission and EUnetHTA, which is a network for HTA across Europe with the aim of developing reliable, timely, transparent and transferrable information to contribute to HTAs in Europe. EUnetHTA supports the collaboration between various HTA bodies and, therefore, represents an initial attempt to harmonise HTA methods and processes and, thus, HTA requirements in Europe (61).

In parallel, a regular and intensive communication and collaboration between international competent authorities and HTA bodies aiming at a common interpretation and implementation of the AL concept would be highly desirable. Such harmonisation activities would facilitate the generation of global MP development programmes and would, therefore, support pharmaceutical R&D and ensure a timely access of patients to new MPs at a global level.

Taken together, in the recent past there has been much debate about adaptive pathways for MP licensing known as “adaptive licensing”, “staggered approval”, “progressive authorisation”, etc. More recently, the terms “Medicines Adaptive Pathways” or “Medicines Adaptive Pathways to Patients” have been brought up for discussion as a potentially more appropriate terminology (60). Although there are still various obstacles to the implementation of more comprehensive AL approaches, the AL concept seems to be a promising approach to provide patients with the most urgent medical need for certain MPs with early access to these products. Moreover, AL would support pharmaceutical innovation and counteract the decline in R&D efficiency by reducing the risk of late-stage failure due to an early and intensive collaboration between sponsors, regulators and HTA bodies.

5. Outlook

The crisis in pharmaceutical R&D efficiency (1) as well as the occurrence of an unmet medical need in several therapeutic areas has become a broadly acknowledged issue in the last years. Patients often do not have timely access to new MPs due to long development processes (approximately 9 years from the beginning of the clinical development to market access). The cost, size and complexity of clinical trials required to obtain a MA have been increasing continuously without a concomitant increase in the number of new MP approvals or a decrease in attrition rates in MP development (62). Thus, the common goal of all stakeholders (sponsors, regulators and HTA bodies) should be to provide patients with new, efficacious, safe and affordable MPs in a timely manner while, in parallel, supporting pharmaceutical innovation. However, this can only be achieved by combined efforts made by all stakeholders in a highly collaborative way. Thus, it seems to be unrealistic that legislators and regulators alone can solve the problem of unmet medical needs and a decline in R&D productivity by exclusively changing the MP licensing paradigm. Pharmaceutical companies need to develop better approaches to preclinical and clinical development of MPs characterised by a higher predictability of the success of a MP in earlier stages of development. However, legislators and regulators are required to support these activities and create new incentives for pharmaceutical innovation.

From a present day perspective, AL might address some of the issues currently faced by patients as well as the pharmaceutical industry. Some elements of the AL approach could per se considerably improve the situation, for example, the establishment of an early and close collaboration between sponsors, regulators and HTA bodies in order to optimise research strategies and streamline MP development programmes. However, the implementation of the AL concept would be associated with a variety of challenges. Moreover, it seems obvious that AL alone cannot overcome the phenomenon of a declining R&D efficiency or increasing R&D costs.

Indeed, a large proportion of rising R&D costs is due to the high failure rate in clinical development (about 90%) (8). However, though AL would potentially allow some MPs, which would otherwise be abandoned, to be brought to the market and to be further developed, the AL concept would not address the scientific uncertainty and prediction failures of the success of a MP that underlie the high attrition rate.

Recently, it was shown that 66% of the combined phase III and submission failures from 2007 to 2010 were attributable to a lack of efficacy (nearly half against placebo) and 21% to a lack of safety (63). Similarly, from 2011 to 2012, the proportion of failures attributable to a lack of

efficacy or safety was 52% and 35%, respectively (64). This lack of predictability cannot be addressed only by changing the MP licensing paradigm. However, an early and close communication and collaboration between sponsors, regulators and HTA bodies might result in a decrease of late-stage failures. Moreover, the AL approach combines various authorisation steps occurring earlier in MP development with shorter and less expensive clinical trials, thus, potentially decreasing R&D costs by reducing the expenditure of time and money up to the decision of abandoning a MP.

However, it was shown that a large number of failures occurs with MPs possessing novel mechanisms of action in areas of high unmet medical need – especially cancer (28% of phase III and submission failures from 2007 to 2010) and neurodegeneration (18% of failures from 2007 to 2010) (63). These are lucrative areas in terms of potential revenues, however, science is challenging in these areas resulting in an increased risk for failure – a fact that cannot be addressed by AL.

Thus, it appears obvious that combined efforts from pharmaceutical companies, regulators and HTA bodies will be required to overcome the crisis in pharmaceutical R&D efficiency and the occurrence of an unmet medical need in several therapeutic areas.

6. Summary

The pharmaceutical industry has been confronted with a considerable decline in R&D efficiency during the last years (1). In parallel, there is a high unmet medical need in several therapeutic areas and patients often do not have timely access to new MPs due to long development processes (62). Thus, calls for regulatory changes to support pharmaceutical innovation and timely access for patients to new MPs have been put forward. One concept that has been proposed as a potential approach to solve the problem of the decline in R&D productivity and the unmet medical need in a variety of therapeutic areas is AL (7, 8).

Under the traditional, binary MP licensing approach, the life cycle of a MP is divided into two distinct phases – the pre- and the post-approval period – separated by the granting of the MA. In contrast, the basic principle of AL is the idea that evidence generation in MP development is a continuum and, thus, MP licensing should follow a stepwise approach characterised by continuous learning and progressive reduction of uncertainty about a MP. Therefore, in an AL setting, the traditional key event of receiving a single MA that raises the status of a new pharmacological therapy from "experimental" to "safe and efficacious" would be replaced by multiple regulatory assessment and authorisation steps. Initially, administration of a new MP authorised under AL would be restricted in accordance with the current level of knowledge, for example, to a certain patient population with the highest medical need for the MP, and would be extended during subsequent authorisation steps based on the continuous generation of evidence (7).

However, in order for AL to be a successful approach a variety of prerequisites would have to be fulfilled including an increased acceptability of uncertainty about a MP by all stakeholders, the prevention of off-label use, a truly continuous, robust and reliable generation of knowledge during the product's life cycle as well as an intensive communication and collaboration between sponsors, regulators and HTA bodies starting early and continuing throughout MP development.

Currently, there is a variety of regulatory mechanisms in place that would facilitate the implementation of AL, for example, by allowing for a continuous knowledge generation (possibility to impose PASSs or PAESs), a controlled distribution to prevent off-label use and minimise risks associated with a MP (legal status of the MP, MA subject to certain conditions, PAMs, RMP, additional risk minimisation measures, etc.), a staggered approval process (conditional MA) and iterative rounds of regulatory assessment (PSURs, renewal of the MA) as well as an early communication between sponsors, regulators and HTA bodies (parallel Scientific Advice).

However, there are several outstanding issues and gaps in the current regulatory and legal framework that counteract the implementation of more comprehensive AL approaches. This includes the limited flexibility of current licensing schemes defined by the current MP legislation, the restricted applicability of the existing staggered approval pathway (conditional MA), the fact that the establishment of a tripartite communication and collaboration between sponsors, regulators and HTA bodies is still in progress, the limitations of robust data generation following the granting of an initial MA, the limited generation of revenues in early licensing stages given the limited number of patients initially eligible to the new MP as well as a potential lack of acceptance of increased uncertainty about a MP or the whole AL concept by all stakeholders.

Therefore, the current MP legislation does not constitute an appropriate legal basis for the implementation of more comprehensive AL approaches. However, current provisions might certainly allow for the initiation of pilot projects following a less comprehensive AL approach. Insights gained from these pilot projects might serve as a valuable source of information on the implications of utilising AL as well as the extent of legislative changes required for a successful implementation of AL.

Ultimately, a broad implementation of more comprehensive AL approaches would most likely require an extensive revision of the current MP legislation aiming at the introduction of a variety of new provisions and regulatory mechanisms, e.g. a new legal basis for multiple steps of iterative regulatory assessment and MP authorisation at flexible intervals, new ways of communication to ensure awareness and understanding of a certain level of acknowledged uncertainty about a MP, novel reward and data exclusivity provisions to support pharmaceutical innovation, additional mechanisms to prevent off-label use, etc.

Moreover, substantial efforts are still required in order to establish a close collaboration between sponsors, regulators and HTA bodies as a standard feature in MP development – with an enhanced level of bindingness of the advice provided. Furthermore, an attempt to harmonise European HTA / reimbursement requirements for MPs would be highly desirable. In parallel, a regular communication and collaboration between international competent authorities and HTA bodies aiming at a common interpretation and implementation of the AL concept in order to facilitate the generation of global development programmes would be a preferable path forward.

Taken together, although there is a variety of obstacles to the implementation of more comprehensive AL approaches, the AL concept seems to be a promising approach to provide patients with the highest medical need, thus, potentially willing to accept a higher level of uncertainty about a MP, with early access to new MPs. Moreover, AL would support pharmaceutical innovation and counteract the decline in R&D efficiency by reducing the risk of late-stage failure and, therefore, the costs of MP development by facilitating an early and intensive collaboration between sponsors, regulators and HTA bodies. However, AL alone will probably not suffice to overcome the crisis in pharmaceutical R&D efficiency.

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Bonn, den 31. März 2014