

## Development of Innovative Medicines for European Patients and Impact of Brexit

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### Abstract

European patients may benefit from innovative medicines only at the end of a complex process with a sequence of positive decisions on different levels by different stakeholders. The decision of the industry to invest in a usually global clinical development must be followed by a European marketing authorization decision and a mostly national decision on price and reimbursement until finally patients and their physicians can make an individual treatment decision. Development strategies must consider the evolution of scientific and procedural requirements. Current trends are characterized by an enhanced cooperation of regulators and health technology assessment-bodies. The increasing availability of innovative personalized or precision medicines is reflected in the new procedural tools like European Medicines Agency's priority medicines scheme and adaptive pathways concept. The UK decision to leave the EU will have consequences for their contribution to the European regulatory and health technology assessment network. Current strategies for the successful development of innovative medicines may need adjustments to address both scientific and political changes.

**Keywords:** Regulatory affairs; Marketing authorization; Health technology assessment; Reimbursement; European Medicines Agency; Innovative medicines; Precision medicine; Personalized medicine; Brexit

### Abbreviations:

CHMP: Committee for medicinal products for human use; EMA: European Medicines Agency; EU: European Union; FJC: Federal Joint Committee; HRQL: Health-related quality of life; HTA: Health technology assessment; MAH: Marketing authorization holder; MHRA: Medicines and healthcare products regulatory agency; NICE: National institute for health and care excellence; SME: Small and medium sized enterprises; UK: United Kingdom

### Introduction

During the past 10 years the centralized procedure has become the preferred and de facto only way to a European marketing authorization for innovative medicines. The European Medicines Agency (EMA) has been working on several initiatives for updating and improving the content and procedures of their scientific assessments [1]. The historic decision of the United Kingdom (UK) to leave the European Union (EU) is expected to precipitate profound political, economic and legal changes, which must be expected to include the regulation of medicines. Brexit-induced changes in EMA's regulatory procedures are not expected before negotiations between the UK and the EU are finalized (i.e., not before 2019). In light of the usual long time frame for the development of an innovative medicine, the proactive adaptation of the development strategy in advance of the expected changes of European regulators' and possibly Health Technology Assessment (HTA)-bodies' procedures may be helpful.

Cooperation between the EMA and national HTA-bodies has been intensified [2] based on the common goal to foster an early and broad access of EU patients to innovative medicines. The UK's Medicines and Healthcare products Regulatory Agency (MHRA) and the National Institute for Health and Care Excellence (NICE) have been important contributors. In the centralized procedure for EU marketing authorization, the UK resp. MHRA has been in the crucial role of Rapporteur more often than any other member state, and NICE has been a most important partner. As UK and the diminished post-Brexit-EU redefine their relation we may expect more or completely independent assessments by the UK authorities that will differ from the European consensus EMA has created in the centralized procedure so far. And we may also expect that the position of the remaining post-Brexit EU regulators (without the important UK contributions) may not be quite the same as it used to be in consensus with UK colleagues. Particularly procedures like EMA's priority medicines (PRIME) scheme that involve not only regulators, but aim for an early participation of various stakeholders, may be affected by this development. The early and sustainable access of patients to innovative medicines both in the post-Brexit EU and in the UK may require significant adaptations in the development strategies.

### Milestones in the Development of Innovative Medicines

For European patients to benefit from innovative medicines a series of crucial decisions on different levels is required, from the global clinical development through the European Marketing Authorization, national price and reimbursement decisions to the final individual treatment decision.

In this series of sequential decisions several stakeholders – each with different interests and mandates – must agree; each stakeholder must contribute their own positive decision. Table 1 gives a simplified overview on decision points in the development of innovative

medicines for patients in the EU. Although separate decisions, they are interconnected and there is an increasing awareness of the mutual influence between different parts of this sequence. For example, there are several initiatives promoting the incorporation of patients' perception into the overall process as early as the assessment for marketing authorization [3,4].

Decision Point	Initiation of Clinical Development	Marketing Authorization	Pricing and Reimbursement	Treatment Decision
Decision Maker	Industry, Investors	European Medicines Agency, European Commission	HTA payers, bodies	Patients, Physicians
Level	Global	European	National or regional	Individual
Decision criteria	Expectation of economic success	Evidence of a positive benefit risk balance	Evidence of quantifiable benefit for patients, cost-effectiveness	Expectation of treatment success for patient

**Table 1:** Stakeholders in the development of innovative medicine for European patients.

The first crucial decision is the initiation of the clinical development. Clinical development will usually be global, and frequently it will be multinational companies, global players who make this decision based on their expectation of an attractive return on investment.

Until now multinational development usually tried to balance the geographic and ethnic distribution of study participants considering the EU as one entity. In the future it may be challenged whether UK patients may be fully representative for post-Brexit EU patients and vice versa. EMA's current initiative to update their guidelines on first in human clinical trials [5] was meant to provide improved and harmonized safety standards. It remains to be seen whether and to what extent UK – the country with the second highest number of clinical trials in Europe will adopt this guideline nationally or whether different safety standards for clinical trials in the UK and in the EU will emerge.

### Regulators Assessment for the Decision on Marketing Authorization

The clinical development of a medicine may be global; the next crucial step, the marketing authorization application is not. There are separate applications and procedures e.g., for the USA, the most profitable market where most innovative medicines become available for patients for the first time, or for China, the market with the most numerous potential patients, or the EU – and in future possibly for the UK. In the EU the EMA will assess the new medicine in the Committee for Medicinal Products for Human Use (CHMP), with one CHMP member from each member state (until now including the UK). The CHMP will decide – preferably finding a consensus in a scientific discussion or if necessary by majority – whether or not a medicine shall be granted a marketing authorization by the European Commission for the EU. This decision will be based on the balance of

efficacy and safety, or favorable and unfavorable effects, or the benefit-risk balance.

Of particular interest for innovative medicines are two new regulatory concepts: Adaptive pathways and the priority medicines scheme (PRIME). PRIME is meant to support the marketing authorization application, to accelerate and facilitate the regulatory procedure for medicines that are expected to fulfill an unmet medical need to a significant extent and to set new standards in treatment [6]. Exceeding the support for the regulatory procedure for marketing authorization, EMA embraces the new role not only as gatekeeper but as driver or enabler of development [7,8] reaching out to other stakeholders e.g., HTA-bodies and payers to ensure that the early marketing authorization is not made meaningless by delayed or negative decisions on reimbursement. To that end, in a PRIME procedure a CHMP member will be appointed Rapporteur for the medicines possibly years before the actual submission of a marketing authorization application. This Rapporteur will use the vast resources of the full EMA network to prepare for a fast and successful assessment, enlisting experts from various working parties and committees for support. Together with EMA staff, the Rapporteur will explore option of waiving or reducing EMA fees. The Rapporteur will furthermore involve other stakeholders like HTA-bodies and patients' organizations to proactively clear obstacles that may prevent an early access for patients after the marketing authorization.

To get this first class express ticket to the European market only two conditions must be met: firstly an unmet medical need and secondly the reasonable expectation of a significant benefit, the potential to become a game-changer.

Special features of PRIME are the privileges for small and medium-sized enterprises (SME) and academia. Not only will they profit from fee waivers or fee reductions, they may start much earlier than multinational companies to receive PRIME's additional support by EMA, e.g., consult the appointed Rapporteur and get multi-stakeholder advice from regulators, HTA-bodies and patients' organizations. Whereas usually the proof of concept would be expected for eligibility for PRIME, the absolute minimum SMEs need to show for PRIME is the proof of principle, mostly non-clinical data – although, some evidence for pharmacological activity in humans would certainly be helpful.

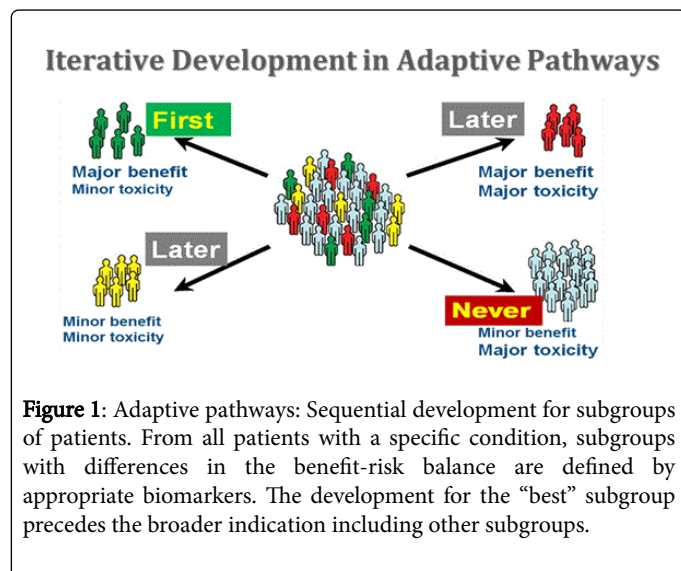
Within PRIME or on its own, adaptive pathways is another recent European regulatory initiative. First introduced under the name of adaptive licensing [9] its principles are increasingly incorporated and may be expected to become the preferred approach in the development of future medicines [10].

With the objective to get innovative medicines to patients more quickly the EMA's homepage elaborates the defining characteristics of adaptive pathways:

- Iterative development – in stages or with a conditional approval
- Early involvement of HTA-bodies and patients
- Using real world data as supplement to clinical trial data

It seems important to emphasize that the real world data are to be used as supplement to, not as substitute for clinical trial data. This means, the adaptive pathways concept does not lower the bar for marketing authorization. On the contrary, if the adaptive pathways concept uses approval in stages, the benefit-risk balance in the initial marketing authorization application may even be particularly positive.

The idea is to identify subgroups of patients who are most likely to have the most pronounced benefit – and/or who have the lowest risk for adverse effects. The initial marketing authorization application would be for this “best” subpopulation. Only later variation procedures would expand the indication to other patient populations with a less impressive but still positive benefit-risk balance.



**Figure 1:** Adaptive pathways: Sequential development for subgroups of patients. From all patients with a specific condition, subgroups with differences in the benefit-risk balance are defined by appropriate biomarkers. The development for the “best” subgroup precedes the broader indication including other subgroups.

The other approach is the use of a conditional approval based on convincing effects on a surrogate endpoint, for example some imaging method. The condition for a switch from the conditional to a full marketing authorization would be the confirmation by the clinical outcome, which may include the ultimate endpoint “survival”.

### The Interface between Regulatory Assessment and HTA

From HTA-bodies’ or payers’ perspective it is important to realize that regulators’ assessment of the benefit-risk balance, particularly in the adaptive pathways scenario, may focus on conclusive evidence that the absolute benefit-risk balance of a medicine is positive, whereas regulators may be more lenient regarding matters of relative benefit-risk, i.e., the comparison with alternative therapeutic options.

As the appropriate use of a medicine may strongly depend on national medical practice or the availability of alternative treatment options, it will be difficult to define the new medicines’ exact place in the therapeutic armamentarium at the time of the assessment for marketing authorization. Theoretically, this might even mean that EU-regulators could approve a medicine that is inferior to a previously approved product. Patients for whom the alternative product is not an option (e.g., due to a negative or delayed reimbursement decision) may of course benefit from the possibly inferior product – as long as the absolute benefit-risk balance is positive. At the same time it is conceivable that – depending on the availability of the previously approved superior medicine – the prescription of the inferior product may not be justified in other regions or EU Member States. The wording of the approved indication would reflect this, e.g., by restricting the indication to patients, for whom treatment with the superior medicine “is not an option”. It may be interesting to see whether MHRA approvals that no longer need to compromise with other EU members will use different indication wordings. If a comparator that has an impact on the indications has not been

authorized or is not marketed in the UK but in any of the post-Brexit EU Member States, differently worded indication may be unavoidable.

### Health Technology Assessment for Decisions on Price and Reimbursement

The collaboration with HTA-bodies is one of the principles of PRIME and the concept of adaptive pathways has explicitly been included in the Medicines Agencies Network Strategy [11]. Since HTA-bodies use the regulators’ benefit-risk assessment with its rationale and conclusion as basis or starting point for their own assessment, a divergent development between UK’s NICE and the HTA-bodies of post-Brexit EU Member States seems likely. Without the valued contribution of NICE the majority positions in organizations like EUnetHTA may shift. At the same time the example of Brexit may strengthen the conviction of several participants that a European approach to HTA will not be possible for the foreseeable future and HTA, price and reimbursement decision must remain in the national (or even regional) responsibility. With that in mind the next crucial step in the development of innovative medicines will be discussed for the example of Germany, the biggest market with the highest number of patients in the post-Brexit EU.

After a medicine has been granted a European marketing authorization the German “Gemeinsame Bundesausschuß” (Federal Joint Committee, FJC) will assess the so-called “additional” benefit of this medicine, which is crucial for reimbursement and pricing decisions. In the FJC, payers (Central Federal Association of Health Insurance Funds), providers (German Hospital Federation, National Association of Statutory Health Insurance Physicians, and National Association of Statutory Health Insurance Dentists) and patients (or rather their representatives nominated by The German Council of People with Disabilities, the Federal Syndicate of Patient Interest Groups, the German Syndicate of Self-Help Groups and the Federation of German Consumer Organisations) come together. They will determine whether or not the new medicine is better than the alternative treatment options already available in Germany.

Usually the evidence required by the FJC will exceed what is needed for a marketing authorization [12]. Demonstration of an additional benefit will usually mean a direct head to head comparison with the standard treatment. Regarding endpoints the national German legislation makes the FJC quite conservative or demanding with mortality or morbidity as the preferred endpoints and little or no place for surrogate endpoints. The explicit encouragement for the use of Health-Related-Quality-of Life-(HRQL)-data is an interesting opportunity. HTA-bodies and regulators alike will certainly welcome sound and meaningful HRQL-data.

The lack of a generally accepted gold standard methodology and different preferences by different HTA-bodies may have hindered a more widespread and more meaningful use. With UK’s NICE leaving the EU network of HTA-bodies the FJC’s requirements for HRQL-data and FJC’s expectations regarding methodology and data quality may gain weight particularly if they can be aligned with the evidence required by regulators. The use of surrogate endpoints in pivotal clinical trials is explicitly recommended by EMA in the adaptive pathways concept, but may be a challenge for HTA-bodies and decision makers on price and reimbursement. For the FJC the legal framework defines relevant endpoints, for example mortality, morbidity, quality of life, or fewer side effects, whereas surrogate parameters are not mentioned [13]. Other HTA-bodies may be less

categorical, but most feel some unease to accept surrogates as basis for pricing.

An interesting problem is the relative weight given to surrogate or clinical endpoints, if these show different results. Assuming a first price is based on surrogates, will the price later be corrected when the outcome data become available? If the outcome data confirm the positive benefit-risk balance but are not quite as good as expected, i.e., the effect on the clinical outcome is not as big as hoped for; this may certainly justify a price decrease. But vice versa? What if the final clinical outcome data are surprisingly good, exceeding expectations? It is hardly conceivable how an increase of the previously agreed price would be politically feasible.

The approval in stages is characteristic for adaptive pathways that may be integrated in the development of medicines in the PRIME scheme. From a regulator's perspective, the advantages of an early market authorization for a selected subgroup of patients are counter balanced by the disadvantage that this very first marketing authorization sets the relevant date for the data protection period. There will not be the full protection period for the expanded, broader indication but only for the first possibly small subgroup. For HTA and price and reimbursement decisions, however, the "approval in stages" approach may bring some challenges. An initial marketing authorization for the very best subgroups supposedly with the most impressive benefit-risk balance and the biggest additional benefit will favor a high price. But thereafter, the indication will be expanded, possibly repeatedly. Further patient groups will be added to the supposedly best patient population of the initial marketing authorization. Their benefit-risk balance will certainly be positive but not as outstanding as in the first, "best" population. To reflect this it may become necessary to adapt the price to the new expanded indication. The new scientific findings may precipitate a new benefit assessment by the FJC and new price negotiations [14]. It is quite conceivable that there could be several variations adding various subgroups. The repeated stepwise expansion of the initial, narrow indication requires repeated re-assessments of the additional benefit and negotiation on price adaptations, possibly in rapid succession.

### Patients Access to Innovative Medicines

It is remarkable that the clear majority of presumably innovative medicines are not considered to provide an additional benefit. Distinguishing different indications, this is particularly obvious for the indication diabetes mellitus. At variance, the indication cancer has the highest percentage of new medicines that provide even a considerable added benefit [15]. The FJC's assessment of an additional benefit is of great importance since it is the basis for the next step, the price negotiation between Marketing Authorization Holder (MAH) and payers. If there is no additional benefit at all, with other words, if the new medicine is not better than medicines already available the price of the comparator becomes the so-called reference price, i.e., the maximum acceptable price. If the FJC did find an additional benefit the price will be negotiated between MAH and payers based on the size of

the additional benefit and the cost of the available alternative treatment. For the duration of the negotiations, up to but not exceeding 12 months, the MAH sets prize. After 12 month, the usually lower price agreed in the negotiations is applied.

If negotiations fail to reach an agreement, a prize can be set in an arbitration procedure. The MAH may or may not agree to the result of the arbitration. If the arbitration is accepted by the MAH the arbitration price applies retroactively from the time point the negotiation ended unsuccessfully, i.e., 12 months after the marketing authorization. The ultima ratio for a MAH who cannot or will not accept the arbitration price is the withdrawal from the German market.

So far, only very few medicines for which no compromise between MAH and payers on a fair price was possible have been withdrawn from the German market [15]. In line with the results of the FJC's assessment of the additional benefit, medicines for diabetes mellitus are withdrawn most frequently (Table 2) whereas only one oncology medicine has been taken off the German market as reaction on a "no additional benefit" assessment and the resulting low price [16,17]. As a result, almost all innovative medicines are available for patients and reimbursed by the health system. In addition the acceptance of the MAH's price until the negotiations between MAH and payers are concluded is a strong incentive to launch marketing as soon as possible after the marketing authorization was granted.

There are huge national differences in the delay from regulatory approval to factual availability, i.e., first sales. In 2015 the range exceeded a tenfold delay with as little as 1.9 months for the USA and 21.3 month for Greece [18].

In Europe access of patients to innovative medicines was best in Germany with 30 innovative medicines entering the market in 2015 on average 3.5 months after marketing authorization and UK with 25 innovative medicines entering the market in 2015 on average 3.9 months after marketing authorization (all data from 18). Although Germany and the UK were best in Europe they still cannot match the USA (42 innovative medicines in 2015 with 1.9 months from marketing authorization to launch).

With UK leaving the EU, the difference in patients' access to innovative medicines between European and US-patients must be expected to widen. The loss of MHRA's and NICE's contribution to the European networks will at least temporarily impede the progress towards a better convergence of regulatory and HTA positions. Remaining EU member states will have to fill the gap. With an important share of the European market and established cooperation between strong national HTA-bodies and regulators France, Germany Italy and Netherlands appear likely candidates with Spain in a less favorable position due to the regionally divided responsibilities of HTA-bodies. Preparing for the impact an unmitigated Brexit may have on the development of innovative medicines for the European market it appears prudent to seek joint advice from HTA-bodies and regulators who are most likely to take a leading role in a post-Brexit EU.



Active Substance	Indication	Marketing Authorization Holder
Aliskiren/Amlodipin	Hypertension	Novartis Europharm Ltd
Bromfenac	NSAID	Croma-Pharma GmbH
Canagliflozin	Diabetes Type II	Janssen-Cilag International N.V.
Canagliflozin/Metformin	Diabetes Type II	Janssen-Cilag International N.V.
Colestilan	Phosphate binder	Mitsubishi Pharma Europe Ltd
Collagenase clost. hist.	Dupuytren's contracture	Swedish Orphan Biovitrum AB
Gaxilose	Lactose intolerance	Venter Pharma S.L.
Linaclotid	IBS	Allergan Pharmaceuticals International Ltd
Linagliptin	Diabetes Type II	Boehringer Ingelheim International GmbH
Lixisenatid	Diabetes Type II	Sanofi-Aventis Groupe
Lomitapid	Hypercholesterinaemia	Aegerion Pharmaceuticals
Lurasidon	Schizophrenia	Sunovion Pharmaceuticals Europe Ltd
Perampanel	Epilepsy	Eisai Europe Ltd.
Regorafenib	Colorectal cancer	Bayer Pharma AG
Retigabin	Epilepsy	Glaxo Group Limited
Taflopust/Timolol	Glaucoma	Santen Oy
Vildagliptin	Diabetes Type II	Novartis Europharm Limited
Vildagliptin/Metformin	Diabetes Type II	Novartis Europharm Limited

**Table 2:** Medicines withdrawn from German market during or after price negotiations [15,16].

## Conclusions

Strategies for the development of innovative medicines need continual adaptation to address the changes of scientific and procedural requirements. The rise of personalized or precision medicines, new regulatory tools like “adaptive pathways” and “priority medicines” and the enhanced exchange between regulators and HTA-bodies require consideration. The decision of the UK to leave the EU added an extra layer of uncertainty. Brexit may not become fully effective for several years but well within the timeframe of currently active development programs for innovative medicines. The closest conceivable cooperation of the UK with a post-Brexit-EU, similar to the integration of Iceland or Norway, would be the least interruptive scenario. The worst case scenario would be an unregulated termination of UK's EU membership, two years after invocation of Art. 50 and utterly failed exit negotiations. It seems therefore prudent to prepare contingency plans to minimize delays in the availability of innovative medicines for European patients and to proactively seek advice from regulators and HTA bodies that are expected to become opinion leaders in a post-Brexit EU.

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