

REGULATORY EFFICIENCY REPORT 2015

PATIENTS

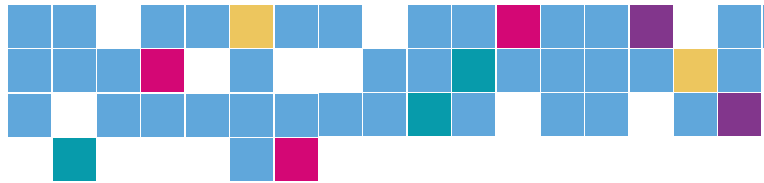
QUALITY

VALUE

SUSTAINABILITY

PARTNERSHIP

Bringing new generic medicines to European patients more quickly by improving the efficiency of the EU Regulatory Systems



About the EGA

(European Generic and Biosimilar Medicines Association)

The EGA represents the European generic, biosimilar and value-added medicines industries, which provide high-quality cost-competitive medicines to millions of European patients. Companies represented within the EGA provide over 160,000 skilled, high value direct jobs in Europe. Generic medicines save EU patients and healthcare systems over €40 billion each year and account for 55% of all dispensed medicines but for only 21% of the pharmaceutical expenditure in Europe.

The European generic and biosimilar medicines industries' vision is to provide sustainable access to high quality medicines for all European patients, based on 5 important pillars:

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PATIENTS	QUALITY	VALUE	SUSTAINABILITY	PARTNERSHIP
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Executive Summary of key findings and recommendations

This report has been written to help identify more opportunities for improvement within the current regulatory system for generic medicines and is based on the experience of EGA member companies. The overarching theme is simplification through removing duplication, redundancies and increased optimisation. The scope covered includes the research & development, new product approval procedures and lifecycle maintenance of generic medicines. Pharmacovigilance and information management systems are also touched upon. Across all areas, the scale of regulatory fees has been considered with the aim of simplifying and reducing costs for both regulated companies and regulators.

“Simplification through removing duplication, redundancies and increased optimisation”

The objectives of the review project have been to:

- Identify and analyse examples where the European regulatory system does not facilitate a timely access to generic medicines.
- Analyse situations where the regulatory system does not achieve the principles of better regulation which aim to balance regulatory objectives with the need to reduce administrative burden for companies
- Explore how the EU regulatory system can be improved taking account of the technological and strategic evolution of the generic medicines industry

Proposals are made to remove duplication of research studies to achieve a single development program for generic medicines, across world regions.

“Optimise use of the Decentralised and Centralised procedures for the regulatory approval of new generic medicines”

To ensure timely patient access to generic medicines and to improve the operational aspects of EU marketing authorisation procedures, several suggestions have been made to optimise use of the Decentralised and Centralised procedures for the regulatory approval of new generic medicines. The report addresses the current limitations to a broader use of the Centralised Procedure. Repeat Use Procedures have been pinpointed as the weakest part of the system. The objectives of proposed solutions are to streamline procedures, eliminate unnecessary duplications of approvals and enable rapid addition of new countries and Marketing Authorisation holders. These improvements would more closely reflect the operation of the generic medicines industry and more importantly give the possibility to respond faster to patient and market needs.

“The spread of GMP and wider supply chain aspects into the variation system should be rolled back into the domain of the GMP inspectorate”

EGA member companies have recorded a progressive increase in the number and scope of variations, including several administrative and minor changes, where it is hard to identify the benefits for patients and better protection of public health. This trend needs to be reversed so that industry and authority regulatory resources can focus on activities that have the most impact on public health and deliver more benefit for patients, such as for example implementing important safety information changes quickly. The spread of GMP (Good Manufacturing Practices) and wider supply chain aspects into the variation system should be rolled back into the domain of the GMP inspectorate, where a more practical oversight can be maintained instead of regulating this via the variations process. This will help to achieve the right balance between control of the medicines supply chain and administrative regulation without undermining the provision of high quality medicines to patients. Over time, Active Pharmaceutical Ingredient (API) changes can be better regulated

by making the holder of the Active Substance Master File (ASMF) a more independent operator in the regulatory systems, being able to ask for an assessment of the ASMF separately from the product dossier and being responsible for its maintenance (similarly to the concept of the European Pharmacopoeia Certificate of Suitability). Building on the ASMF working sharing programme will be a step towards delivering this.

“Several proposals are made to better use telematics tools to support regulatory processes”

The effective use of IT systems can be a powerful enabling tool for regulatory efficiency across Europe. Several proposals are made such as maximising the opportunity of the Article 57 database to simplify variations, building on the success of CESP (Common European Submission Platform) to harmonise and make redundant national portals and to capitalise on the ISO IDMP in the future. There is a major opportunity by linking systems and making multiple use of databases, to accelerate procedural efficiency, accuracy and at the same time remove redundant infrastructure.

“One possible solution could be an annual flat fee for the maintenance of the Marketing Authorisation”

This report has also provided an opportunity to look at regulatory fees. The fees for new product approvals should be better differentiated between RMS (Reference Member State) and CMS (Concerned Member State) to reflect the different assessment responsibilities. Thus, the level of fees charged by many Concerned Member States should be reduced to reflect lower workloads. In view of significant increases in the number of variations and associated maintenance fees over recent years, incentives need to be introduced stimulating the authorities to optimise the variations process. One possible solution could be an annual flat fee for the maintenance of Marketing Authorisations, as already introduced in a few member states.

The new Pharmacovigilance legislation of 2012 has provided several improvements. However the full hoped for benefits have yet to be achieved. Simplification for example in Risk Management Plans and removing duplication as in Periodic Safety Update Reports and some signal detection activities, will help unlock the efficiency benefits.

Conclusion

This report is the most detailed review of the European regulatory environment for generic medicines since 2010. The issues identified are many and in each case solutions are proposed. Some of these can be implemented quickly with little or no cost. Others will take longer to achieve, including legislative changes. Overall this report demonstrates that favourable interpretation of existing legislation can streamline regulatory systems at the same time as improving outcomes both in protecting public health and enabling more high quality generic medicines to be made available faster to patients, supported by a secure supply chain.

EGA calls for a deep analysis of the recommendations from this report as a contribution to strategic thinking for the further development and simplification of the EU regulatory environment.

The scope recommended for analysis and improvement covers research & development, new product approval procedures and lifecycle maintenance of generic medicines.

Raising efficiency and streamlining the regulatory processes will bring tangible benefits for all participants in the healthcare network of patients, governments, regulatory authorities and the generic medicines industry.



Recommendations

Research & Development

Overcome R&D duplication by moving into a single development program

- 1.1 To confirm officially that based on the EU Directive 2001/83/EC sourcing of the reference product from a non-EU territory with high regulatory standards is accepted for single R&D programmes of generic medicines.
- 1.2 The Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) should be amended to explicitly allow the sourcing of the reference product from other world regions with high regulatory standards.

New Product Approval Procedures

Increase use of the Centralised Procedure (CP) by Generic Medicines

- 2.1 Reinterpret the eligibility criteria to broaden access for generic medicines.
- 2.2 Address the areas of inflexibility that have limited generic medicine applications fully utilising the Centralised Procedure.
- 2.3 Address the issue of brand naming of duplicates agreed on use patent grounds to allow patient access to medicines in the cross-border healthcare setting and to avoid market hurdles once the patents have expired.

Further improve the Decentralised Procedure (DCP) through more flexibility

Optimally interpret DCP to permit new models of working reflecting the practices of the generic medicines sector:

- 2.4 “Backbone DCP” - a single harmonised assessment enabling Marketing Authorisations to be obtained quickly and only when needed, so reducing the number of non-marketed MAs in the system.
- 2.5 “Basket DCP” - one Reference Member State assessing a “full package/basket” of elements for a given product; with the Marketing Authorisation Holder choosing a tailored option for each Member State.
- 2.6 “Worksharing DCP” concept, with one Reference Member State (RMS) assessing on behalf of several RMS, and the addition of Concerned Member States permitted later.

Improve operational aspects of the current DCP:

- 2.7 DCP validation to be completed in 14 days, through automatic validation by the RMS.
- 2.8 Mandate DCP day 106 clock restart within one month after the applicant submits answers to questions.

- 2.9 Speed up the National phase by fast track processing, dedicated resources and dropping compulsory translation from English of patient information texts if no immediate launch/or no marketing foreseen in this country (e.g. only RMS)

- 2.10 Rapidly introduce a mechanism to link and de-link the Marketing Authorisations (MAs) in DCP to align with company needs and simultaneously remove any redundant MAs and RMS roles (splitting and merging).

National registration route

- 2.11 Timeline for a national registration application should be in line with EU procedures to ensure a level playing field between application routes.

Solve the problem of MRP/Repeat Use Procedures in product approval

- 2.12 Introduce “slot booking” for Repeat Use Procedures (RUP) and drop the requirement for no on-going regulatory activities before a MRP/RUP starts and while a RUP is running.

Regulatory Fees

Modernise the EU fees structure and disconnect from number of procedures

- 3.1 Introduce a flat annual fee per product. This flat fee is covering all maintenance costs including variations.
- 3.2 The fee structure for new product registrations should fairly reflect the workload of the assessment (e.g. the ratio of RMS:CMS fees, duplicates, multiple strengths)

Lifecycle Maintenance – Variations

Maintenance fees exceed initial submission fees

4.1 The variation fee structure should be reshaped so that maintenance fees, in the first renewal period after MA grant, are lower than initial submission fees.

Variation Fee structure

4.2 Regulatory agency fee income should be disconnected from the number of variations processed, to stimulate proactive optimisation of the variations process.

4.3 Introduce a single annual maintenance fee, covering all types of variations.

Variation timelines

4.4 Type IB variations should be given more priority so that timelines are met, including a predictable Day 0.

Safety referral variations

4.5 Safety referral outcomes should be more easily accessible with clear instructions for submitting the necessary variations.

4.6 Safety referral variations should be prioritised in order to enable timely update of patient information.

Concomitant variation & renewal applications

4.7 The procedural guideline should clearly allow the concomitant submission of renewal and variation applications.

Grouped variations

4.8 The fee structure for variations should be thoroughly revised so that fees for grouped variations are always less than fees for a Type II variation

4.9 Finished product optimisation should, like API optimisation, be eligible as Type II variation.

Company-wide changes

4.10 For a number of changes, particularly when company-wide, a mechanism should be found to maintain regulatory compliance whilst reducing administrative burden, together with a reduced fee structure.

CEP/TSE certificate updates

4.11 For administrative changes to CEPs/TSEs certificates a simplified regulatory pathway should be implemented.

Single country changes

4.12 For country specific changes within DCP or MRP, the guidance should be simplified so that the change is only submitted where it applies. Non-impacted member states would be notified through an update in the “Article 57”-database. Fees would only be payable in the countries where the change takes place.

Reporting within 12 months

4.13 The European Commission and member states should evaluate the “up to 12 months” reporting provision and identify the underlying causes for underuse.

4.14 Consideration should be given to the possibility to report within 12 months as a notification.

API related variations

4.15 The ASMF work-sharing pilot should be further strengthened.

4.16 Long term consideration should be given to legislative change whereby the API (Active Pharmaceutical Ingredient) regulatory documentation would be managed independently from the medicinal product regulatory dossier.

4.17 A direct role should be developed for API manufacturers in regulatory procedures based on the model of the current European Pharmacopoeia CEP (Certificate at Suitibility) procedure.

Excessive API GMP and supply chain information in the regulatory dossier

4.18 To balance transparency in the API supply chain and supply chain resilience, there should not be more additions of API GMP (Good Manufacturing Practice) or supply chain elements into the regulatory dossier.

4.19 The regulatory dossier API information should be limited to the final API manufacturer(s) and the final intermediate manufacturer(s) only for intermediates when applicable. All other involved sites should be appropriately managed through manufacturers’ quality systems and regulators’ supervision as part of GMP inspections, both API and Finished Product (FP).

4.20 Transparency of the API supply chain should build on initiatives such as IDMP (Identification of Medical Products) database.

Lifecycle Maintenance – Renewals

Simplify Renewal

5.1 Simplify the Renewal procedure for well known active substances with established safety profiles to become an automated administrative step only, without blocking other regulatory activities.

Lifecycle Maintenance – Pharmacovigilance

Deliver the intended benefits from the 2012 Pharmacovigilance legislation

6.1 Stop duplication of signal detection in the Eudravigilance database.

6.2 Introduce the single submission of PSURs per active substance.

6.3 Simplify the Periodic Benefit Risk Evaluation Report format.

6.4 Simplify the Risk Management Plan format for standard generic medicines and make just one EU assessment.

6.5 Streamline the content of Post Approval Safety Studies to avoid the unintended consequence of companies withdrawing from the market.

Lifecycle Maintenance – Telematics

Telematics and Information Management

7.1 Maximise the opportunity of the Article 57 database by using the single data collection to serve many purposes, including by connection to regulatory procedures.

7.2 Utilise the Article 57 database for administrative and many Type 1A changes, instead of variations to maintain oversight but simplify procedures.

7.3 Build on the success of CESP to harmonise or make redundant national portals.

7.4 EGA should be a key partner in setting the road map for ISO IDMP implementation and for the long term EU regulatory telematics strategy.

e-leaflet

7.5 To explore e-leaflet as a future option for disseminating information on medicinal products to patients.



INTRODUCTION

The regulatory framework for medicines has continuously evolved over time. This has enabled faster access to new medicines, both those for unmet medical conditions and high quality affordable generic and biosimilar alternatives.

The procedures have also adapted to help meet the needs of more categories of patients, in particular children and those with rare diseases. This has led to a highly developed mature Europe wide system which is broadly effective in delivering its' twin roles of protecting public health at the same time as making safe and effective medicines quickly available to the patients of Europe. These are shared objectives of patients, carers, health insurers, governments, regulatory agencies and the pharmaceutical industry. Looking forward, there are opportunities for taking an ambitious approach to identify future improvements to benefit all stakeholders.

About the European Generic and Biosimilar medicines Association (EGA)

The European Generic and Biosimilar medicines Association's vision is to provide sustainable access to high quality medicines for all European patients, based on 5 important pillars: patients, quality, value, sustainability and partnership. For patients, the generic and biosimilar medicines sectors create enhanced access to medicines, reducing inequalities so directly leading to improved patient outcomes. Generic companies compete with each other and the originator so stimulating the medicines industry to innovate. The generic and biosimilar medicines sectors provide a stable and resilient supply of high-quality medicines, manufactured and developed according to stringent EU regulatory requirements, for Europe's patients and healthcare providers.

The EGA builds constructive partnerships, focused on a strong and stable collaboration with patients and patient organisations, the EU institutions, governments and regulators, healthcare professionals and others to further enhance public health in Europe.

The contribution of generic medicines to public health and the European economy

Generic medicines account for 55% of all dispensed medicines but for only 21% of the pharmaceutical expenditure in Europe. The volume and percentage of generic medicines used to treat patients in Europe is steadily increasing year to year. The contribution of generic medicines helps to increase patient access to treatments and delivers sustainability of the health care systems. Based on the IMS studies published in 2015 , generic medicines competition has almost doubled the access to medicines across seven key therapy areas. Without generic medicines, healthcare systems and patients would have had to pay an estimated additional 100 Billion Euros in 2014. Although the benefits of generic medicines accrue differently across EU member countries, the implication is clear: the generic medicines industry has been vital in sustaining healthcare benefits in the region. This role has become even more important during the recent years of difficulty for the national economies of Europe. The industry is responding to that challenge by providing a wider range of essential, first line treatments for the majority of chronically ill patients and by increasingly offering new, complex medicines to treat more specialised conditions . Large investments by industry in biosimilar and value added medicines have been at the forefront of research and scientific innovation by generic medicine manufacturers.

“The contribution of generic medicines helps to increase patient access to treatments and delivers sustainability of the health care systems”

Many biological medicines are used to treat long-term conditions such as diabetes, cancer, chronic kidney failure and multiple sclerosis. On average, biopharmaceuticals cost much more per patient than conventional pharmaceuticals, and their use is growing at a much higher growth rate than that of the overall pharmaceutical market. It is therefore critical that everything possible be done to maximise patient access to cost-effective biopharmaceuticals. This means a rapid introduction of biosimilar medicines as soon as patents expire.

“EGA member companies invest 7-17% of their turnover into research and development”

Generic medicines contribute directly to European economic growth, with research, development and manufacturing activities in most European countries for the majority of medicines used in the EU, sustaining more than 160,000 high skilled, high value direct jobs. Based on an internal survey, the EGA member companies invest 7-17% of their turnover into research and development. Despite worldwide competition, the majority of generic medicines offered in the European market are still manufactured locally in Europe. As a leading knowledge based industry the sector works with

Europe's policy makers, legislators and regulators to create the right environment to support and strengthen the economic sustainability of the industry so that it can continue to contribute to European patients, society and economy.

Why this report has been written

The regulatory framework is critical to achieving the twin objectives of timely patient access to medicines and assuring the sustainable long term development of the industry to meet patients' needs in the future.

From the perspective of 50 years of pharmaceutical legislation, enormous progress has been made to achieve better quality, safety and efficacy of medicinal products. Significant effort has been made to build a strong European regulatory structure and harmonised European standards.

However, the current regulatory systems and their implementation do not always support the objectives of timely access and operational efficiency.

The purpose of this report is to help identify more opportunities for improvement within the marketing authorisation systems.

The objectives of the review project have been to:

- Identify and analyse examples where the European regulatory system does not facilitate a timely access to generic medicines
- Analyse situations where the regulatory system does not achieve the principles of better regulation which aim to balance regulatory objectives with the need to reduce administrative burden for companies and authorities
- Explore how the EU regulatory system can be improved taking account of the technological and strategic evolution of the generic medicines industry

Ideally the recommendations should be resource neutral or saving for both regulatory agencies and pharmaceutical companies. A major success of the EU regulatory framework is that it has succeeded in being flexible to meet changing needs. Therefore another reason for this report is to identify how additional optimisation can be applied, ideally avoiding the need for legislative changes. Looking longer term, some more ambitious improvements, probably needing legislative amendment, will also be identified.

“it will be increasingly important to maximise worksharing opportunities, particularly to meet new challenges with existing resources.”

The scientific assessment standards developed and applied by the European Medicines Agency (EMA), its expert advisory committees, working parties and the member state Agencies are globally leading. Therefore this report is focused on regulatory processes and not the science that forms the foundation of regulatory review, ensuring that medicines have a positive benefit – risk balance for patients. The European regulatory network has established high standards which are well understood by industry and applied within their internal quality management systems. This has put in place a platform based on increasing trust between regulator and industry which is enabling more work sharing and some self-responsibilities to take place. This worksharing can be between different regulatory authorities and increasingly involves companies, based on building trust in assessment and enabled by shared access to information technology tools. Recognising that resources within regulatory agencies are limited, and likely to remain so, it will be increasingly important to maximise worksharing opportunities, particularly to meet new challenges with existing resources.

In October 2010 the EGA published “Vision 2015 – the EGA’s thoughts on how to improve the legal and regulatory framework for generic and biosimilar medicines”.



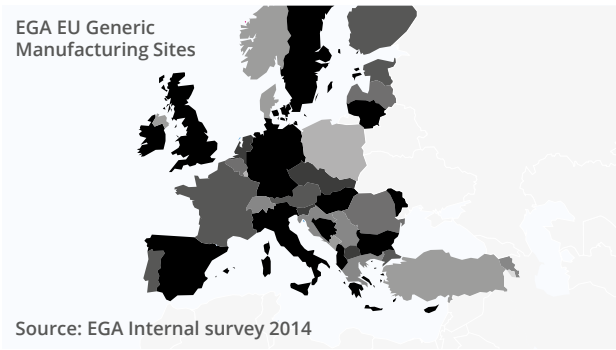
It is a good time to reflect on how many of the goals from that report have been achieved and which still remain a target. Steps have been taken to streamline the Decentralised Procedure, but more can be done. Country specific requirements have reduced in number but have not totally gone away. The goal of more equal participation from member states in the EU regulatory network has been largely achieved. Linked to this, more examples of successful work sharing have come about. However the harmonisation goal of no repeat assessments in the network still lies in the future. One feature of the 2010 EGA report which remains a challenge today is how to more efficiently handle duplicate Marketing Authorisations within the new product registration procedures.

The generic medicines industry today is changing- support from the regulatory environment is needed to progress

The companies that make up the generic medicines sector are evolving. At the same time as some companies combine and become more global in nature; there are still new entrants coming to Europe from other parts of the globe as well as local start up companies. One significant trend in recent years for all types of pharmaceutical companies has been for the supply chain to become more complex. Today, even the largest and best resourced companies do not carry out all activities in-house. Many active pharmaceutical

ingredients (API) are acquired from specialist companies. As well as the spread of activities, the locations involved as part of a single products supply chain can also be dispersed, with capabilities in particular fields building up in different parts of the world, including beyond Europe. This has been pronounced in the manufacture of APIs and their starting materials, where a significant percentage comes from India and China.

Despite global opportunities, the majority of generic and biosimilar medicines provided to European patients are still manufactured in Europe. The interest of decision makers should be to preserve this situation and to create the regulatory/ legal framework encouraging companies not only to maintain production but also to further invest and to develop manufacturing capacities for European and export markets.



Some generic medicines companies focus entirely on Research and Development (R&D) and do not directly sell products themselves. These companies provide solutions for marketing focused companies, those who want to enlarge their pipeline and portfolios. Therefore the R&D generic medicine companies enable timely market access and help to contain R&D costs. An often overlooked contribution of these companies is that they generate competition in the research & development phase of the generic medicine development cycle.

“The research and development pipelines of generic medicine companies are becoming more scientifically innovative”

The research and development pipelines of generic medicine companies are becoming more scientifically innovative and making available a more diverse range of products. In addition to traditional small chemistry products there is an increasing investment in more complex molecules and pharmaceutical forms, value added medicines and targeted delivery systems. Special emphasis is being given to developments in biosimilar medicines, delivering a solution for increasing access to expensive biological therapies for more patients. In view of this evolution, in the coming years this is likely to lead to greater use of Article 10.3 hybrid

applications in addition to the conventional Article 10.1 full generic submissions. Hybrid applications are very varied in nature, so this will further test the fitness of the European regulatory systems to coming needs. The case by case interpretation on whether a particular application is best classified as 10.1 or 10.3 is set to continue. This flexible approach can be helpful since the scenarios are many and varied, depending on the scientific and innovation principle involved. However this “case by case” approach by the regulators does lead to uncertainty and a lack of predictability for companies. Due to this diversity there is likely to be an emerging trend of companies seeking more Scientific Advice meetings to determine the most appropriate regulatory strategy on a tailored basis. With increasing dialogue and more examples going through the system it is hoped that more harmonised views between member states will be reached in the next one to two years.



Chapter 1 – Research & Development

1.1 Globalisation of research & development – the case for avoiding unnecessary repetition

Generic and biosimilar medicines companies are becoming more global in their outlook. This has been brought about both through businesses merging and consolidating as well as companies looking to achieve a wider reach for their development pipelines into regions of the world beyond Europe.

The increased sophistication of generic medicines R&D has led to companies seeking a more globally integrated approach to scientific and clinical data generation and an objective to avoid duplication, particularly in the area of in vivo trials. Performing a single development programme to support the registration of a generic medicine in multiple world regions would curtail unnecessary and probably unethical involvement of healthy subjects and patients in redundant studies. It would also facilitate a significant reduction of clinical trial programme investments and as such foster enhanced competitiveness for the EU generic medicines sector. This economic benefit could also encourage more global development studies to be performed

in Europe, to more fully utilise the scientific expertise of European companies and research centres. It would also free up further investment in the development of new products instead of spending on unnecessary repeat clinical studies.

To achieve this objective, there is a need to:

- Source the reference product from other regulated jurisdictions with equivalent regulatory standards
- Achieve more convergence between health authority requirements, particularly for clinical and pre-clinical data, onto a single high quality standard

Divergences in regulatory frameworks between regions have emerged as a major hurdle in the development of generic, biosimilar and value added medicines. Therefore regulatory convergence and alignment is a key opportunity to improve efficiency in the regulatory systems. In the area of clinical trials there is an important opportunity to avoid involving healthy volunteers and patients in unnecessary duplicate tests.

1.2 Biosimilars show the path to overcome duplication of R&D studies

The highly successful collaborative work on biosimilar medicines is paving the way for a wider acceptance for a single data set in global markets for complex generic medicines categories. In parallel with harmonising data requirements, it is to be hoped that assessment opinions will also become closer over time, probably facilitated by assessment work sharing models.

Today the possibility to use a single global reference product for global R&D programmes of generic medicines is hampered by the regulatory agencies' interpretation of EU Directive 2001/83/EC, as amended. The directive states that the reference product should be authorised under Article 6 in accordance with the provision of Article 8. Although the Directive only mentions the need for authorisation of the reference product in the EEA, the EU regulators generally require the reference product to be 'physically' sourced from within an EEA country. This is insisted upon even when there is substantial evidence that the reference product in other world regions is the same.

A breakthrough has recently been achieved to facilitate the single development programme for biosimilar medicines. In 2014 the guideline CHMP/437/04 Rev 1 on “Similar Biological Medicinal Products” was amended, explicitly allowing sourcing of the reference product from other regions with stringent regulatory requirements comparable to the EU. The guideline CHMP/437/04 Rev 1 on “Similar Biological Medicinal Products” states that:

“However, with the aim of facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials, it may be possible for an Applicant to compare the biosimilar in certain clinical studies and in in vivo non-clinical studies (where needed) with a non-EEA authorised comparator (i.e. a non-EEA authorised version of the reference medicinal product) which will need to be authorised by a regulatory authority with similar scientific and regulatory standards as EMA (e.g. ICH countries). In addition, it will be the Applicant’s responsibility to demonstrate that the comparator authorised outside the EEA is representative of the reference product authorised in the EEA.”

Since one and the same definition of the reference product in Article 10 point 2 (a) of the EU Directive 2001/83/EC, as amended, applies to biosimilar, generic and hybrid applications (under Art. 10.1, Art 10.3 and Art 10.4), it is a logical extension that sourcing a non-EU reference product should also

be allowed for generic and hybrid applications in the same way as for biosimilars. Consequently the relevant guidelines on studies supporting generic and hybrid applications (i.e. Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/) should also be amended to explicitly allow the sourcing of the reference product from other regions with high regulatory standards, such as the US. This logic established for biosimilar medicines, can be extended to generic and value added medicines.

1.3 The scientific rationale for not duplicating studies

Currently, an applicant for a marketing authorisation in both the US and EU would have to carry out two distinct clinical trial programmes because the interpretation of the legal requirements implies that the reference product would need to be sourced and tested separately, from the US and the EU respectively.

Even in situations where the US and the EU reference products are known to be the same by the respective regulatory agencies, the programmes both have to be completed in duplicate. In many cases the study design and protocols are the same with the only difference being the source of the reference product samples.

Purchasing the reference product batch or batches for a clinical trial programme (and pharmaceutical

development) and executing the clinical studies are key contributors to the overall cost of generic and biosimilar medicine development. Based on a recent EGA member’s survey, it can be concluded that the use of a global reference product in the development of generic medicines could generate cost savings in the range of Euro 200,000 for a standard pharmacokinetic bioequivalence study and potentially up to Euro 4.5 million for development projects involving a complex clinical trial programme (e.g. transdermal patches).

Further work should focus on agreeing between industry and global regulators what is required to demonstrate “that the comparator authorised outside the EEA is representative of the reference product authorised in the EEA”. Maximum use should be made of in vitro physico-chemical tests, with well defined acceptance criteria.

By removing unnecessary duplication of research and investment from clinical trial programmes, the use of a global reference product would facilitate increased patient access to high quality, safe and effective generic medicines with earlier availability to generic medicines in multiple regions simultaneously.

1.4 Case Studies

A recent EGA member survey identified several examples of generic medicines that would benefit from the single reference product interpretation. Cost saving would come from (1) savings related to a reduced need for purchasing the reference product and (2) less duplication of clinical trial programmes when studies can be shared over several geographic areas including EU, US and Canada. Of even more importance than financial savings would be removing the ethical issue of duplicate exposure to test medicines on healthy volunteers and patients in clinical trials.

- **Transdermal Patches.** A cost saving up to 4,5 Million Euro per product is possible based on utilising single dose pharmacokinetic studies and skin Irritation/sensitisation studies across several geographical areas (EU/US/Canada and Japan)
- **Immediate Release generic medicines** such as oral solid dosage forms (tablets), oral liquid dosage forms (syrups, solutions) and topicals (ointments and creams) A cost saving is possible of 0.45 Million Euro per product
- **Long Acting Injectables.** A cost saving of 0.45 Million Euro per product is anticipated
- For products requiring a **large clinical endpoint** study, cost savings of up to 35 Million Euro per product are possible

EGA Recommendations

- 1.1** To confirm officially that based on the EU Directive 2001/83/EC sourcing of the reference product from a non-EU territory with high regulatory standards is accepted for single R&D programmes of generic medicines.
- 1.2** The Guideline on investigation of bio-equivalence (CPMP/EWP/QWP/1401/98 Rev. 1/), should also be amended to explicitly allow the sourcing of the reference product from other world regions with high regulatory standards.



Chapter 2 – New Product Approval Procedures

Learning from 10 years of experience to identify areas for further improvement

The registration systems for new medicines in Europe have followed an evolutionary ladder. The starting point was national applications, country by country. To this was added the Mutual Recognition Procedure in 1994 (with mandatory use since January 1998), enabling an approval in one member state to be extended to others. The next major milestone was the introduction of a more flexible model with the Decentralised Procedure (DCP) in 2005. The generic medicines industry has in the main chosen the DCP as the primary route for product registration. The reasons for that trend will be examined and options for improvements identified, mainly based on increasing flexibilities in comparison with the MRP.

As a part of the revision of the legislation in 2004, the Centralised Procedure (CP) was opened for generic and biosimilar applications, introducing an opportunity of a single Community marketing approval. The scope and the practical capacities of using the CP by generic companies still remain low due to several limitations discussed further in the next pages and illustrated in the graph on page 22.

2.1 Centralised Procedure (CP)

The Centralised Procedure (CP) has many significant benefits in a transparent process:

- A single submission
- Reliable validation
- One assessment
- One approval covering the whole of EU, including future member states
- Few specific national requirements in comparison to DCP
- Predictable timelines, including national phase

However this strong list of benefits is often outweighed by the limitations for generic medicine companies:

- Access to all markets in Europe may not be needed
- Long term marketing in all member states may not always be required depending on the market situation
- Duplicating MAs is limited

- Single market design prevents multiple product names when needed for marketing purposes
- Limited eligibility criteria

2.1.1 Benefits of the Centralised Procedure

The Centralised Procedure (CP) is attractive to generic companies who want to market directly throughout the Community. The granting of a single Community marketing authorisation instead of national approvals per country has the important public health benefit of making the generic medicine available at the same time in all member states. Another positive feature is the predictable timeline. The procedure works very smoothly, as the SmPC is fully harmonised, if there is only a single MAH and one name is needed.

Pre-authorisation: Marketing authorisation applications* via the Centralised Procedure*

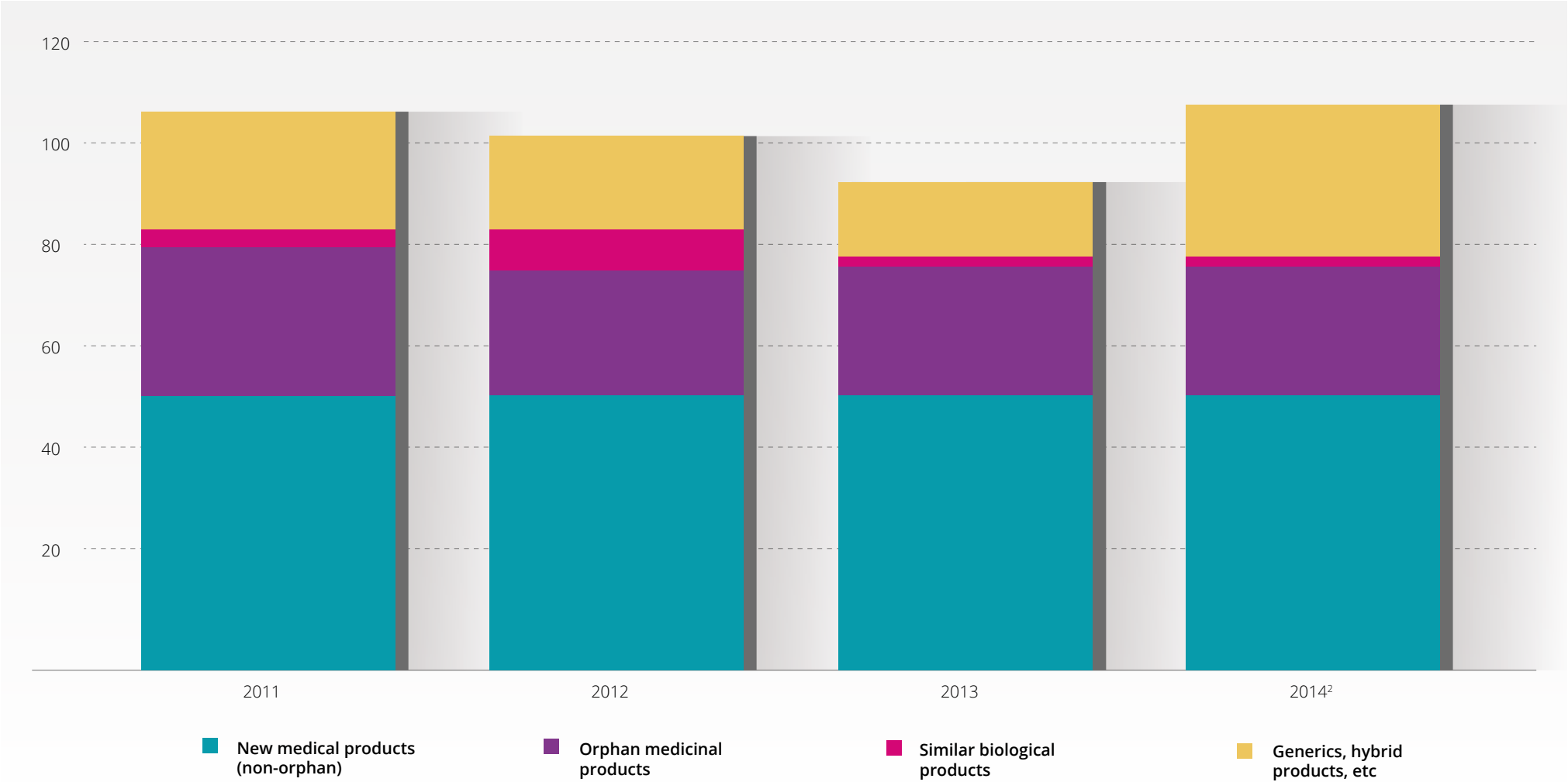
Source: European Medicines Agency (EMA)

	2011		2012		2013		2014 ¹	
	Started	Finalised	Started	Finalised	Started	Finalised	Started	Finalised
Non-orphan medical products								
New products	46	37	44	35	48	46	37	42
Advanced-therapy medial products	1	0	1	0	0	2	1	0
Advanced-therapy Art, 29 transition products	1	0	2	0	N/A	0	N/A	0
Paediatric-use (PUMA) products	1	1	0	0	1	0	0	1
Well-established use, abridged, hybrid and non-prescripton switch products	8	8	5	6	6	4	12	15
Generic products	25	34	16	13	5	16	25	6
Similar biological products	3	0	8	0	1	4	3	3
Sub-total product applications	85	80	76	54	61	72	78	67
Orphan medical products								
New products	19	11	16	14	16	14	20	17
Advanced-therapy mediact products	0	0	2	0	2	0	1	1
Total product applications	104	91	92	68	77	86	99	85

* Finalised application exclusive application withdrawn prior to option
¹ Figures for the current year are cumulative, year to date. Figures for preceding years are totals for the year

Source: European Medicines Agency (EMA)

Graph representing the number of Marketing authorisation applications according to the legal basis (pre-authorisation) via the Centralised Procedure



² Figures for the current year are cumulative, year to date. Figures for preceding years are totals for the year.

2.1.2 **Limitations of the Centralised Procedure for generic medicines**

There is a perception that the Centralised Procedure (CP) was not designed with generic medicines in mind, leading to some of its steps being cumbersome and constraining for generic medicines. This has limited the use of the CP by generic medicines to a very small fraction compared to the number of applications to DCP.

To encourage more companies to register generic medicines via the CP, the CP MA process could be more tailored and its eligibility criteria widened, including its optional use. Allowing access to the procedure when the originator product was not approved by CP would also increase access to the Community Authorisation, contributing to the greater availability of generic medicines throughout the EU.

One long standing constraint to more generic medicines companies choosing CP has been the interpretation on the use of product names, which does not reflect the use of generic medicines within the Community. Naming conventions differ between member states and in some countries are linked to pricing and reimbursement systems. The current policy does not take into account that some member states prescribe by International Non Proprietary Name, others by an invented name (especially CEE countries) and some with a mixture of both depending on the nature of the medicine. Examples include mandatory brand names for modified release products in the UK, compared to

INN plus MAH being obligatory in other countries.

Also to reach different sectors of the market such as specialist prescribers or separate health payers, a company may need to make its medicine available through more than one marketing identity and MAH within one company organisation. Generally CP is less attractive to companies who operate in a selection of countries only or in co-operation with other marketing partners. For smaller companies it would be helpful not to invest in more than one MAA purely because of the requirement for different names.

Another constraint of the CP for generic and biosimilar medicines is when the originator benefits from a second medical use patents. Such situations are cumbersome for the generic and biosimilar CP applicant, requiring duplicate approvals and alternative names to navigate the system.

Under Article 821, the Commission shall agree to the application for a duplicate if there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients.

This requires a case by case assessment but arguments that are not linked to the availability of the product cannot be considered.

The most common case in which a duplicate is justified on public health grounds is when there is an indication or pharmaceutical form in the SmPC of the original application/ marketing authorisation that is protected by patent law in one or more Member States. In this context it is noted that

Article 3(3)b Reg 726/2004 specifically allows for the submission of different SmPCs on grounds related to patent law. While this article refers to generic applications the same considerations (i.e. the need to ensure availability of the product in the Member States where there is patent protection) are applicable in the case of duplicate applications. In such cases and in order to maintain the harmonisation of the SmPCs, the applicant should be required to provide a commitment letter undertaking to extend the indication/ pharmaceutical from of the duplicate marketing authorisation as soon as the patent restrictions no longer exist. Alternatively, the applicant may also commit to withdraw the marketing authorisation with restricted indications/pharmaceutical forms after the relevant patents are no longer in force. The harmonisation of SmPCs across the Union being one of the basic pillars of the centralised procedure, applicants of duplicate marketing authorisations should not market two products with different indications/ pharmaceutical forms in the same country. The commitment letter should be provided with the marketing authorisation application dossier.

EGA welcomes the recognition of the use patents in CP issue by the European Commission and the EMA and that only an administrative fee for the duplicates agreed on use patent grounds has to be paid. By agreeing only an administrative fee, the product with the full SmPC and the duplicates with shortened labels are consequently regarded as the same product.

However a single name application is required for the full and shortened labelled products, which has major negative consequences:

- **Impact on patient access to the prescribed medicine:** The same product will have different names in different countries, which prevents patients in a cross border healthcare setting from getting access to their prescribed medicine. This is especially problematic for biosimilar medicines since INN prescribing for biologicals is not legally allowed in a cross border prescription setting. Furthermore, having several names for the same medicinal product across the EU is very confusing for healthcare professionals and patients since doctors would need to switch the names of the same prescribed medicine, once the patents have expired
- **Impact on market access:** Since the applicant will be required to provide a commitment letter undertaking to extend the indication/pharmaceutical form of the duplicate marketing authorisation as soon as the patent restrictions no longer exist, it is paramount that the full and shortened labelled medicinal products bear the same single name. This is also to prevent the company having to restart marketing the product from scratch

Recommendations

To tackle the above limitations, EGA proposes the following solutions:

Option one: allow the removal of the infringing part of the SmPC before marketing at national level as per Article 11, point 12, second paragraph of Directive 2001/83/EC, as amended. The shortened labels should be part of the approval process in the CP procedure. This would negate the need for these administrative duplicates and would be in line with the aim to reduce red tape.

Option two: in case option one is rejected: allow duplicates with shortened labels, agreed on use patent grounds, to bear the same name as the product with the full SMPC. This requires a new legal interpretation of article 6 of the Regulation (EC) N° 726/2004. This should be possible since duplicates, agreed on use patent grounds, should not be regarded as new separate products, requiring a single name.

EGA Recommendations

Increase use of the Centralised Procedure by Generic Medicines

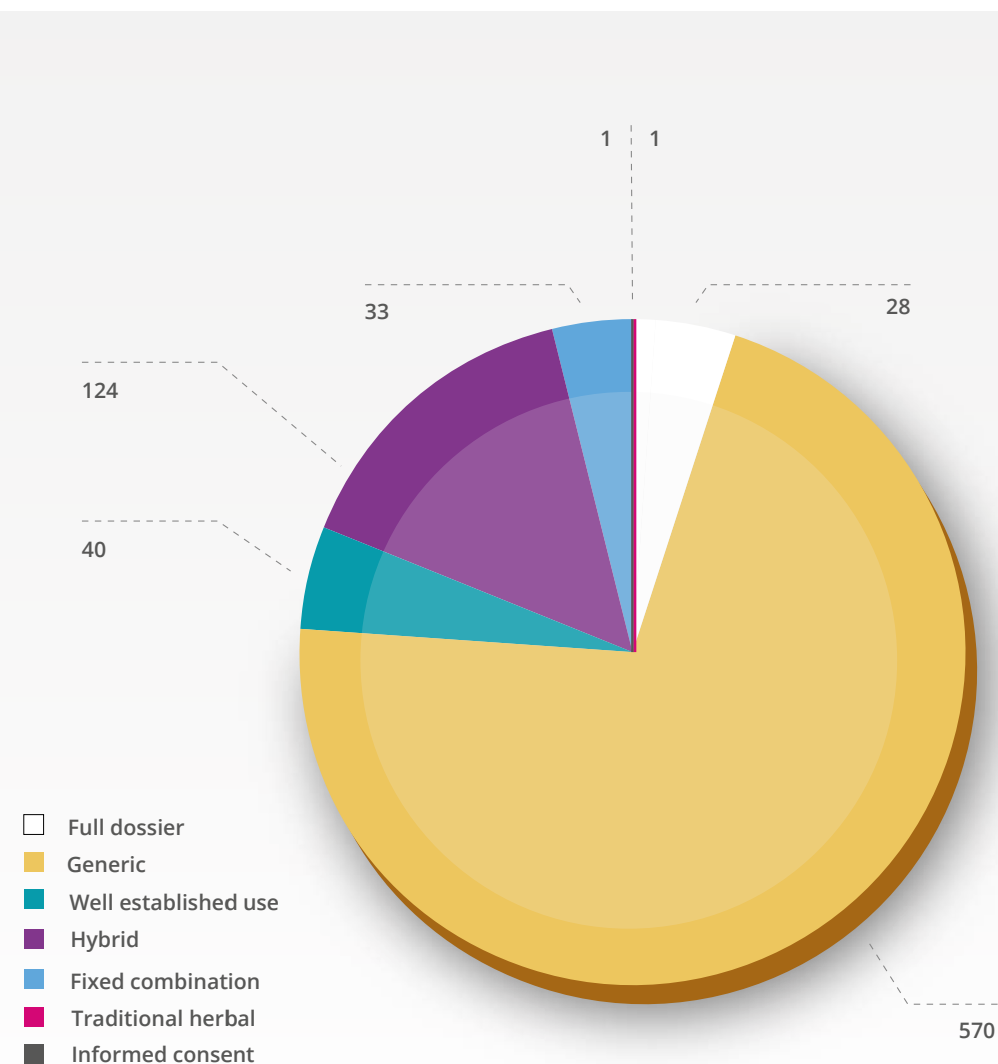
- 2.1 Reinterpret the eligibility criteria to broaden access for generic medicines.
- 2.2 Address the areas of inflexibility that have limited generic medicine applications fully utilising the Centralised Procedure.
- 2.3 Address the issue of brand naming of duplicates agreed on use patent grounds to allow patient access to medicines in the cross-border healthcare setting and to avoid market hurdles once the patents have expired.

2.2 Decentralised Procedure (DCP)

2.2.1 The Decentralised Procedure is the main route for registering generic medicines in Europe

Over 85% of the medicines being registered in Europe through DCP every year are generic medicines (including hybrid applications). Therefore it is crucial to focus efforts on further improving this route as the best way to make these important medicines more widely and quickly available to the patients of Europe and providing the value which sustains the EU healthcare systems.

87% of DCP applications in 2014 were for generic medicines – including hybrid applications.”



Source: CMDh Statistics 2014

2.2.2 Strengths of the Decentralised Procedure (DCP)

The Decentralised Procedure (DCP) is firmly established as the most popular route for registering new generic medicines in Europe. After its introduction 10 years ago the DCP was rapidly adopted as the new product registration procedure of choice by the generic medicines industry. This is mainly because of its better predictability and timelines when compared to its' predecessor MRP (Mutual Recognition Procedure). This has enabled companies to more accurately plan their research & development; product registration and market entry activities. The DCP fosters open discussion between applicant and regulator with early involvement from Concerned Member States.

The core principle of the DCP is mutual recognition of an assessment report and not a granted Marketing Authorisation. This delivers a much more flexible regulatory platform that the older Mutual Recognition Procedure where the first step is to achieve a national approval and then ask for that to be recognised by one or more other member states.

Through the opportunities for dialogue and learning through experience, the number of Referrals needed to resolve assessment issues for new generic medicines has progressively reduced over time. The application of learning has also enabled common understanding on procedural difficulties, which have then been cemented in updated guidelines, to prevent recurrence.

2.2.3 Limitations of the Decentralised Procedure

Ideally a company would run a single DCP procedure to cover all its market needs, both immediate and longer term. However the limits and complexity of the procedure are illustrated by the number of parallel and repeat uses procedures that are sometimes run for a given medicinal product. There is fluctuation in the demand for specific generic medicines over time which means that companies frequently wish to add MAs in additional countries at a later date, sometimes several years after the first EU approval. Unfortunately Repeat Use Procedures (RUP) are not providing a rapid procedure for medicines to reach new countries and meet patient needs. Access to generic medicines for patients in countries where a need emerges later are not being well served by the RUP, which is cumbersome and often inefficient.

Within the DCP, several steps have been identified by both regulators and industry as frequent bottlenecks:

- Initial validation
- The question answering phase and “clock stop”
- Closing the procedure before Day 210
- Granting national Marketing Authorisations after the European assessment phase

Almost all DCP procedures successfully complete and lead to the granting of Marketing Authorisations. However the constraints of the DCP

sometimes result in Repeat Use Procedures and a large number of variations between initial Marketing Authorisation grant and product launch. This is time and resource intensive for both regulatory agencies and generic medicine companies.

2.2.4 Options for refreshing the Decentralised Procedure

Any improvements to the DCP should protect its successful attributes. The fixed timelines within an overall 210 day procedure give reasonable predictability. Consistency of the process whichever Reference Member State is leading the procedure is another key benefit. Valuable flexibilities include the opportunity to close the procedure early at several steps during the timetable and if unavoidable to withdraw member states up to Day 106.

Regular meetings with CMDh and other platforms for industry / regulator dialogue have enabled a continuous conversation on how to improve the DCP, based on experience. Topics covered have included slot booking, validation, clock stop duration, national phases, repeat use and post approval changes. The CMDh Best Practice Guide has been key to implementing these improvement steps and has been frequently updated to implement continuous improvement. This has been supportive for industry, reflecting shared learning and an openness by regulators to change and improve procedures.

In the early years of DCP there was an under capacity problem and companies experienced

severe difficulties in booking submission slots, often having to wait between 6 months and one year to start a procedure. This was partly due to only a few member states taking the role of RMS. At one point this was limited to Germany, Denmark, UK, Netherlands, Sweden and Finland. Now up to twenty five member states take on that role, to differing extents. This active work sharing has increased capacity in the system and removed delays due to slot booking, both of which have assisted industry greatly.

2.2.5 DCP Validation time is still too long

The time taken to accept a DCP application into the system as valid has been a permanent area of challenge.

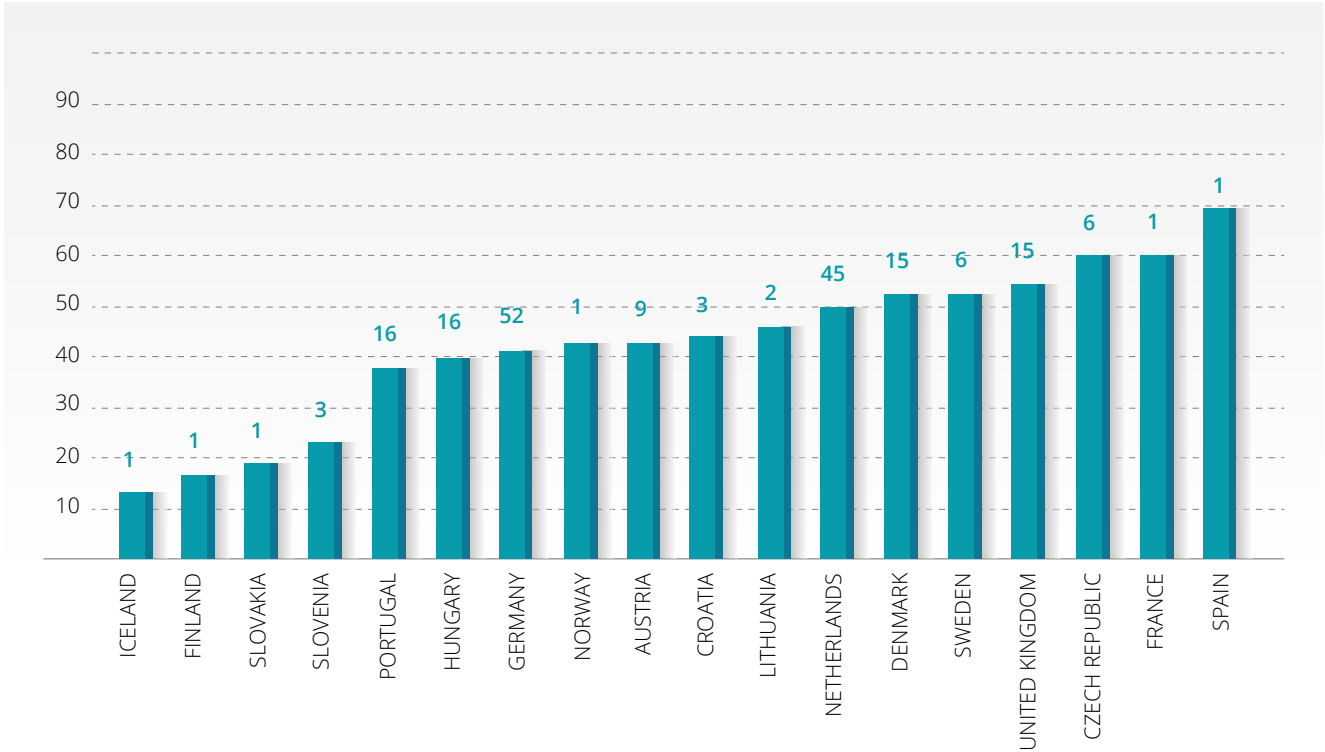
DCP validation time is improving but still too long and inconsistent, as demonstrated by EGA survey data:

Although validation time performance has gradually improved there is still significant variation between countries. The objective of a fourteen day validation is still a distant target. There are a number of steps that could be taken to drive improvement, including increasing automation and by passing some steps from the regulator to the applicant company.

However the main issue is the persistence of local national requirements by some member states. Examples of continuing country specific requirements which delay validation include local

Validation period per RMS, 2014 onwards

Source: EGA internal survey



Mean duration	2013	2014 onwards
Days	52	46

# of CMS	Duration in days
1-2	38
3-10	46
11-20	53
21-30	58

Results based on 231 procedures or sets of parallel procedures

language application forms and product-specific powers of attorneys.

The recently established Common European Submission Platform (CESP) is rapidly becoming the filing route of choice for new product applications. The breakthrough attribute of CESP is allowing submission of an application once to reach all required Agencies in a simple and secure way. It would be a logical next step to integrate a technical validation tool into CESP. That technical validation could be performed and confirmed by the applicant so reducing workload for the regulatory agencies. As CESP gains traction it could be time to question

the continued need for local portals, which in some member states lead to additional steps being required in the validation procedures.

From the reported experience of EGA member companies, the most frequent causes of validation delay are slow pick up in some countries and validation points being raised late in the timetable. These issues consequently delay the RMS starting the DCP clock. Validation is also sometimes delayed because the RMS waits for the CTS tracker to be updated, the procedure for this is unclear and seems to change in practice.

After a decade of experience gained it is surprising that individual member states can still impose specific national requirements or administratively delay validation of an application.

- Validation delays could be minimised by adding an automatic 14 day validation function to the Communication and Tracking System (CTS) used by the regulatory agencies to manage the workflow of European regulatory applications.
- If individual countries do have meaningful validation issues it should be mandatory to detail these using the invalidation template developed by CMDh.
- As information technology architecture is becoming more aligned between regulators and industry, transparency could be enhanced by making the CTS status of a company's application visible to the applicant, on a read only basis.

2.2.6 Reducing the length of DCP “clock stop”

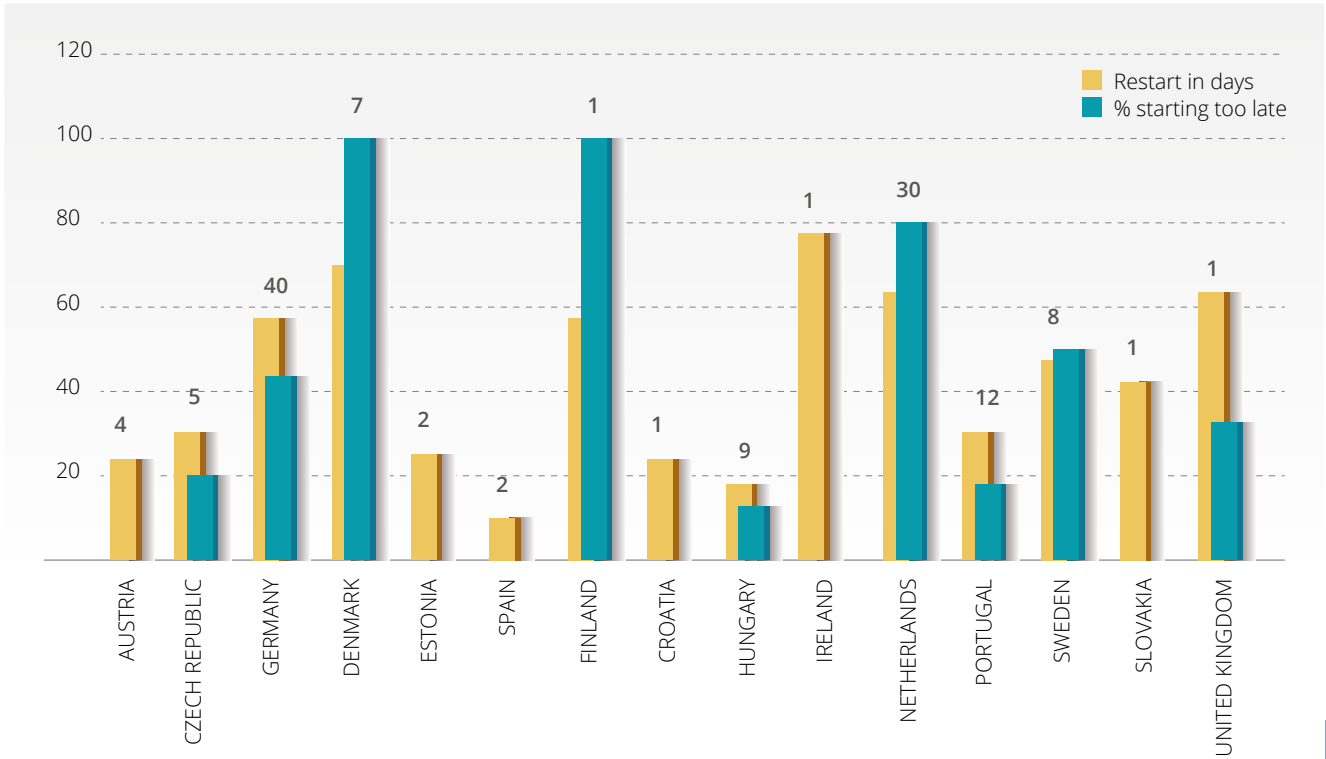
The main period for applicant companies to answer regulatory assessment questions and for the regulators to review their answers is in the so called “clock stop” between Days 105 and 106 of the DCP procedure. Re-starting the clock after the company has submitted its replies should ideally take no more than a month, a target which often not met.

EGA member survey data on how many DCPs restart in a month shows that much improvement is needed in this area.

Full implementation by all member states of the

EGA Annual survey on the DCP, restart of clock, results per RMS

Source: EGA internal survey



January 2014 best practice SOP for DCP would go a long way to reducing this time, particularly if a single feedback is based on the complete company response and focuses on Potential Serious Risk to Public Health issues only.

Mean duration	2014 onwards
Days	51

Criteria	Percentage
Starting within 42 days	50
Starting within 60 days	65
Starting within 90 days	87
Not started after 90 days	13

Results based on 135 procedures or sets of parallel procedures

2.2.7 **National phase delays at the end of DCP is largest single challenge**

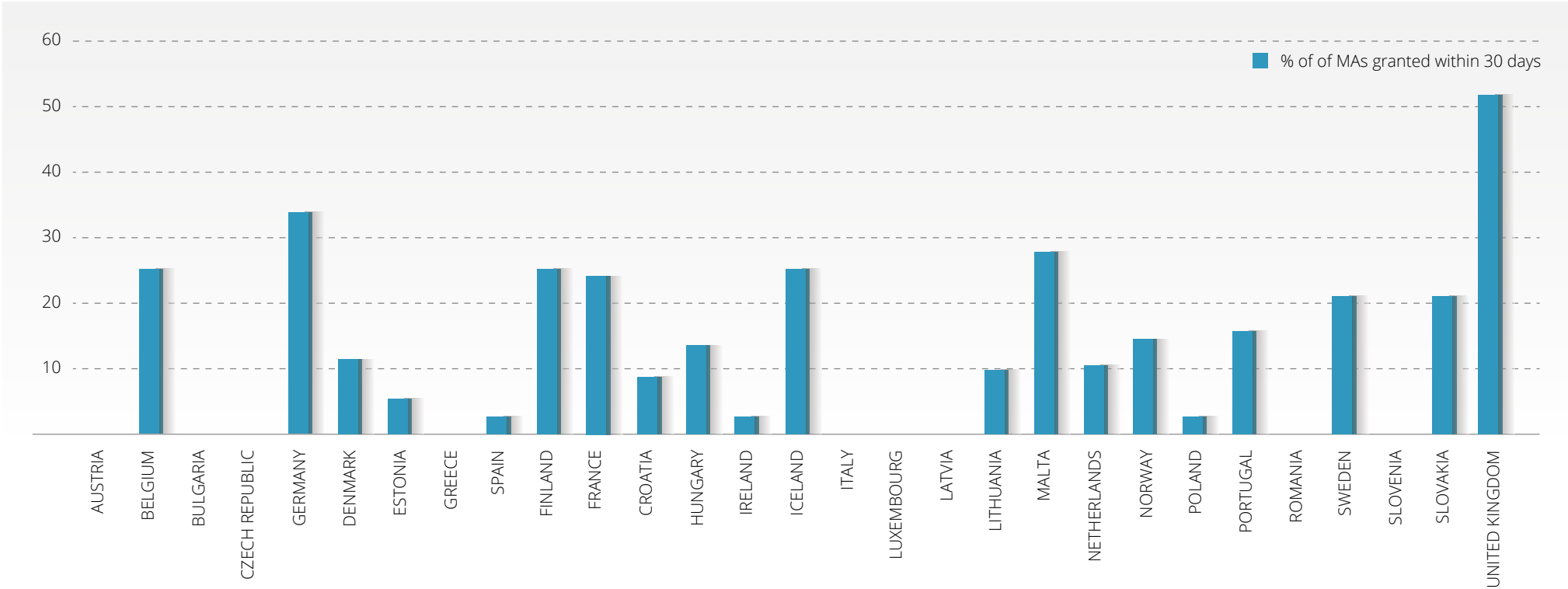
Today the length of the final national phase of DCP and the wide range of difference between countries is the most important target area for improvement.

The time taken to grant the national marketing authorisations after a DCP procedure spans a very wide range. Some member states routinely grant

within the procedural objective of 30 days. But for the vast majority, the 30 days deadline remains a big challenge.

Delays in the MA phase have a negative impact on following steps such as, starting national reimbursement, substitution or pricing procedures. Therefore granting the MA quickly within the legally foreseen deadline is crucial for timely access to generic medicines.

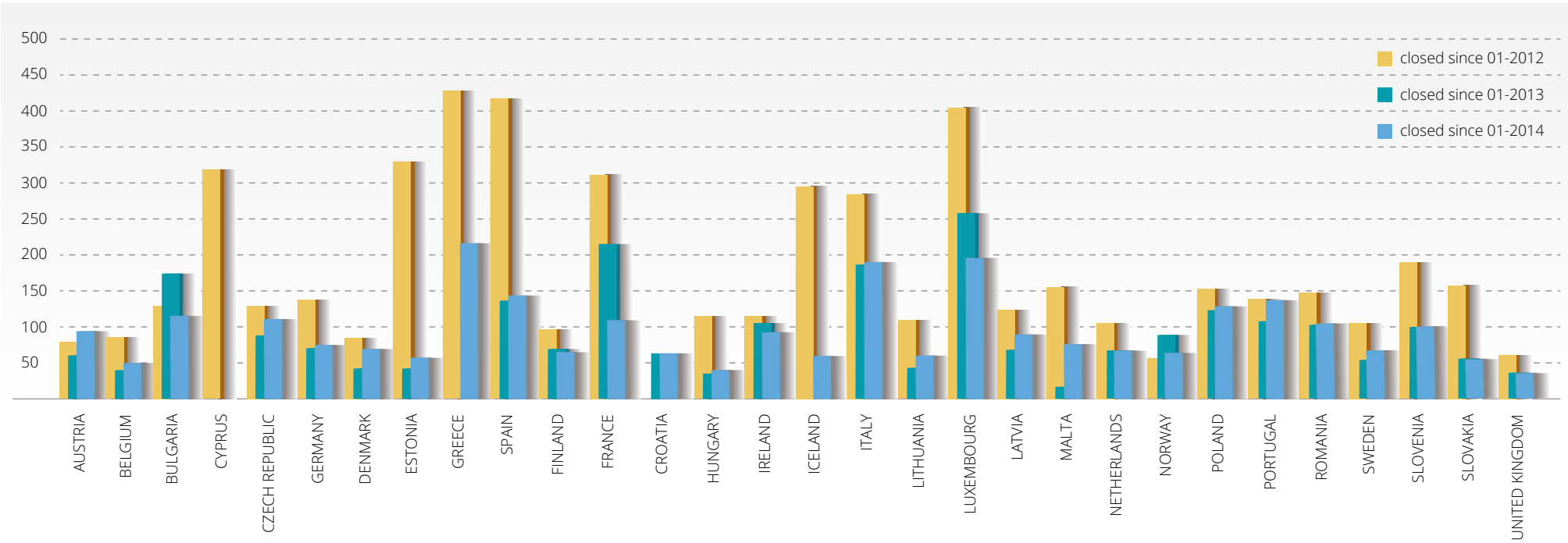
National finalisation, % in time



Results based on 2000 Marketing Authorisations issued

National phase outcome survey

Source: EGA internal survey



High variation in national phase duration between countries

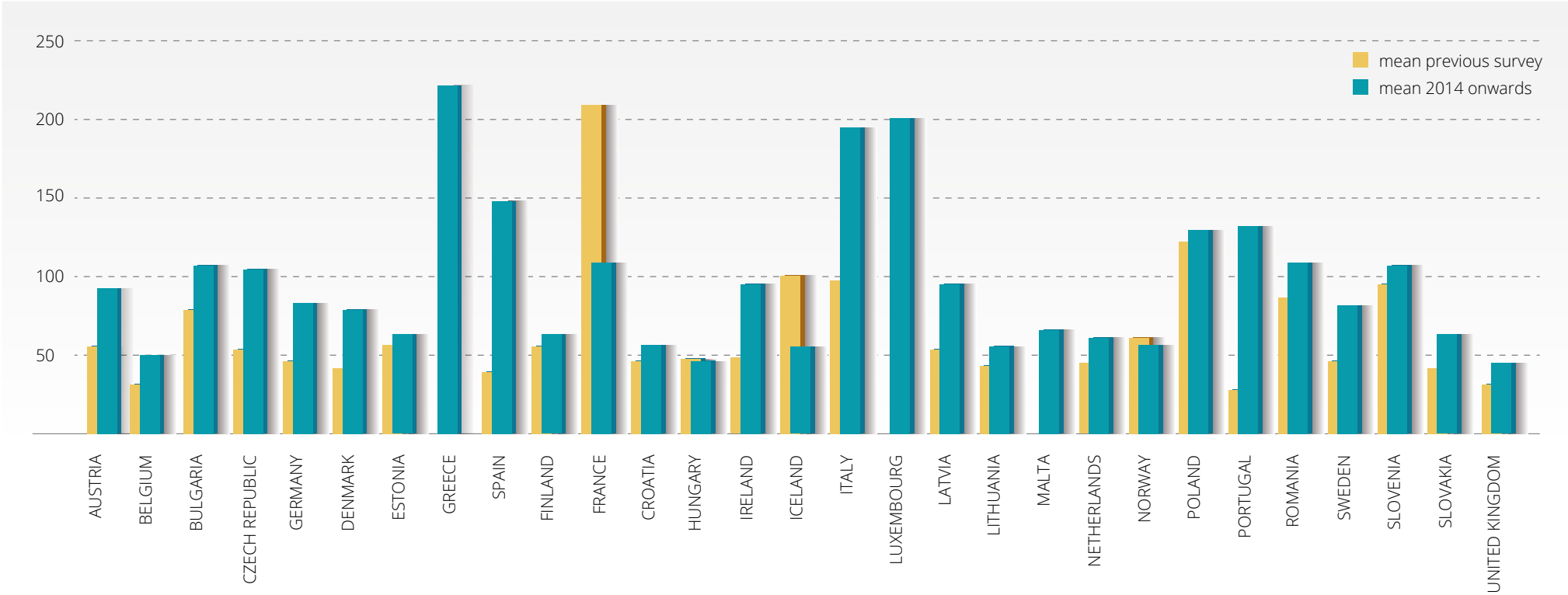
The importance of issuing the MA in a timely manner has been identified as one of the EGA top priorities to tackle in discussions with competent authorities. Several member states have invested substantial effort to reduce the backlog and to shorten time taken for granting the MA.

The overview of progress made by all countries over the two years (2012-2014) is presented on the graph above.

Unfortunately it seems this positive trend has been recently reversed. Based on most up to date EGA national phase duration data (EGA survey 2015), increasing delays have been observed.

EGA calls on the Heads of Medicines Agencies to analyse internally causes of those delays and to put in place mechanisms to remove delays and achieve the 30 days legal target.

National finalisation, MS statistics



Long term monitoring of national phase shows continued need for improvement

Reductions in the time taken for national phases are achievable.

- Timely submission of a good quality translation of the SmPC/ PIL by companies could be incentivised by fast track MA processing
- Inclusion of translations within the second phase of the DCP (from Day 106) would remove this issue from the critical path timeline

- National authorities could put dedicated resource into national phase processing (achieved by optimising/ simplifying other activities)
- Countries with separate pricing & reimbursement processes could start sooner if marketing authorisations were granted without translation from English of the patient information texts

Generic medicines registration is moving into the procedural timetable where submission is permitted after 8 years of originator data exclusivity, with marketing no less than 2 years later. During

the two year “window” it will be critical that product registration, national phases, pricing and reimbursement procedures are all fully completed to be able to launch the product immediately after expiry of IP rights. This will be challenging to achieve with the existing ways of working so some national system and work routines re-design is becoming urgent. These actions will be important to prevent potential issues in the future.

2.2.8 DCP should more closely reflect the industrial practices of the generics medicines sector

An important sector of the generic medicines industry is the group of companies that focus

totally on research & development and then license their products for commercialisation by marketing companies. Such an R&D company may run multiple DCP procedures in parallel from a single Reference Member State, to serve its multiple clients. If the product had several strengths this could lead to a large number of marketing authorisations in the RMS, of which only a fraction are needed for marketing. This way of working is cumbersome and wasteful of resources for all parties.

The issue does occur often and some recent and complex examples include:

Product A (1 strength): 8 DCP waves leading to 8 MAs granted in RMS, of which only 1 marketed

Product B (4 strengths): 14 DCP waves; 56 MAs granted in RMS; none marketed

Product C (2 strengths): 17 DCP waves; 34 MAs granted in RMS; only 2 marketed

Why do generic companies need duplicate MAs?

Generic companies sometimes require more than one MA in a member state.

The requirement for duplicate MAs in a given country is a frequent need for generic medicines companies. The reasons why duplicates are needed are perhaps not fully understood and need to be better communicated by the generic medicines industry. The drivers are usually legal, commercial or supply related.

These duplicates are needed to reach all channels and sectors of the market, particularly where

specialist marketing partners are needed to achieve this. Currently duplicates require parallel DCP procedures to be run, placing a high administrative burden on agencies and companies. It is proposed that duplicates can be made within the core DCP procedure. For some products a specific generic medicine company may have different marketing strategies or more than one commercial brand identity in a country, perhaps due to legacy issues such as mergers between companies.

The patents surrounding an active ingredient, formulation or product design can vary between countries. Therefore a generic company may develop a first formulation that can only be launched in some markets and in parallel develop or acquire from a R&D partner a second formulation to cover a separate set of countries.

R&D companies need duplicate MAs in order to cover their licensing partners.

Generic companies invest in the long term lifecycle of their medicines. This can require the creation of duplicate MAs for example to optimise material costs, increase manufacturing efficiency or improve shelf life and storage characteristics.

2.2.9 The Repeat Use Procedure – the weakest link

“a lengthy, cumbersome and unpredictable process”.

At present the only way to add more CMS to a completed DCP or set of DCPs is to run a Repeat Use Procedure (RUP). This is a lengthy, cumbersome and unpredictable process.

Another scenario is when a DCP includes different marketing companies in different countries or a single company ends up with several DCP waves to cover its entire marketing needs. A mechanism to link and de-link the MAs in DCP to align with a single company and remove any redundant MAs at the same time would deliver simplification and long term reductions in workload.

Due to these difficulties with RUP, companies have frequently reverted to starting a brand new DCP procedure. This tactical approach leads to duplication and unnecessary work for both agencies and companies. A more efficient solution should be designed. Unwanted MAs in countries, some duplicates and multiple DCPs are all symptoms of RUP not working well.

A more flexible approach would be useful when a new duplicate MA is desired in a country that has already reviewed the product in a completed DCP.

One short term solution could be to introduce “slot booking” for RUPs, as soon as the requirement is known. At the same time the requirement for no ongoing regulatory activities before a RUP starts could be set aside.

In the longer term, a new look at the current way of operating within the framework of the DCP is needed to avoid so many duplicates in the system, which are a burden for companies and authorities to maintain.

2.2.10 DCP is a listening procedure

The European regulators have responded to feedback to regularly improve the operation of the DCP.

- DCP gives valuable flexibilities in national product name (unless the originator is Centrally approved) and legal status. However Centrally approved originators are becoming the norm, so this benefit for generic product naming will diminish. This may lead to an unintended consequence of generic companies having to limit countries of registration
- DCP can give flexibility in pack sizes per country, although this sometimes reverts to a national issue
- DCP permits the submission of multiple applications to the same RMS, even if the list of CMS differs from one DCP to the next
- There has been progressive effort to reduce parallel assessments and build trust in the RMS assessment report
- Member states acting as RMS have been empowered to be more assertive during the validation phase, to start the official 210 day timetable even if there are a few minor issues unresolved

- Best practice has been developed to give applicant companies feedback on their answers to Day 105 questions within four weeks of replying and then starting the clock again by six weeks
- In efforts to reduce the length of the national phase at the end of DCP, countries are sharing their models of working in order to spread best practice

The generic medicines sector is made up of different types of company both in terms of size and focus, with some dedicated to research and development and not directly selling products. One thing they all have in common is an objective for rapid, flexible, transparent and predictable processes to achieve marketing authorisations in Europe. This is not expected to lessen as the data exclusivity periods limiting generic regulatory submissions move from a mixture 6 and 10 years to a uniform 8 years, followed by two years before marketing can start.

2.2.11 Some ambitious new concepts as the next phase of DCP improvement

To respond to existing challenges and to overcome inefficiencies identified in the current DCP operating practices, the EGA has developed several proposals for refreshing the DCP.

To develop these proposals careful consideration has been to the current legal framework. Two of the options fit within the current legislation:

1. Work sharing DCP

2. Tailored DCP

The other two suggestions could require changes to legislation:

3. Basket DCP

4. Backbone DCP

In all proposals the following criteria for improvement have been taken into consideration:

- Single harmonised assessment
- Transparency with respect to assessment responsibility
- High dossier compliance

The target objective is quick access to new marketing authorisations, potentially leading to a reduced risk of medicines shortages

The **Work sharing DCP** could be rapidly implemented and act as a milestone on the route to more significant improvements. The **Backbone DCP** is the ideal vision for future reform and deliver the greatest improvements for generic medicine companies.

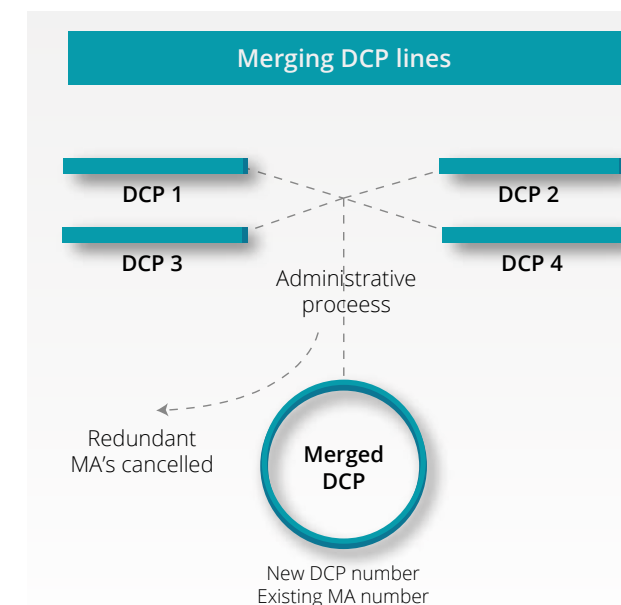
In addition, immediate benefits can be gained from proposals for **Merging DCP** lines and **Splitting DCP** lines, which would be relatively simple to implement.

How would the different DCP improvement solutions work?

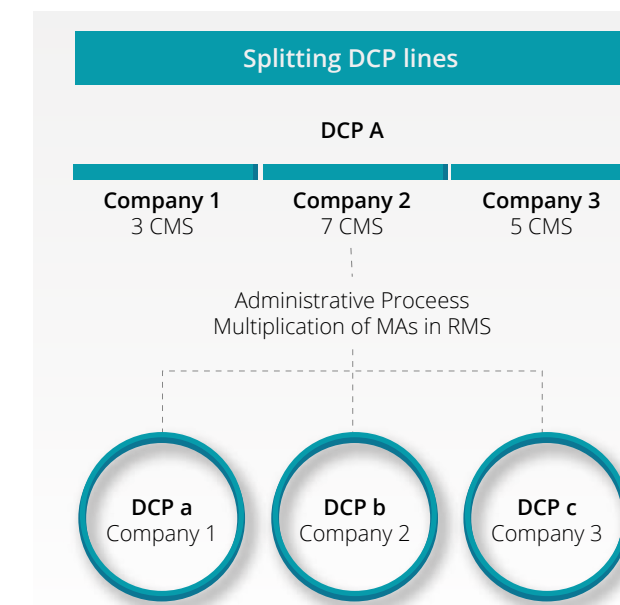
2.2.12 Merging DCP lines and Splitting DCP lines

The proposals for **Merging DCP lines** and **Splitting DCP lines**, would give immediate benefits and would be relatively simple to implement.

Due to the limitations of the current DCP format some medicinal products end up being part of several DCP procedures. This regulatory web leads to a multiplication in the number of post-approval variations submitted and also each applicable Reference Member State having to write an assessment report. **It is proposed that an optimisation is adopted that enables a merging of DCP lines, with a single RMS chosen by the applicant then taking lead responsibility for the product.** The RMS selection could also take into account member states who have developed specialist capability in certain therapeutic areas or technologies. This would be another utilisation of work sharing and would lead to measurable regulatory workload reduction, particularly for the Agencies, as well as for industry.



Conversely there are situations where a company wishes to separate MAs in one or more country for example if a part of a company is bought or sold, or in cases where an R&D developer licenses-out one DCP wave to more than one marketing company. **Therefore a flexibility to de-merge or split DCPS is also recommended.** A combination of merging and de-merging DCPs would drive a rapid consolidation in the total number of DCPs, so reducing overall regulatory complexity in the system.



This simple new flexibility would improve compliance oversight by separating companies who have become connected through a DCP structure.

This proposal would sweep away the use of parallel RMS for the same dossier and remove redundant MAs. So as to avoid reimbursement impacts MA numbers should not change. Tracking would be achieved by a new DCP number.

2.2.13 **Backbone DCP**

The thinking behind the **Backbone** DCP is adopted from the Centralised Procedure.

There would be a single submission involving a rapporteur and co-rapporteur the assessment would be confirmed by CMD(h).

Thereafter the application would carry a “core approval certificate”, which would be the basis for issuing Marketing Authorisations in Member States upon request via an administrative local process.

In this process the “core” Marketing Authorisation holder would be allowed, within a given timeframe, to obtain a Marketing Authorisation (and if needed more than one), in any Member State, in the name of any Marketing Authorisation holder, based on reference to the “core approval certificate”.

The number of Marketing Authorisations per Member State would be unlimited.

The timeframe within which the request is made could be capped.

How would the Backbone DCP meet the EGA criteria for improvement ?

Single harmonised assessment

There will be one fixed rapporteur and potentially co-rapporteur allocated to the product throughout the lifecycle.

Since the Marketing Authorisations in all Member States are linked to the core assessment harmonisation is guaranteed.

There would be no assessment capacity wasted.

There would be no need to maintain unused Marketing Authorisations for unforeseen situations, since the Authorisation for the product concerned could be obtained quickly when actually needed.

Transparency with respect to assessment responsibility

Since there is only a single dossier there is full transparency.

With CMD(h) involved in the final decision they will set the approval standards.

High dossier compliance

In this model there will normally be only one version of a dossier in Europe.

This will facilitate transparency and also increase dossier compliance. There will only be one version of the dossier to maintain for the whole EU.

Quick access to new marketing authorisations, potentially leading to a reduced risk of shortages

The national Marketing Authorisations to be issued could be granted at any time within a certain validity period of the assessment.

The issuing of the national Marketing Authorisation would only require an administrative process. This would enable very quick access to the product

concerned in case there is an immediate need to make the medicine available to specific marketing authorisation holders or for particular markets.

A significant public health advantage of this additional option would be to provide a rapid response tool for companies with established supply chains to enter a market experiencing potential supply vulnerability.

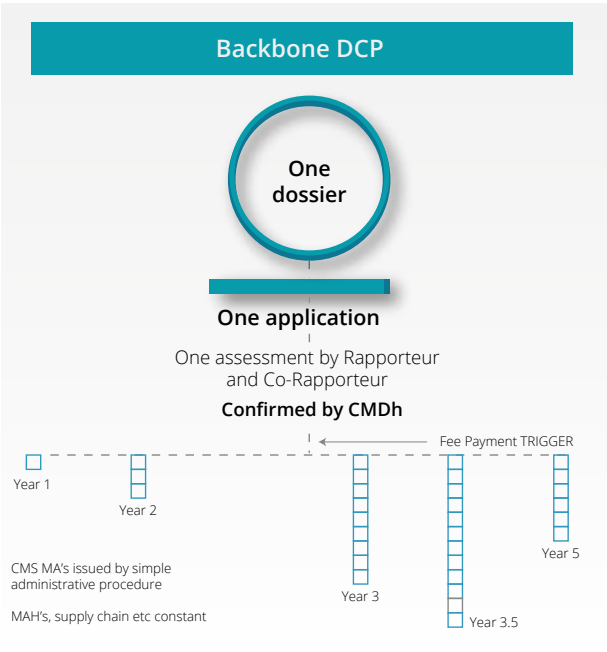
In addition this example also fits well with the business models of the generic industry.

There would be two levels of assessment fees.

The first fee would be for the actual EU assessment.

A second much lower fee would be related to the actual issue of the Marketing Authorisation at the national level.

If adopted, the Backbone DCP would give maximum flexibility to solve the vast majority of problems encountered in operating DCP for generic medicines.



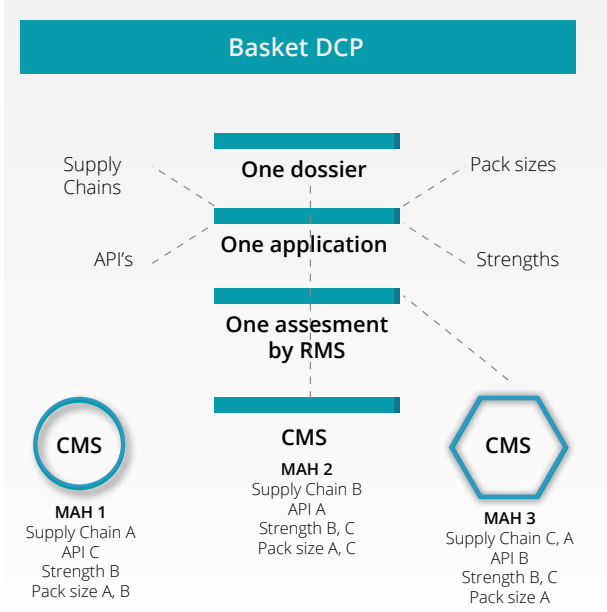
2.2.14 **Basket DCP**

In the Basket DCP design the sum of all potential MA needs are included in the approval, from which the company selects the parts required per country. This would include supply chain options, so avoiding a frequent cause of post approval pre launch variations. More than one MA per CMS country could also be permitted.

For implementing such a structure there should be agreement reached which elements in an

application are considered core elements and should be present in all related Marketing Authorisations and which elements could be considered to be part of a local administrative addition.

A single assessment would lead to a adaptable approval. The key feature would be enabling a CMS marketing authorisation which exactly meets the needs of the company, reducing the need for variations. A limitation with this proposal is how to manage post approval requirements., There could be a risk of generating more administrative burden and less harmonisation across the Community. It could be made more practical if limited to Module 1 information.



2.2.15 **Worksharing DCP**

Worksharing DCP as a new pathway would be particularly suited to R&D only companies and fits comfortably within the existing legislative framework.

Today it could happen that a R&D company sells its dossier to several customers which would each run their own application procedures.

The Worksharing DCP would allow these procedures to run for the specific set up of each customer with the assessment being done via one RMS and not by each of the RMS chosen by the individual customers.

The procedure could be tailored to fit with the requirements of the marketing partner.

How would the Worksharing DCP meet the EGA criteria for improvement ?

Single harmonised assessment

If several RMS were involved, one would make the scientific assessment on behalf of all, so sharing workload. If adopted, this principle would allow the addition of more CMS at a later date, so solving current issues around duplication of MAs.

Transparency with respect to assessment responsibility and use of existing marketing authorisations

This model would avoid unused RMS marketing

authorisations. There could be an option to continue worksharing during the lifecycle of the product.

The increased transparency of the Worksharing DCP option might require additional steps to protect commercial confidentialities.

High dossier compliance

The Worksharing DCP would meet the target of high dossier compliance if the Worksharing principles could be maintained during the lifecycle for Module 2-5 related variations.

Quick access to new marketing authorisations, potentially leading to reduced of risk of shortages

Although probably not the best solution it could however be achieved for countries already involved in any of the lines in the initial procedure. A simple duplication process could be introduced.

Work sharing between regulatory authorities is becoming increasing popular, not just for resource saving but also as a way to avoid divergent regulatory decisions. This Worksharing DCP model would enable maximum flexibility for extending an approval both vertically and horizontally.



2.2.16 Tailored DCP

The Tailored DCP model was part of the exploratory phase of this project but has not been carried forward as a recommendation.

The Tailored DCP concept could deliver a workable alternative to Repeat Use Procedures. It would introduce a standard “administrative Repeat Use Procedure” that could be executed for any Member State as soon as the weighed majority of Member States has given its positive opinion in a DCP.

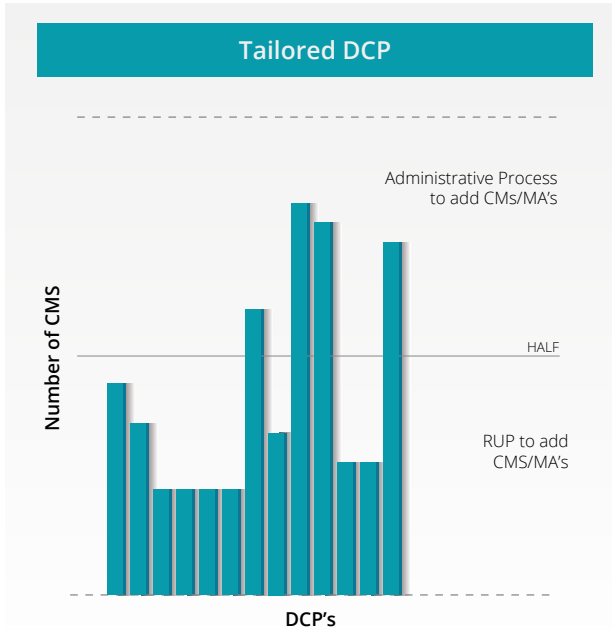
The weighing of Member States with a positive opinion would probably have to follow a model as currently used in the CHMP opinion phase for Centralised Procedures. The simple administrative notification extension process would deliver almost immediate access to additional member states.

There is already positive experience in EU with administrative Repeat Use Procedures in some smaller Member States. These procedures run in parallel with activities on the already closed DCP, such as variation execution or renewal and are operating well.

It can be argued that a completed DCP sets a “regulatory design space” for a generic medicine. The Reference Member State led scientific assessment report, reinforced by CMS review, demonstrates that an approved product meets EU public health protection standards and that a harmonised European view has been achieved.

Therefore it is proposed that additional member states could be added to a completed DCP by administrative variation for a limited period after closure of the DCP. The option should be time limited to perhaps five years. There would also be some circumstances when this new flexibility should not be used e.g. safety related referrals or ongoing restrictive regulatory action for the drug product involved. This proposal would avoid additional DCP procedures, which are now sometimes run due to challenges in getting a RUP started. It would be a fresh application of the “work sharing” principle, whereby the regulatory scrutiny applied by the countries of the initial DCP

enables more member states to make the medicine available to their patients. A particular public health advantage of this additional flexibility would be to provide a rapid response tool for companies with established supply chains to enter a market experiencing potential supply vulnerability.



Other routes to a Marketing Authorisation:

2.3 Mutual Recognition Procedure (MRP)

When introduced in 1995 the Mutual Recognition Procedure was a breakthrough by enabling a granted Marketing Authorisation in one member state to be spread to one or more additional countries through a harmonisation process. However over time and particularly since the introduction of the Decentralised Procedure, MRP has become progressively less popular for several reasons:

- The requirement for no other ongoing regulatory procedures e.g. variations and renewals
- The time taken for the Reference Member State to provide an assessment report, which is often much longer than the 90 days defined in the process
- Difficulties in achieving harmonisation with an already granted Marketing Authorisation
- A perception that the regulatory agencies see MRP as a lower priority than EU procedures with a more fixed timetable compared to DCP and the Centralised Procedure (CP)

By its structure MRP is inherently more constrained than DCP since it is seeking to achieve harmonisation with a regulatory fixed point, the granted Marketing Authorisation . A situation has been reached where MRP is rarely used today and has been superceded by the Repeat Use Procedure (RUP). Therefore MRP will not be discussed in more detail for this report.

2.4 National Applications

National applications remain important for local companies. All other EU product registration procedures rely on harmonisation of regulatory science and procedures between two or more member states. There are still situations where the practise of medicine is not the same in all countries, resulting in local one country products. Also the recommended first line treatment for many conditions continues to be medicines that have been in existence for several decades. A third scenario is where the legal basis of an application may not be clear on an EU level, for example for some over the counter medicines. In these cases the national registration route is an important option for generic medicines companies. However timelines are difficult to predict and sometimes extended. This significant variability is both between countries and from one application to the next.

It is recommended that the national regulatory agencies collectively commit to applying the DCP 210 day procedure length to national procedures as well. This would produce a level playing field for all applicants, applications and across all procedure types. It is welcomed that this approach has been taken up by a small number of member states already, such as UK. Within the continuing role of national applications it will be important that they do not act as a source of national specific requirements that then permeate into other procedure types, such as DCP.

EGA Recommendations

Further Improve the Decentralised Procedure through more flexibility

Optimally interpret DCP to permit new models of working reflecting the practices of the generic medicines sector:

2.4 “Backbone DCP”- a single harmonised assessment enabling Marketing Authorisations to be obtained only when needed, so reducing the number of non-marketed MAs in the system.

2.5 “Basket DCP” - one Reference Member State assessing a “full package/basket” of elements for a given product; with the Marketing Authorisation Holder choosing a tailored option for each Member State.

2.6 “Worksharing DCP” concept, with one Reference Member State assessing on behalf of several RMS, and the addition of Concerned Member States permitted later

Improve operational aspects of the current DCP:

2.7 DCP validation to be completed in 14 days, through automatic validation by the RMS.

2.8 Mandate DCP day 106 clock restart within one month after the applicant submits answers to questions.

2.9 Speed up the National phase by fast track processing, dedicated resources and dropping compulsory translation from English of patient information texts if no immediate launch/ or no marketing foreseen in this country (e.g. only RMS)

2.10 Rapidly introduce a mechanism to link and de-link the MAs in DCP to align with company needs and simultaneously remove any redundant MAs and RMS roles (splitting and merging).

National registration route

2.11 Timeline for a national registration application should be in line with EU procedures to ensure a level playing field between application routes.

Solve the problem of MRP/Repeat Use Procedures in product approval

2.12 Introduce “slot booking” for Repeat Use Procedures and drop the requirement for no ongoing regulatory activities before a MRP/RUP starts and while a RUP is ongoing.



Chapter 3 – The impact of increasing regulatory fees

Alongside a refresh of the regulatory procedures there is also an opportunity to review **regulatory fee structures** to achieve a more sustainable financial model for both industry and authorities. It is recognised that the funding models and the mix of industry and state contributions do vary from one member state to the next. On one hand the trend of constantly increasing regulatory expenses for industry needs to stop; on the other hand financial stability of the Agencies needs to be ensured.

The table below demonstrates the wide variability in DCP fees between member states, for a typical example of a generic medicinal product with two strengths and two pack sizes. It is difficult to rationalise the large disparity in RMS fees for what is in essence the same work. Also in many countries the CMS fee seems to be too high relative to being RMS in the same country considering that workload is very much reduced when a country acts as CMS..

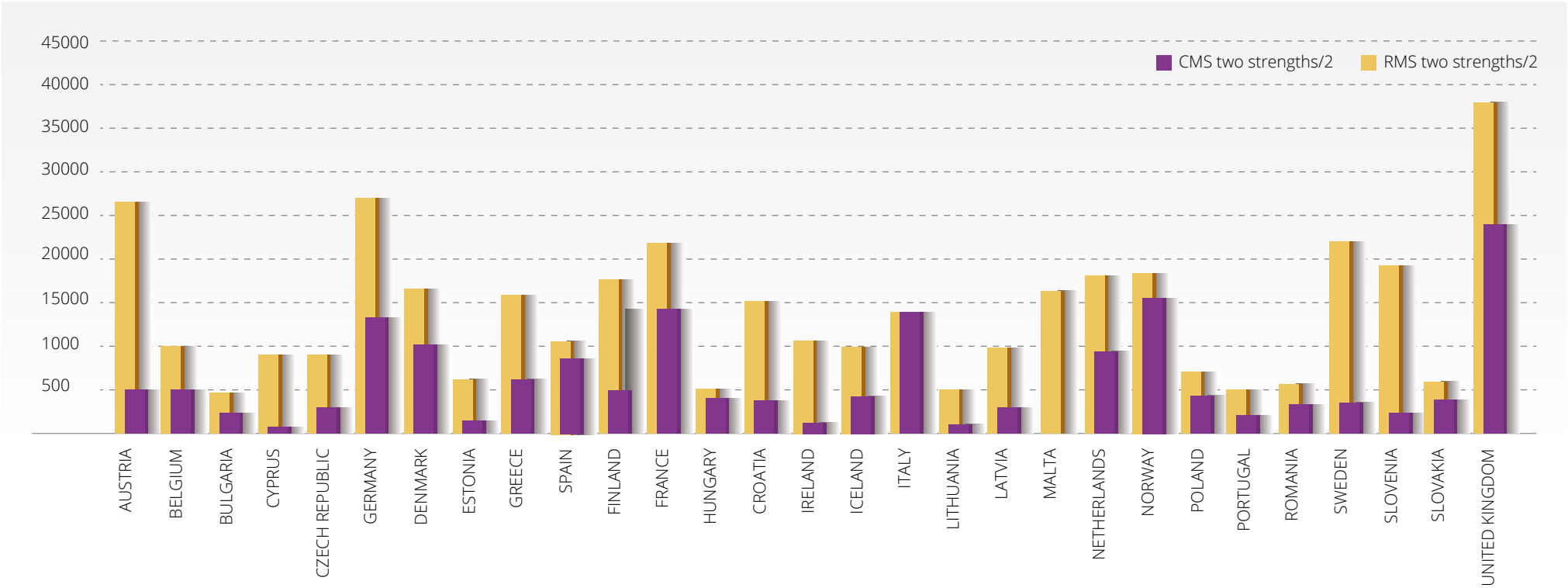
Fees only incurred due to system constraints e.g. multiple RMS fees for parallel procedures seem to be redundant. The overall objective is to reduce both complexity and hence costs. New legislation has tended to lead to increases in company infrastructure and more fees, particularly in the area of variations.

Overall there should be a fresh look at the ratio of fees between new product applications and lifecycle maintenance where the balance appears to have moved too far towards maintenance costs. High regulatory maintenance fees seems to be particularly misplaced if a generic medicine cannot yet be marketed because a limiting patent has not expired.

The systems for charging regulatory maintenance fees differ between member states but can be divided into two main types, charges per procedure or a flat annual fee per product. A model based on fees per application could give an unintended consequence of regulators facing reduced income if they improve efficiency. An annual fee based model gives more budget certainty for both companies and regulatory agencies.

A successful example of maintenance fees has been running in Netherlands for several years and can be used as a case study for potential adoption by other countries. The annual fee is either Euro 1,120 or 1,270 per marketing authorisation number (2015 data). Another useful case study is the recent modernisation of the Austrian fee model.

Variability in DCP new product registration fees between member states (for a formulation with two strengths) EGA member data, June 2015



Modernise the EU fees structure and disconnect from number of procedures

3.1 Introduce a flat annual fee per product. This flat fee is covering all maintenance costs including variations.

3.2 The fee structure for new product registrations should fairly reflect the workload of the assessment (e.g. the ratio of RMS:CMS fees, duplicates, multiple strengths)



Chapter 4 – Lifecycle Maintenance, Variations

The work done by pharmaceutical company regulatory departments can be broadly divided into new product registration and life cycle maintenance. In recent years the proportion of resources spent on maintenance has substantially increased. A point has now been reached where **generic companies with large portfolios are spending the same in three years of regulatory maintenance as they invest in R&D per year for new product development.**

The introduction of Type 1A “do and tell” variations was requested by the industry and has delivered a welcome simplification. However as an unintended consequence the overall number of variations submitted by companies has increased. This in turn has increased workload substantially for regulatory agencies. It could be argued that this increase in volumes makes it more challenging for both companies and regulators to focus on important changes that have the most potential impact on product quality. The consequential procedural delays also put a risk on supply chain continuity and delay efficiency improvements.

The volume increase in variations has also been driven by a number of specific events. Some are legislative changes and there is a perception that Variations is the default implementation mechanism.

EGA recommendations to improve the EU Variation Procedure

Maintenance fees exceed initial submission fees

- 4.1** The variation fee structure should be reshaped so that maintenance fees, in the first renewal period after MA grant, are lower than initial submission fees.

Variation Fee structure

- 4.2** Regulatory agency fee income should be disconnected from the number of variations processed, to stimulate proactive optimisation of the variations process .

- 4.3** Introduce a single annual maintenance fee, covering all types of variations

Variation timelines

- 4.4** Type IB variations should be given more priority so that timelines are met, including a predictable Day 0.

Safety referral variations

- 4.5** Safety referral outcomes should be more easily accessible with clear instructions for submitting the necessary variations.
- 4.6** Safety referral variations should be prioritised in order to enable timely update of patient information.

Concomitant variation & renewal applications

- 4.7** The procedural guideline should clearly allow the concomitant submission of renewal and variation applications.

Grouped variations

- 4.8** The fee structure for variations should be thoroughly revised so that fees for grouped variations are always less than fees for a Type II variation
- 4.9** Finished product optimisation should, like API optimisation, be eligible as Type II variations.

Company-wide changes

- 4.10** For a number of changes, particularly when company-wide, a mechanism should be found to maintain regulatory compliance whilst reducing administrative burden, together with a reduced fee structure.

CEP/TSE certificate updates

- 4.11** For administrative changes to CEPs/ TSEs certificates a simplified regulatory pathway should be implemented.

Single country changes

- 4.12** For country specific changes within DCP or MRP, the guidance should be simplified so that the change is only submitted where it applies. Non impacted member states would be notified through an update in the “Article 57”-database. Fees would only be payable in the countries where the change takes place.

Reporting within 12 months

- 4.13** The European Commission and member states should evaluate the “up to 12 months” reporting provision and identify the underlying causes for underuse.
- 4.14** Consideration should be given to the possibility to report within 12 months as a notification.

API related variations

- 4.15** The ASMF work-sharing pilot should be further strengthened.
- 4.16** Long term consideration should be given to legislative change whereby the API regulatory documentation would be managed independently from the medicinal product regulatory dossier.

- 4.17** A direct role should be developed for API manufacturers in regulatory procedures based on the model of the current European Pharmacopoeia CEP procedure.

Excessive API GMP and supply chain information in the regulatory dossier

- 4.18** To balance transparency in the API supply chain and supply chain resilience, there should not be more additions of API GMP or supply chain elements into the regulatory dossier.
- 4.19** The regulatory dossier API information should be limited to the final API manufacturer(s) and the final intermediate manufacturer(s). All other involved sites should be appropriately managed through manufacturers’ quality systems and regulators’ supervision as part of GMP inspections, both API and Finished Product (FP).
- 4.20** Transparency of the API supply chain should build on initiatives such as IDMP database.

Part 1 – General Overview

Note: the variation classification guideline is not addressed as part of this report. It would need to be re-evaluated concomitantly to a future variation regulation revision.

Overview of the evolution of the variation number per marketing authorisation

Issue Statement: The average number of variations per marketing authorization (MA) and per year has increased over time.

It is hard to indicate a number of variations/ per MA/ per year. Variations (and their number) are a consequence of a number of factors / reasons.

- The main issue is the introduction of the 'grouped variations' approach from the last variation regulation revision. In practice, instead of submitting one variation (combining different changes), applicants are now required to submit distinct variations within a 'grouped' variation application

Illustrative examples of grouped variations (in the case of MRP/DCP):

Variation to change name of the finished product in three MS in now a grouped application of three variations instead of only one.

Change in specification of the finished product is instead of one type II variation, a grouping of 2, 3, 4 or even more Type IA, Type IB variations.

Optimisation of the finished product is instead of one Type II variation, a grouping of many variations.

Other issues include:

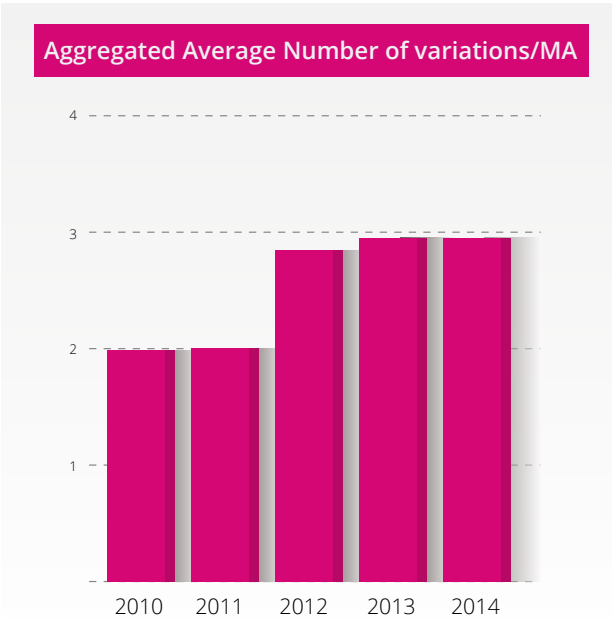
- The introduction of new variations categories: introduction of the summary of pharmacovigilance system (PSMF) for each MA (representing hundreds of identical Type IAin variations to be submitted by one company). These resulted in many variations causing an increase in costs

The tables on the right summarise

- the total number of executed variations
- the total associated variations budget

Figure 1 – Aggregated Average Number of Variations per Marketing Authorisation (MA) and per Year

Year	Aggregated Average Number of variations/MA	Aggregated Total number of MAs
2010	2.0	17723
2011	2.1	64107
2012	2.8	64267
2013	2.9	94937
2014	2.9	62757



Conclusion:

Based on data gathered on a minimum of 18000 MAs each year and over a 5 year timeframe, the number of variations per MA and per year appears to have increased about 45% i.e. 1 additional variation / MA and per year.

For the responding companies in 2014, it implies over 60 000 additional variations filed.

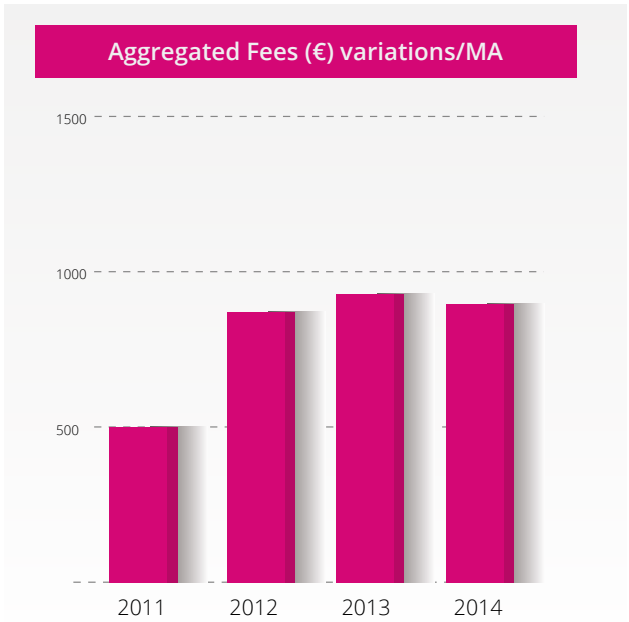
Of course, EGA recognise that the reasons for the increase of the number of variations per marketing authorisation per year are multiple and can also include company specific situations such as mergers/acquisitions or rebranding.

4.2 Overview of the evolution of the variation fees per marketing authorisation

Issue Statement: The average variations fees paid per marketing authorisation (MA) and per year have increased over time.

Figure 2 – Aggregated Variation Fees (€) per Marketing Authorisation and per Year

Year	Aggregated Fees (€) variations/ MA	Aggregated Total number of MAs
2011	690	16608
2012	1302	40267
2013	1312	48937
2014	1266	47595



Note: the overview data regarding the actual amount of variation fees per MA and per year was partial and could not always be aggregated. One reason for this difficulty is the way the maintenance fees are accounted.

Conclusion:

Based on data gathered on an average of over 16500 MAs each year and over a 4 year timeframe, the variation fees per MA and per year appear to have increased by 45% over the last 4 years amounting to an average of an extra 570€ / MA and per year.

4.3 Overview Of The Evolution Of EU Member States (MSs) Variation Fees

Variability of variations fees applicable across EU Member States (2015)

Issue Statement: Fees applicable for each variation type vary greatly between EU MSs

For Type IA

The observed variation fees range from 0€ to 1400€.

Where no fees are charged, EU MSs typically have an annual fee structure taking Type IA variations into account.

Figure 3 - Range of applicable fee (€) in EU MSs Type IA variations (2015)

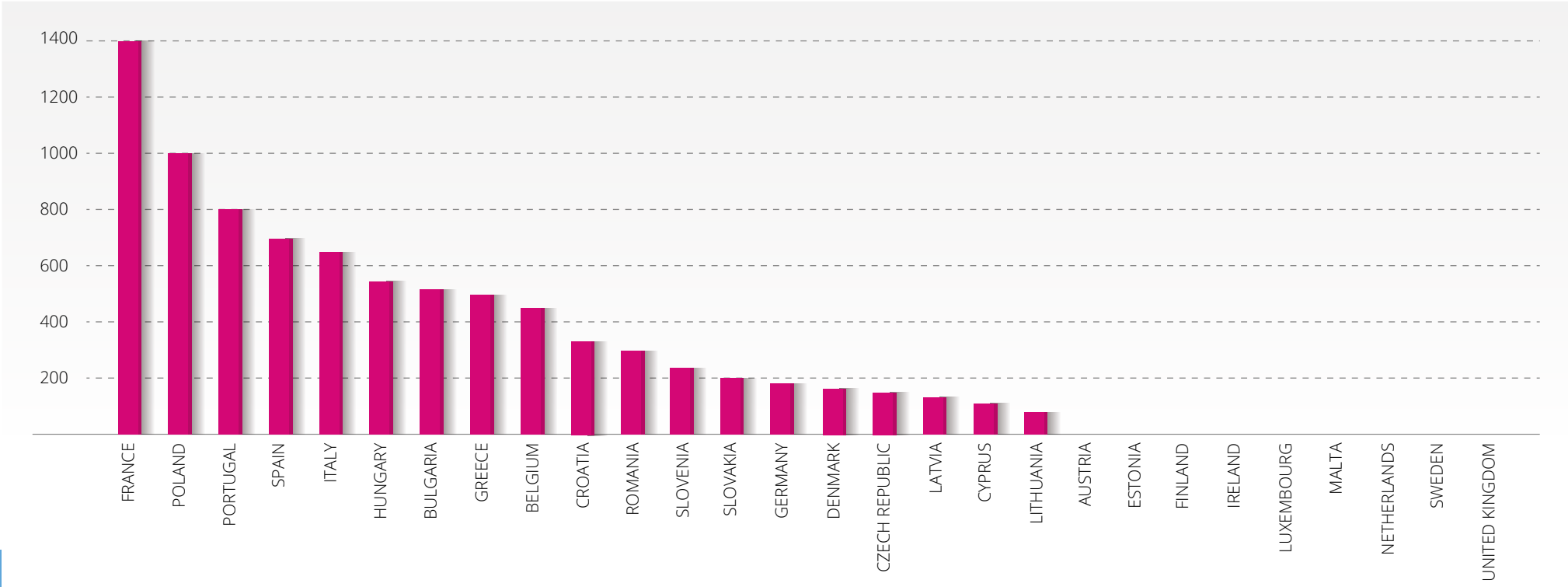
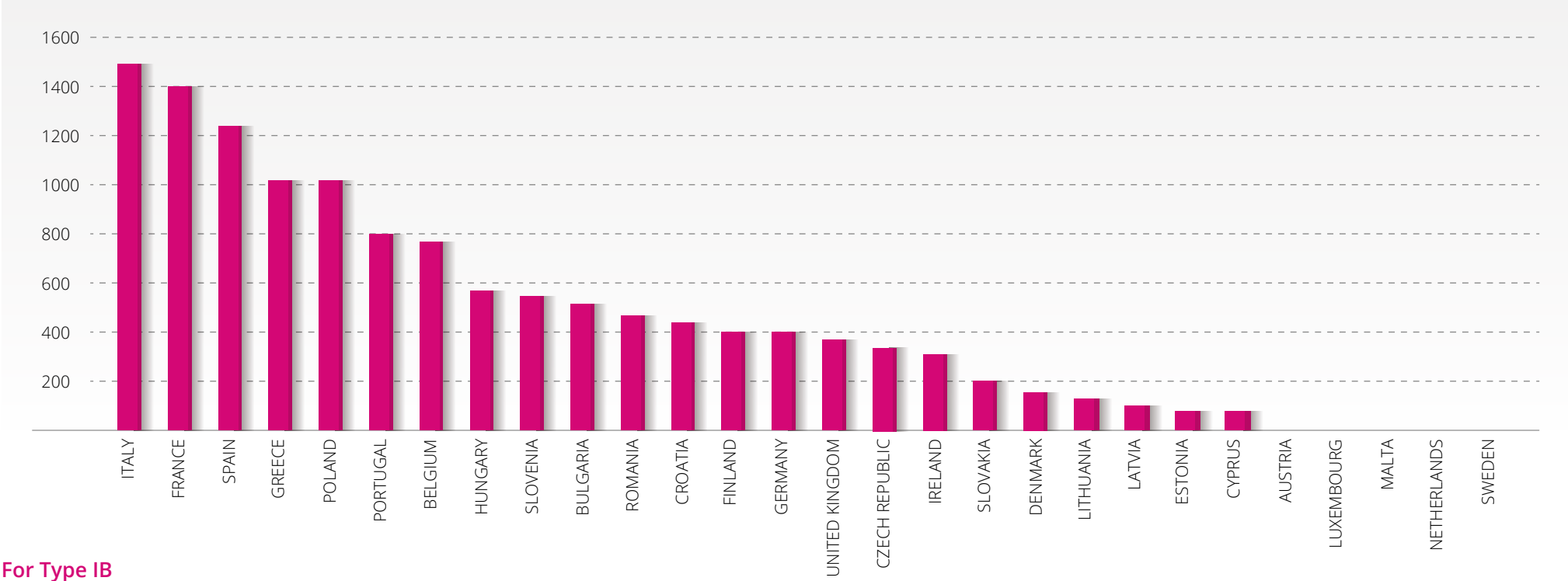


Figure 4 - Range of applicable fee (€) in EU MSs Type IB variations (2015)

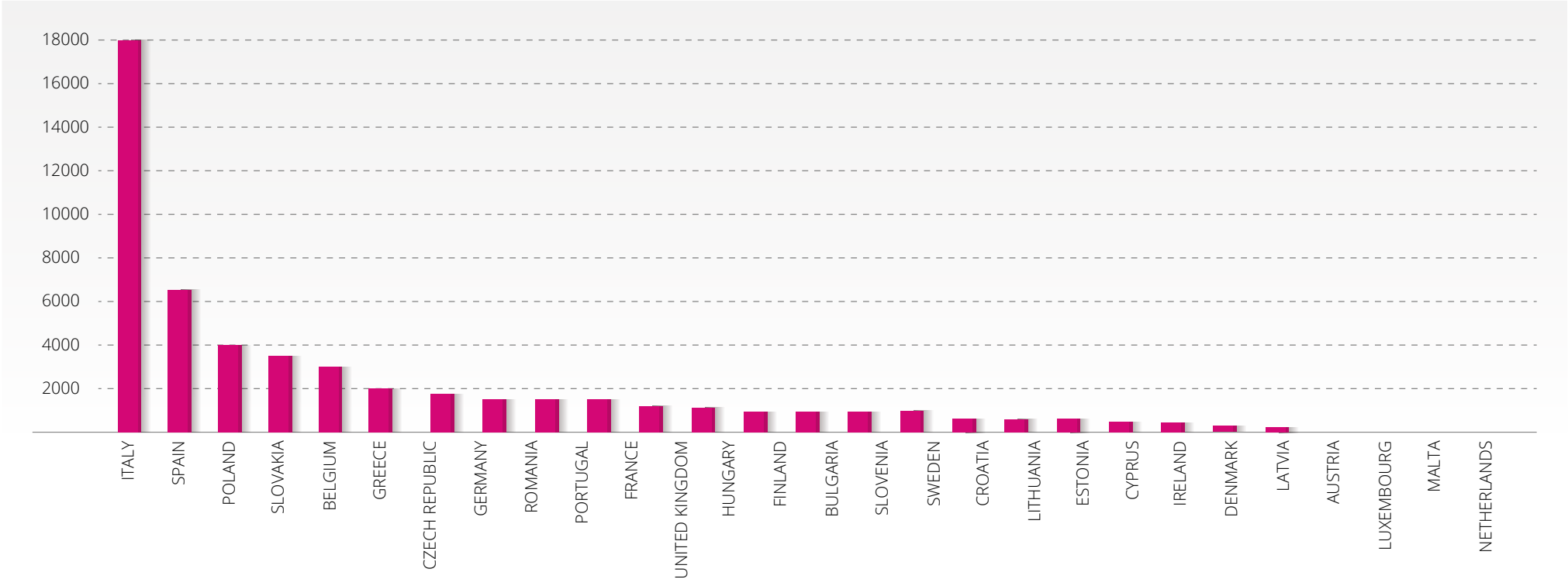


For Type IB

The observed variation fees range from 0€ to over 1500€.

Where no fees are charged, EU MSs the annual fee structure takes variations Type IB into account.

Figure 5 - Range of applicable fee (€) in EU MSs Type II variations (2015)



For Type II

The observed variation fees range from 0€ to over 18 000€.

Type II variations are an area of significant disparity in EU MSs fee structure.

For Type II variations, where EU MSs apply a different range of fees depending on the nature or complexity of the variation, the lowest applicable fee was retained

Conclusion:

Based on the data gathered for most EU MSs, it appears that while applicable variation fees vary among EU MSs, the greatest variability is observed for Type II variations where the fees range from 0€ to over 18 000€.

Issue Statement: Fees applicable for each variation type within each EU MS have increased over time

For Type IA variations, evolution of variation fees charged by EU Member States for the period 2011-2015. Historical data were not available for Croatia, Latvia, Lithuania and the UK.

The evidence gathered and presented in Figure 6 below suggest that fees charged by EU MSs for type IA variations have slightly increased over the last 4 years in the following countries: BE, IT, PL and ES.

Decrease in fees were recorded in AT, CZ, DK, DE and SI.

Figure 6 – Fee Comparison – Type IA variations (2011 vs 2015)

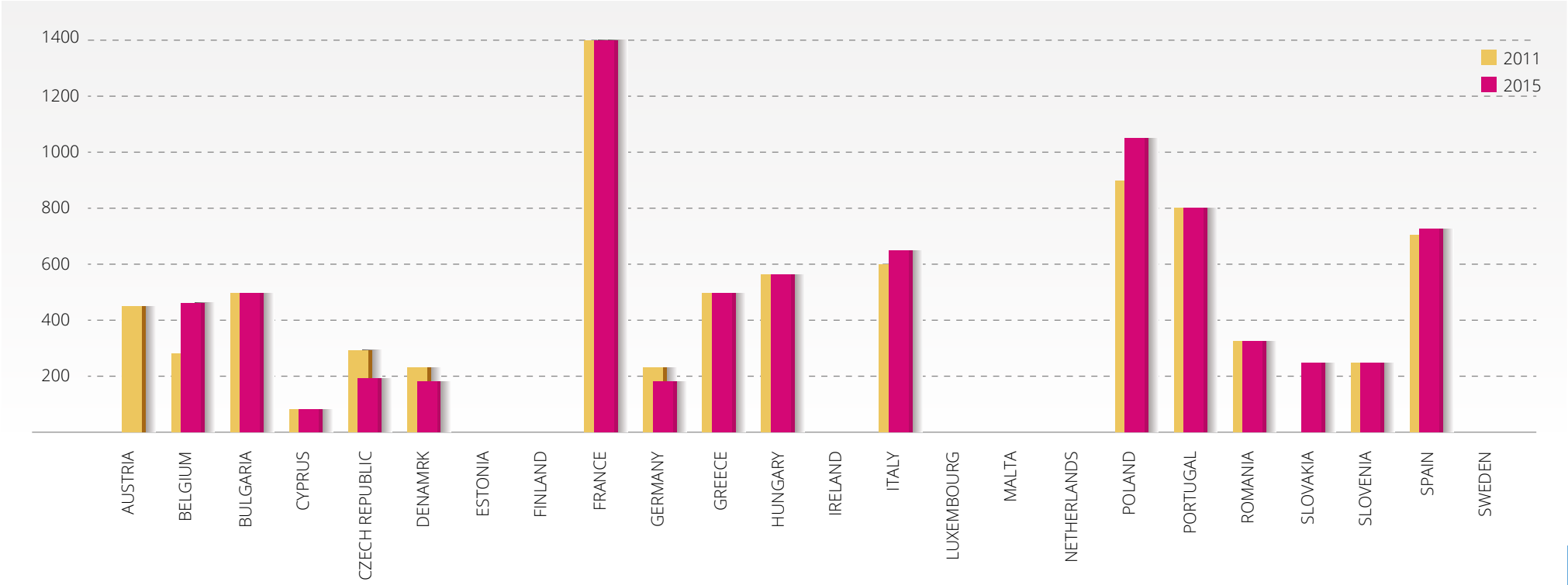
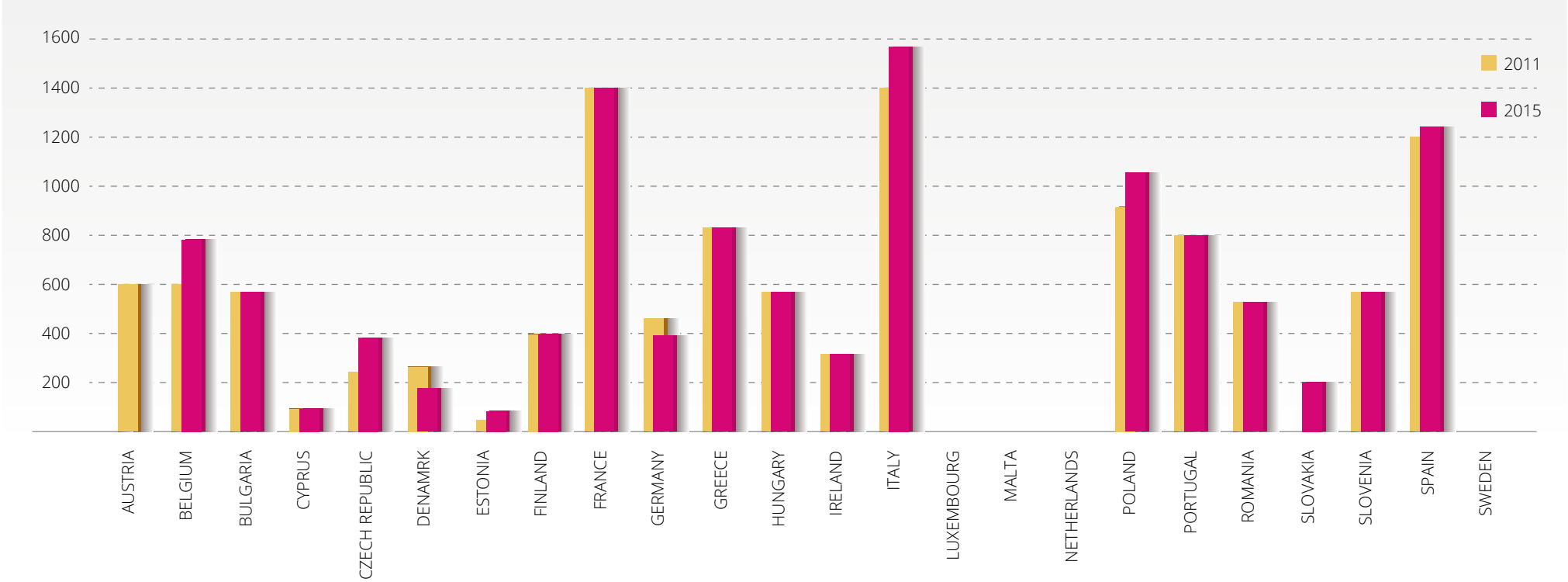


Figure 7 - Fee Comparison - Type IB variations (2011 vs 2015)

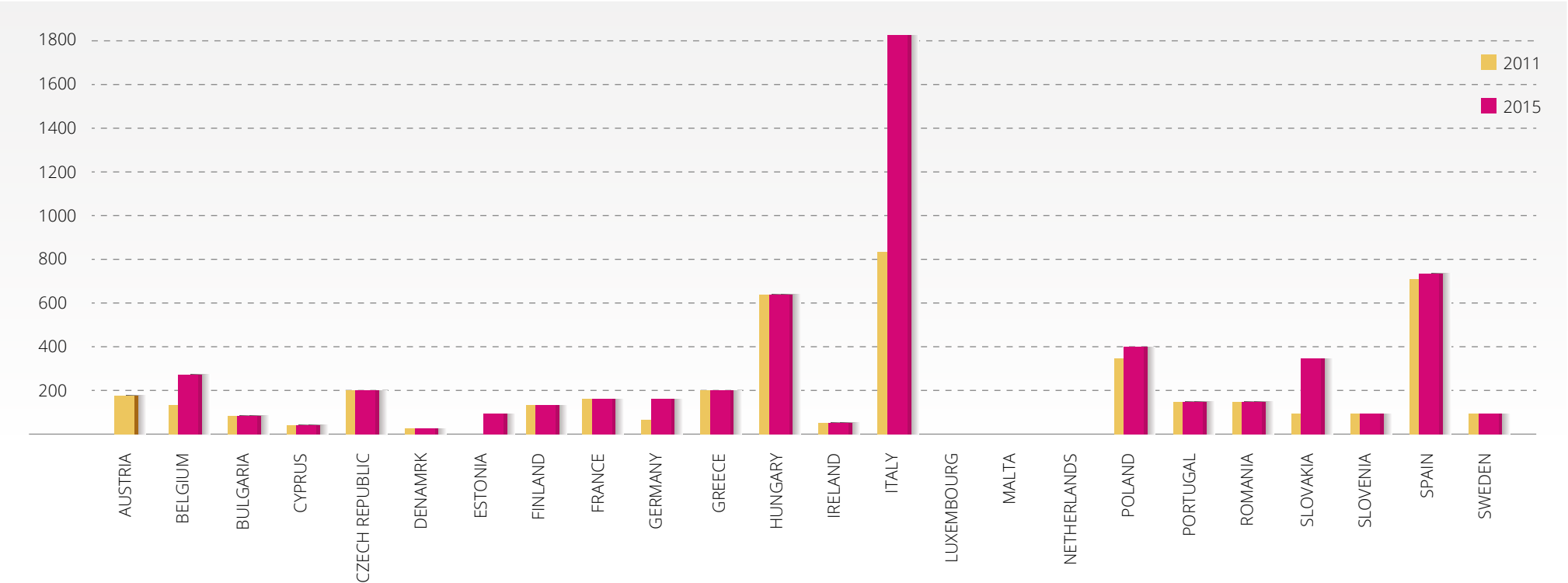


For Type IB variations

The evidence gathered and presented in Figure 7 suggest that fees charged by EU MSs for Type IB variations have increased in a number of countries over the last 4 years: BE, CZ, EE, IT, PL, ES and SK.

Decrease in fees were also recorded in AT, DE, and DK.

Figure 8 - Fee Comparison - Type II variations (2011 vs 2015)



For Type II variations³

The evidence gathered and presented in Figure 8 suggests that fees charged by EU MSs for Type II have undergone the most significant changes over the last 4 years.

Increases were observed for BE, EE, DE, IT, PL, SK and ES, with IT being by far the largest rise (the applicable fee doubled).

Decrease in fees were also recorded in AT.

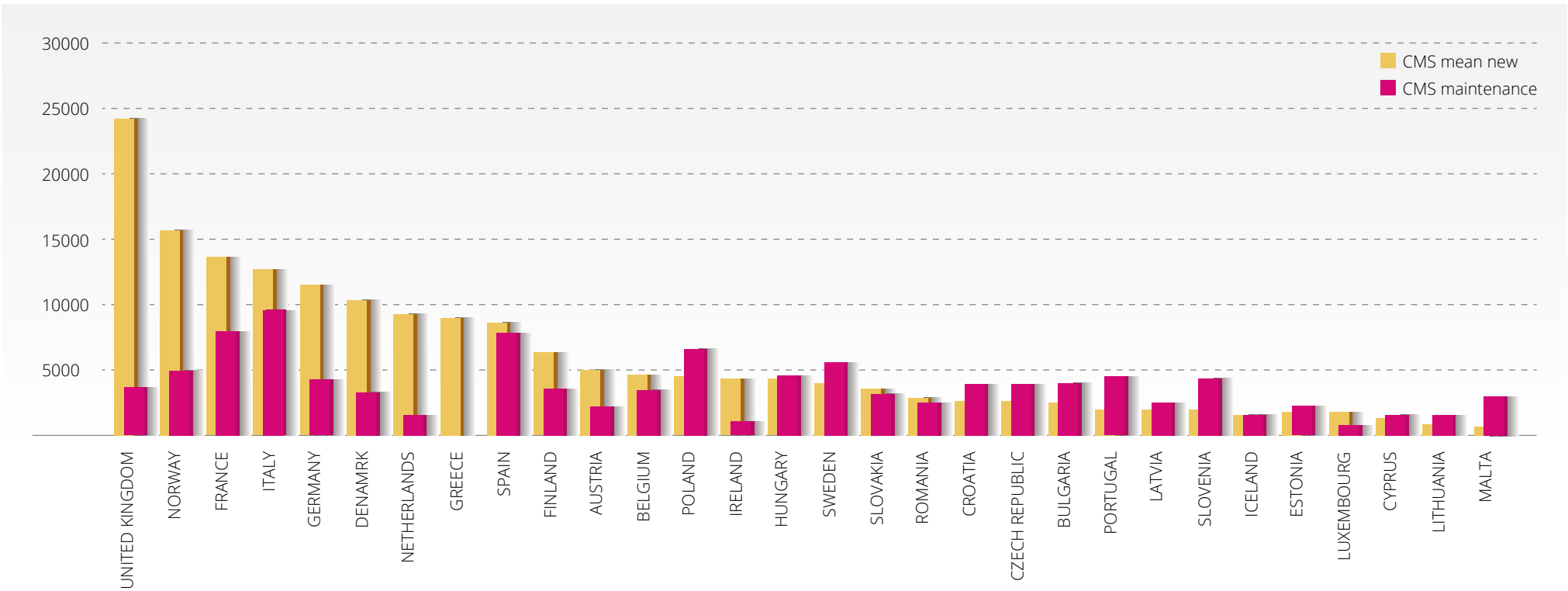
Conclusion:

Based on data gathered from most EU MSs it appears that while applicable variation fees for Type IA and IB variations have remained stable for most EU MSs, the biggest fee changes

in EU MSs concern Type II variations where in some countries (BE & IT) the fees (the highest of all variation types) have nearly doubled over a 4 year time period.

³ For Type II variations, where EU MSs apply a different range of fees depending on the nature or complexity of the variation, the lowest applicable fee was retained

Figure 9 - Comparison between Variation/Maintenance fees and initial application fees (CMS) in the various EU Member States



Issue Statement: Maintenance Fees outweigh initial marketing application fees in a large number of EU MSs.

Comparison between Variation/Maintenance fees and initial application fees (CMS) in the various EU Member States³

In order to assess the overall ‘maintenance’ fee, a comparison was done for each EU MS between a standardized theoretical maintenance fee⁴ and the new submission fee⁵ for the same theoretical scenario.

Explanatory note:

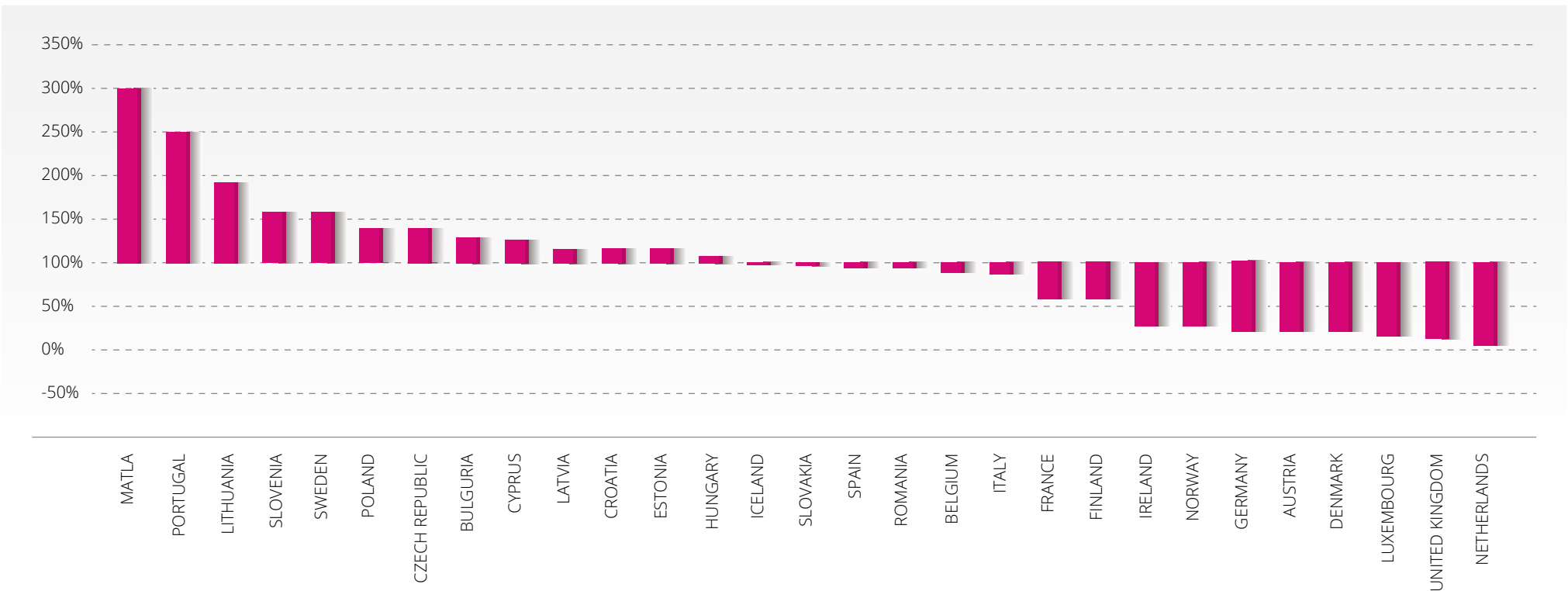
The new submission fee is the fee for a two strength CMS application divided by two.

The detailed results are presented in Figure 9 - Comparison between Variation/Maintenance fees and initial application fees (CMS) in the various EU Member States.

Figure 10 clearly illustrates the trend according to which 1 EU MS out of 2 does impose maintenance fees that exceed the applicable initial application fee.

³ Figures are those available in March 2015. There is no data included for maintenance in Greece.

Figure 10 – Overview of the Variation/Maintenance fees and initial application fees (CMS) ratio



Conclusion:

Initial marketing authorisation application fees are lower than the actual maintenance fee in 1 EU MS out of 2.

³ Figures are those available in March 2015. There is no data included for maintenance in Greece.

⁴ Theoretical maintenance fee is based on the various CMS fees as follows:

- 3 times the variations fees as applicable for the mean number of variations we perform per MA
- 1 time a renewal fee
- 3 times an annual fee All added up and divided by 3 to come to a virtual fee for maintenance per year

⁵ New submission fee is the fee for a two strength CMS application divided by two.

4.4 Overview of the evolution of the Variation Procedure Timelines

Issue Statement: National Competent Authorities (NCAs) have difficulties to cope with the variation timelines foreseen in the EU legislation

The revised variation regulation introduced variations Type IB ‘Tell & Do’ by default as major improvements, creating the opportunity to make the overall system more effective.

In practice, companies do note significant delays in the start of procedures as depicted in Table 1 - Example from one EGA member company with a significant number of MAs.

Table 1 - Example from one EGA member company with a significant number of MAs

Variations	Start within 15 days	Start beyond 15 days	Start within 30 days	1-6 months	Start beyond 6 months
Type IB	15%	85%	36%	46%	3%
Type II	21%	79%	55%	21%	3%

Conclusion:

Less than 1 out of 5 variations procedures for Type IB and Type II currently starts on time. This is illustrating that the promising concept of 30 days Type IB variations by default is not fully delivering.

While the majority of variation procedures for Type IB and Type II start within 30 days of the foreseen timeline, it is important to underline that around 3% can take over 6 months to start.

Issue Statement: The variations following EU referral do not follow the foreseen timelines.

EXAMPLE - Variation following safety referrals

EC Decision	06 AUG 2014 (published 09 SEPT 2014) Deadline for submission 09 OCT 2014	COMMENTS (N=5)
When was the variation submitted after the decision was issued? (in days)	Min: 27 days Max: 102 days	For some licenses (25), the variation could not be submitted because of an ongoing renewal
How many MAs were affected?	1210 MAs	
Which countries were involved?	All EU 28	MRP, DCP and National procedures
Approval date	Min 10 days* Max 118 days (~4 months)*	*for completed procedures A number of procedures are still pending (the PIL requires updating). Some still need to be submitted (after renewal closure)

Conclusion:

The variations triggered by EU referrals have been reported to have timelines that can exceed the foreseen time frame.

The set-up of Day 0 appears to be highly variable and unpredictable. The variation procedure closure can take up to several months which prevents a timely update of the safety information in the PIL.

Companies have referred to other examples (particularly where many products were affected) for which by information on the referral was not easily accessible and the foreseen submission plan (how and when) was unclear.

On-going variations or renewals appear as a barrier to the timely submission, review and approval of such variations

Part 2 – Detailed assessment of specific features of the EU variation system

4.5 HURDLE 1 | Concomitant variation and renewal applications are handled differently and unpredictably

Issue Statement: Variation procedures and approvals can be blocked due to upcoming and on-going renewal procedures

The guideline requirement through which variation procedures cannot proceed due to an ongoing renewal procedure for the same MA can lead to serious consequences, for example:

- Delay in the implementation of changes e.g. manufacturing process robustness or performance (cost-effectiveness) improvements
- Delay in the implementation of safety variations and safety related product information text changes (SmPC, PIL)
- Medicines stock-outs and impaired access to medicines for patients
- Delay in the remediation and mitigation of potential out-of-stock situations

Renewal procedures can extend over long periods of time which can substantially delay the possibility to engage in variation procedures.

Today, regulatory agencies can show flexibility in handling simultaneous renewal and variation procedures however, this is highly unpredictable and depends on the individual assessor involved and the possible room for negotiation with the applicant. This also creates an additional ‘acceptance’ step in getting the variation submitted.

Renewal procedural timelines remain long Table 2 - Evolution of the average start and approval timelines for 4 EU MSs acting as Reference Member States (RMS) – DE, DK, FI, NL between 2008 and 2014

(Example from one EGA member company with a significant number of MAs)

Period	Average time for the renewal procedure to start (days)	Average time for the renewal procedure approval (days)
2008	368	509
2012-2014	194	327

National competent authorities have significantly improved the management of renewal procedural timelines over the last years, especially regarding new renewal submissions.

Renewal application backlog - EGA Member companies data

While renewal procedural timelines have improved over time, the issue of renewal applications backlog from earlier renewal application submissions (particularly 2012, 2013) has not been resolved yet.

EGA Member companies data on the consequences of delayed variations

SAFETY CASE STUDY 1 - Delays in implementation of safety variations

Variation scope	Safety variations and addition of a new manufacturing site could not be submitted as the product/procedure
MA Procedure Type	RMS: IT
ISSUE	A renewal procedure was ongoing
Conclusion	Variations were not accepted (due to the ongoing renewal) and the proposed changes were postponed

SAFETY CASE STUDY 2 - Delays in implementation of safety variations

Variation scope	Safety variations
ISSUE	An ongoing renewal was preventing the submission of a number of safety variations.
Conclusion	This situation led to the medicines market release to be put on hold as safety updates were deemed significant

Conclusion:

The impossibility of filing variations while renewal procedures are ongoing coupled with the long timelines for renewal procedures to be completed lead, in practice, to unacceptable delays for safety variations to be approved and implemented as well as to delayed patient access to generic medicines in certain markets.

4.6 HURDLE 2 | Grouped Variations

Issue Statement: the benefit of grouped variations are limited both in terms of administrative burden relief and cost reduction.

The introduction of the ‘grouped variations’ approach in the last variation regulation revision was welcome and anticipated to create a new dynamic in the overall variation system.

In practice, the system does not appear to have been drastically simplified.

Whereas in the past, one Type II variation (combining multiple minor changes) could be filed, applicants are now required to submit distinct variations within a ‘grouped’ variation application.

There is no reduction in the administrative workload (each variation requires its own detailed classification section in the application form). Some companies report an additional workload associated with the need for each company to request regulatory authority confirmation that the proposed grouping is acceptable.

In addition, the fee structure applicable to grouped variations appears inadequate in most EU MSs where it is only slightly different to those applicable for independent parallel variation applications.

The new variation regulation and the variation classification guidelines have led to a reduction in the number of Type II variations and to an increase in the number of Type IA and Type IB variations which are often submitted as grouped variations. The fee structure for grouped variations is a possible explanation of the observed increase in the variation fees paid per MA/year. The current fee structure is more expensive than before when in many cases consequential changes were free of charge.

GROUPED VARIATIONS FEES | CASE STUDY 1 (theoretical)

DCP with RMS + 16 CMS 4 strengths	Type IA	Type B	Type II
Cost of single variation	17 811€	31 875€	61 542€
Cost of 2 parallel variations	35 622€	63 750€	
Cost of 2 grouped variations	35 662€	64 234€	
Difference between parallel and grouped submissions	+40€ (i.e. +0.1%)	+484€ (i.e. +0.7%)	

GROUPED VARIATIONS FEES | CASE STUDY 2
- Optimisation of the manufacturing procedure for the finished product

DCP with RMS + 14 CMS	4 strengths
	Associated fees
Before 2010 – Single Type II	48 659€
Today: 2 x Type II 4 Type IA 5 Type IB (consequential changes)	241 029€
Difference between 2010 and 2015	The associated fees for the same change were multiplied by nearly 5

GROUPED VARIATIONS FEES | CASE STUDY 3
– Addition of a manufacturing site

DCP with RMS + 18 CMSS	3 strengths (11 CMSS) 2 strengths (7 CMSSs)
	Associated fees
Before 2010 – Single Type II	51 763€
Today: 1 x Type II Several Type IA Several Type IB (consequential changes)	249 402€
Difference between 2010 and 2015	The associated fees for the same change were multiplied by nearly 5

Conclusion:

While the concept of grouping continues to appear attractive, the practical benefits of grouping remain limited.

Applicants face new hurdles, e.g. the need to request confirmation that the planned grouping of variations is allowed. Interpretation of the Annex to the variation regulation⁶ in terms of allowed grouping is rather strict and changes which are not related cannot be grouped.

In some instances where the older regulation allowed multiple changes to be filed as one Type II variation, the new regulation and its grouping concept lead to multiple variations being submitted for the same change.

Inconsistencies are also noted when it comes to active substance or finished product optimisation.

⁶ Commission Regulation (EU) No 712/2012 of 3 August 2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.

4.7 HURDLE 3 |
Missed opportunities

Issue Statement: Some common scenarios were not taken into account in defining variation categories.

- Company specific changes - Pharmacovigilance System

New variations have been introduced in the variation classification guideline, such as the introduction of the Summary of Pharmacovigilance System (PSMF) per MA.

The PSMF is specific to one company and applies to the entire MA portfolio.

Currently, the introduction of the PSMF for one company leads to hundreds of Type IAIN variation applications and the correlated fees, whereas the very same documentation is at stake, i.e. no assessment is involved.

While some EU MSs have put in place pragmatic ways forward and helped decrease the initially forecasted budget, the situation varies for each EU MSs and company administrative burden and applicable fees remain high (up to 1 mio€ for that sole change).

Introducing the PSMF – CASE STUDY

Variation Type	Grouped Type IA (for each RMS)
Variation scope	Introduction of the Pharmacovigilance System Master File (PSMF)
MA Procedure Type	All company procedures
Product specificities	N/A
ISSUE	The Directive concerning Pharmacovigilance System Master File (PSMF) contains a transitional period for the introduction that shall end in July 2015. Since July 2012 (21 July) it has been mandatory to implement PSMF with all new authorization (MA) applications and to submit with renewal applications. For all remaining licenses older then July 2012 for company x where the PSMF cannot be introduced via renewal application, it has to be filed via variation per MA (type IA).
Fees associated	Total estimated cost for all the groups and MAs included is approx. 615.000€ Total number of MAs (counted per strength) is approx. 2750.

Some EU MSs have accepted one single variation for an entire company portfolio of MAs in that country; some accept grouping of variations; some apply reduced fees.

An additional scenario that was not foreseen by the legislator and regulator is where regulatory procedures are mixed (i.e. different MAHs hold the MA in different countries of one procedure). For mixed procedures, all different PSMFs have to be submitted whereas they are only relevant for the MAH in the concerned country(ies).

The perspective that maintenance of the PSMFs will be done by means of the so-called ‘article 57 – database’ (announced to be operational in the second half of 2015) is a relief for companies and a recognition that for such company specific changes, effective solutions need to be found outside the variations regulation and system.

CEP/TSE/European Pharmacopoeia Monographs

Variations which solely consist of administrative updates of the CEP, TSE certificate or to update the API documentation following an EP Monograph revision appear of limited added value given that for CEP/TSE the EDQM has already approved the change and the MAH has assessed the potential impact on the concerned medicinal product.

In addition, the same CEP is typically used by several MAHs and sometimes in a large number of MAs. This implies that besides being already assessed and approved by EDQM, the same information package is submitted and assessed multiple times by EU regulatory agencies.

Duplication of variations procedure for the same changes to the same documentation - CASE STUDY

Variation Type	Type IA
Variation scope	CEP update
MA Procedure Type	MRP, DCP, National
Product specificities	32 MAHs hold MAs based on the same dossier 2 pharmaceutical forms 1) 4 strengths 2) 6 strengths
Issue	exact same change is submitted a large number of times
Fees associated	Total estimated cost for all 32 MAHs (2 pharmaceutical forms and 4+6 strengths) will be approx. 161,000€

Change of CEP holders address – Case study

Further to the creation of the new Indian state of Telangana on 2 June 2014, many of the addresses mentioned on CEPs and in CEP applications which are currently listed as being in Andhra Pradesh are now in this new state of Telangana. This has an impact for existing CEPs and applications for CEPs (new and revision).

For already granted CEPs and where there is no on-going revision, the EDQM invited⁷ CEP holders to submit notifications in compliance with the current EDQM procedures for all affected CEPs by 31 August 2015. These has lead to CEP updates, and consequently to MA updates by means of variations.

As in the previous case study, these variations will be submitted by each and every customer of the API producers (CEP holders) located in the region affected by this administrative change, triggering a wave of variations where no change occurred, and no assessment is required. Next to the amount of resources to submit this change as variations, the amount of fees to be paid for this change was very large.

Country specific changes submitted for all RMS/ CMSs involved in the procedure

In the current framework, there remains a number of variations which, while affecting only one particular and specific country in a MRP or DCP, have to be submitted to all involved RMS/CMSs.

Examples below illustrate this common situation.

Changes affecting one CMS – submitted to all RMS/CMSs - CASE STUDY 1

Variation Type	Grouped Variation (type IAIN & type IB)
Variation scope	• Cyprus focused change • Change the name of finished product in Cyprus • Introduce the summary of PSMF of the MAH in Cyprus
MA Procedure Type	DCP (2013) RMS: PT CMSs (7): CY, DE, DK, IE, MT, NL and PL
Product specificities	1 pharmaceutical form, 1 strength
ISSUE	This change was actually affecting only CMS-CY but was submitted to the RMS and all CMS
Fees associated	Total: 4.921€ Detail: CY: 170€ DE: 730€ DK: 348€ IE: 174€ PL: 1903€ PT: 1596€ MT, NL: no fee
Conclusion	The amount of fees paid in CMS-CY (170 €), which was the only Member state concerned by these changes, was only 3.5% of the total amount paid (4.921 €).

Changes affecting one CMS – submitted to all RMS/CMSs - CASE STUDY 2

Variation Type	Variation Type IA
Variation scope	Change in the name of the HU MAH name
MA Procedure Type	MRP RMS / CMS (7): CZ, EE,HU, IS, LT, MT, PL, SI
Product specificities	3 strengths
ISSUE	Client x in HU within MRP needs to notify the Authorities that its company legal entity status changed from public limited company to private limited company. Due to the change of the company legal entity status the name in HU language is only affected, not the English version of the company name as presented in the common English version of the PI text, the only affected document is the local PI text in HU. The HU authorities requested this to be filed via the MRP procedure
Fees associated	Total: 4.312€ Detail: CZ: 145€ EE: 116€ HU: 1768€ IS: 112€ LT: 66€ MT: 0 PL: 1855€ SI: 250€
Conclusion	The amount of fees paid in CMS-HU (1768€), which was the only Member state concerned by this change, was only 41% of the total amount paid (4312€).

⁷ <https://www.edqm.eu/en/New-Indian-state-of-Telangana-impact-on-CEPs-1585.html?mbID=278>

The transfer of the MA to a new MAH is handled as an independent purely national application. For consistency, we consider that the change in the name and/or address of the MAH should also be processed as a purely national level.

Change in the name of the finished product usually applies to one country in MRP/DCP procedure. For this reason the variation to change name of the finished product should be processed only as a national variation.

Conclusion:

Recurring scenarios have been identified where changes affecting a single EU MS (within an MRP or DCP) have to be submitted to all involved EU MSs. This leads to recurring inefficiencies in the current system.

This issue can be more acute depending on the EU MSs involved.

Reporting within 12-months

EGA member companies have reported that they do not use the possibility to report changes within 12 months and rather submit variations Type IA as they come.

One main reason for this underuse by companies is the necessary complex underlying management system needed to keep track of those variations not submitted immediately.

Another reason for underuse is that some member states still officially approve these type of variations. Companies operating in these countries have to await the formal NCA approval before the product can actually be brought to the market.

Conclusion:

The possibility offered by the regulation to report variations type IA within 12 months has not delivered so far.

It should be evaluated what implementation adjustments would be needed to make this concept more attractive in practice

4.8 HURDLE 4 | API related variations

Issue Statement: There are increasingly more variations filed by MAH which concern solely API information.

Based on EGA member companies’ feedback, it appears that up to 60% of variations (related to quality⁸) submitted by Marketing Authorisation Holders (MAHs) are related to changes to the API.

The data gathered show a general correlation in proportion between the number of variations and the related fees (APIs related variations are not more expensive than others).

The number of variations is higher if the ASMF is under subsequent registration procedures e.g. within the company itself or due to other customers of the ASMF holder undertaking new submissions (themselves triggering harmonisation, updates and new versions of the ASMF). Companies using captive API will generally have less variations than those using outsourced APIs.

In addition, one API can enter several finished products (combinations).

In these cases the ASMF for API is again under evaluation and for existing MAs the harmonisation is done via variations.

EGA observed on a sample of procedures (<15) that where CEPs are used, the overall number of variations is lower than with ASMFs. This is logical considering that in some cases the variation to the CEP dossier does not influence the CEP version,

⁸ Variations related to quality changes represent in average 50% of all variations submitted

therefore there is no variation to be submitted to the MA.

Table 3 – Correlation between the API-related variation number and the API-related variation fees compared to the total number of variations and variation fees for the concerned procedure

Marketing Authorisation Procedure Involving a CEP	Marketing Authorisation Procedure involving an ASMF
13% variations	17% variations
14% fees	23% fees

Illustrative examples (limited number - <15 - of procedures involved)

Conclusion:

Marketing Authorisation Holders are dedicating a large amount of their resources to the API life-cycle management (submission of API related variations).

For outsourced APIs, nearly 2 out of 3 quality variations relate to the API.

In addition, given the high level of API outsourcing in the generic medicines industry, most of these changes will be filed multiple times through each and every ‘user’ of the concerned API.

More API GMP related information in the regulatory dossier

Issue Statement: trend by quality assessors to request more and more API supply chain data in the dossier has the potential to triple the number of variations per MA per year at first and then to lead to an increased number of variations due to maintenance of the newly introduced regulatory dossier information.

While the outsourcing trend within the API manufacturing industry was already a fact in the period 2004-2013, Marketing Authorisation (MA) dossiers submitted did not generally include

information on API supply chain operators involved before the final API manufacturer (particularly not testing sites, in-process testing sites or intermediate manufacturers). These were, and still are managed and controlled through GMP/GDP audit and API manufacturers’ quality systems qualification. It should be noted that this is in line with Article 46 of Directive 2001/83 which clearly states that Manufacturing Authorisation Holders have the responsibility to only use API that has been manufactured in accordance with GMP.

Since 2013, several regulatory guidance documents or forms have undergone changes with regards to the description of what is meant by API manufacturing, bringing consistency to the already existing definitions in the pharmaceutical legislation and the EU GMP Guide Part II, and clarifying regulatory expectation for the information to be put in the dossier.

The release of the CMDh Q&A in 2014 led to concerns for the industry as, it was implying that the current practice could lead to having some sites deemed “unauthorised” under the new regulatory dossier expectations for the term “API manufacturing”.

Another concern is that alignment of EU guidelines is not fully achieved yet, leading to even further interpretation challenges.

Finally, transparency towards interested parties has not been optimal for most of the changes operated in the various documents concerned (e.g. changes done after the initial publication without being re-published highlighting the change, changes not covered in the section ‘changes to the previous version’).

Information gathered from the EGA membership indicates that the situation may vary greatly between captive (vertically integrated) API manufacturing and outsourced API manufacturing.

In case of vertically integrated API, fewer variations are expected with regard to the API supply chain – the control of the API is done at the same site as manufacturing, so information flows are straightforward.

For the ASMFs of partners (so-called ‘outsourced APIs’), often used by multiple customers, the number of sites used by the API and intermediate manufacturers for analytical purposes, is not part of the dossier. The ability of the API manufacturer to qualify its intermediate suppliers and its external analytical laboratories has however been assessed

as part of the API manufacturing site GMP audit programme.

It is also unclear whether the user should list his own manufacturing site as testing site as it is de facto an important quality control site before the API is used in finished product manufacturing. This final testing by the API user appears of much greater relevance to the overall product quality than that of in-process controls (IPCs).

In general, it is understood that intermediate manufacturers do not use multiple contracted laboratories for IPC or control testing. However, the stability testing site and distribution chain operators are not part of the application form (according to the interpretation of Q&A).

In addition, when looking at the parallel situation for finished products, it appears that stability testing sites and distribution channels are not part of the application form whereas well controlled by GMP/ GDP.

Consequently, sites other than those of the API manufacturing and the last intermediate manufacturing, where necessary (e.g. testing site, stability site, brokering site, starting materials site) should be left out as there is no justification why such information should be available for the API than for the finished product.

Today the majority of variations are submitted for deletion/replacement of API supplier(s) due to e.g. GMP changes.

The industry estimates that to fulfil the new regulatory interpretation given to API manufacturing sites description corresponds to a 2-3 fold increase of the total annual number of variations submitted for each medicinal product. This may lead to capacity problems for both Industry and NCAs and subsequent issues to handle this increased amount of variations within the correct timelines and potentially impact the handling of other important safety or quality variations.

The overall public health benefit of the endeavour is unclear and this shift seems contradictory to several EU policies: 1) to have an effective and fit regulatory system, 2) to foster supply chain resilience (prevent temporary supply disruptions) and 3) to value the quality systems approach (ICH Q9 & Q10) by companies.

Examples illustrating the increased presence of API GMP-related information into the regulatory dossier

Example 1: INN A Filmcoated tablets API manufacture is outsourced	Current file	Based on 2013 new interpretation and expectations
	API Source 1 for INN A	API Source 1 for INN A
	Manufacturer of the INN A	Manufacturer of the INN A
		NEW Intermediate A
		NEW Intermediate B
		NEW Stability Testing Site
	1 site	4 sites (i.e. +3 NEW sites)
	API Source 2 for INN A	API Source 2 for INN A
	Manufacturer of the INN A	Manufacturer of the INN A
		NEW IPC testing site
		NEW Release testing site
	1 site	4 sites (i.e. +3 NEW sites)
TOTAL for example 1	2 sites	8 sites (i.e. +6 NEW sites)

Example 2: INN D API manufacture is Captive	Current file	Based on 2013 new interpretation and expectations
	API Source 1 for INN D	API Source 1 for INN D
	INN D manufacturer	INN D manufacturer
	Intermediate A	Intermediate A
	Intermediate B	Intermediate B
		NEW control testing site for intermediate A
		NEW control testing site for intermediate B
TOTAL for example 2	3 sites	5 sites (i.e. +2 NEW sites)

Example 3: INN B/INN C Filmcoated tablets API manufacture is outsourced	API Source 1 for INN B	API Source 1 for INN B
	Manufacturer of the INN B	Manufacturer of the INN B
		NEW Intermediate X
		NEW Intermediate Y
		NEW Stability Testing Site
	1 site	4 sites (i.e. +3 NEW sites)
	API Source 2 for INN B	API Source 2 for INN B

Example 3: INN B/INN C Filmcoated tablets API manufacture is outsourced	API Source 1 for INN B	API Source 1 for INN B
	Manufacturer of the INN B	Manufacturer of the INN B
		NEW Intermediate X
		NEW Intermediate Z
		NEW Intermediate L
		NEW Quality Control
	1 site	4 sites (i.e. +3 NEW sites)
	API Source 1 for INN C	API Source 1 for INN C
	Manufacturer of the INN C	Manufacturer of the INN C
		NEW Intermediate N
		NEW Intermediate M
		NEW Stability Testing Site
	1 site	4 sites (i.e. +3 NEW sites)
	API Source 2 for INN C	API Source 2 for INN C
	Manufacturer of the INN C	Manufacturer of the INN C
		Additional Manufacturing Site
		NEW Intermediate O
		NEW Intermediate P
		NEW Quality Control
	1 site	4 sites (i.e. +3 NEW sites)
TOTAL for example 3	4 sites	16 sites (i.e. +12 NEW sites)

Conclusion:

New regulatory interpretation regarding the inclusion of API supply chain information is anticipated to potentially lead to an increase in the number of variations submitted within a range of about 50% (best case scenario e.g. single source, captive API) to 300% the current number of variations (worst case scenario, e.g. multiple API sources, outsourced API) to introduce the necessary information into the regulatory dossier. An indirect effect is to be expected through the consequential life-cycle management (variations) to be considered for these new sites.



Part 3 – Variation Fee Structure and concept of "Annual Fee" for variations

The current system of financing variations does not create any incentives for the National Competent Authorities (NCA) to implement improved cost-effective mechanisms to deal with changes to Marketing Authorisations. There is no real incentive for NCAs (National Competent Authorities) to consider a reduction of unnecessary administrative steps (e.g. to optimise processes and avoid duplicative applications) as long as they are paid by number of variations processed.

Only a few authorities have introduced "flat fees"/ annual fees to reduce the administrative burden.

The preferable model is the Dutch model with reasonable, well balanced annual fees covering all variations. The Austrian model (with differentiation between Austria being the RMS/CMS) can be also considered.

Both Authorities (MEB and AGES) clearly express the real improvement of efficiency in dealing with variations, without entering into financial difficulties. Although both Agencies are self-financing, the model of flat fees should be also applicable to those systems where national medicines agencies are financed/ co-financed by the government.

The objective of this proposal is to stimulate better efficiency in handling variations without undermining financial stability of the NCAs and their high level expertise in assessing the changes to the MAs. The amount of flat fee in each country can be established based on retrospective data over the last 3 years (e.g. total income from variations' processes per year divided by the number of MAs).

The advantages of flat fees for both Authorities and industry are:

- High predictability of the income/ budget planning for both Authorities and industry
- Significant reduction of administrative burden (staff involved in invoicing, calculation of the right amount, correction of eventual mistakes in calculation etc.)
- Less discussion on the classification of variations
- Disconnection of the agency income from the number of variations processed

Examples of existing fee systems¹⁰

Table 4 - Overview of Various Fee Structures in different EU Member States

	UK	AT	NL	SE	LU	IE	NO	DK	Fi
Fees Type IA	No	No	No	No	€50	No (€100 per MA for Type IA – C.l.3a variations only)	No	Complicated fees Type IA and type IB (CMS) 1,327.00 DKK (€177) First strength 449.00 DKK Each subsequent strength Administrative fee type IA and type IB (CMS) 827.00 DKK First strength 449.00 DKK Each subsequent strength Type IA and type IB (RMS) 2,076.00 DKK (€277) First strength 449.00 DKK Each subsequent strengths	0 EUR if CMS 500 EUR if RMS
Fees Type IB	IB (RMS) £611 First strength £305.50 Subsequent strengths IB (CMS) £308 First strength Minor Type IB Group (RMS) £1,361.00 First strength £680.50 Subsequent strengths Minor Type IB Group (CMS) £691.00 First strength £345.50 Subsequent strengths	No	No	No	€50	IB (CMS) 338.00 EUR Fee if one or two strengths are affected 174.00 EUR Fee if three or more strengths are affected IB (RMS) 345.00 EUR RMS supplement 468.00 EUR Fee if one or two strengths are affected 234.00 EUR Fee if three or more strengths are affected		Complicated fees Type IA and type IB (CMS) 1,327.00 DKK (€177) First strength 449.00 DKK Each subsequent strength Administrative fee type IA and type IB (CMS) 827.00 DKK First strength 449.00 DKK Each subsequent strength Type IA and type IB (RMS) 2,076.00 DKK (€277) First strength 449.00 DKK Each subsequent strengths	400 EUR if CMS 1400 EUR if RMS One fee for all strengths

¹⁰ The overview is simplified and does not go into details in case of more complex calculation (e.g. additional strength)

	UK	AT	NL	SE	LU	IE	NO	DK	Fi
Fees	II (CMS)					II (CMS) Standard		Complicated fees	800 EUR if CMS
Type II	£816.00 First strengths	No	No	20 000 SEK (2150 EUR) if RMS	€150	338.00 EUR Fee if one or two strengths are affected		Type II, standard (CMS)	2800 EUR if RMS One
	£408.00 Subsequent strengths			6 000 SEK (650 EUR) if CMS		174.00 EUR Fee if three or more strengths are affected		1,795.00 DKK (€239) First strength	fee for all strengths
	II (CMS) Complex					II (CMS) Complex		449.00 DKK Each subsequent strength	
	£9,232.00 First strength					1,797.00 EUR Full fee per pharmaceutical strength		Type II, complex (CMS)	
	£816.00 Subsequent strengths					II (RMS) Standard		1,795.00 DKK (€239) First strength	
	II (CMS) Extended Complex					338.00 EUR RMS supplement		449.00 DKK Each subsequent strength	
	£28,492.00 First strength					506.00 EUR Fee if one or two strengths are affected		Type II, standard	
	£816.00 Subsequent strengths					253.00 EUR Fee if three or more strengths are affected		8,300.00 DKK (€1107) First strength	
	II (RMS)					II (RMS) Complex		449.00 DKK Each subsequent strength	
	£989.00 First strength					525.00 EUR RMS supplement		Type II, complex	
	£494.50 Subsequent strengths					2,601.00 EUR Full fee per pharmaceutical strength		13,855.00 DKK (€1847) First strength	
	II (RMS) Complex							449.00 DKK Each subsequent strength)	
	£16,007.00 First strength								
	£989.00 Subsequent strengths								
	II (RMS) Extended Complex								
	£39,829.00 First strength								
	£989.00 Subsequent strengths								
Annual fees	Derivatives with a different route of administration or complex abridged	2900 EUR (if RMS)	1200 EUR	5000 EUR	No	€650 for first 10 MAs per MAH	Annual fee based on medicinal products' net turnover	1250 EUR	1350 EUR
	£10,221	1500 EUR (if CMS)				€812 per MA thereafter (€420 for dormant MAs)			
	Standard fee (depending on sales)								
	£2,556								
	Reduced fee (depending on sales)								
	£1,275								
	'Maintenance' fee (if not marketed)								
	£323								

EGA recommendations to improve the EU Variation Procedure

Maintenance fees exceed initial submission fees

4.1

The variation fee structure should be reshaped so that maintenance fees, in the first renewal period after MA grant, are lower than initial submission fees.

Variation Fee structure

4.2

Regulatory agency fee income should be disconnected from the number of variations processed, to stimulate proactive optimisation of the variations process .

4.3

Introduce a single annual maintenance fee, covering all types of variations

Variation timelines

4.4

Type IB variations should be given more priority so that timelines are met, including a predictable Day 0.

Safety referral variations

4.5

Safety referral outcomes should be more easily accessible with clear instructions for submitting the necessary variations.

4.6

Safety referral variations should be prioritised in order to enable timely update of patient information.

Concomitant variation & renewal applications

4.7

The procedural guideline should clearly allow the concomitant submission of renewal and variation applications.

Grouped variations

4.8

The fee structure for variations should be thoroughly revised so that fees for grouped variations are always less than fees for a Type II variation

4.9

Finished product optimisation should, like API optimisation, be eligible as Type II variations.

Company-wide changes

4.10

For a number of changes, particularly when company-wide, a mechanism should be found to maintain regulatory compliance whilst reducing administrative burden , together with a reduced fee structure.

CEP/TSE certificate updates

4.11

For administrative changes to CEPs/ TSEs certificates a simplified regulatory pathway should be implemented. ,

Single country changes

4.12

For country specific changes within DCP or MRP, the guidance should be simplified

so that the change is only submitted where it applies. Non impacted member states would be notified through an update in the “Article 57”-database. Fees would only be payable in the countries where the change takes place.

Reporting within 12 months

4.13

The European Commission and member states should evaluate the up to “12 months” reporting provision and identify the underlying causes for underuse.

4.14

Consideration should be given to the possibility to report within 12 months as a notification.

API related variations

4.15

The ASMF work-sharing pilot should be further strengthened.

4.16

Long term consideration should be given to legislative change whereby the API regulatory documentation would be managed independently from the medicinal product regulatory dossier.

4.17

A direct role should be developed for API manufacturers in regulatory procedures based on the model of the current European Pharmacopoeia CEP procedure.

Excessive API GMP and supply chain information in the regulatory dossier

4.18

To balance transparency in the API supply chain and supply chain resilience, there should not be more additions of API GMP or supply chain elements into the regulatory dossier.

4.19

The regulatory dossier API information should be limited to the final API manufacturer(s) and the final intermediate manufacturer(s). All other involved sites should be appropriately managed through manufacturers’ quality systems and regulators’ supervision as part of GMP inspections, both API and Finished Product (FP).

4.20

Transparency of the API supply chain should build on initiatives such as IDMP database.



Chapter 5 – Lifecycle Maintenance – Renewals

Although still legally part of the regulatory framework the role of Renewal has become redundant in recent years as focus has moved to continuous oversight. Today Renewal is more of an encumbrance to other activities and it is difficult to identify what value it adds.

EGA recommendations to improve the EU Variation Procedure

Simplify Renewal

5.1 Simplify the Renewal procedure for well known active substances with established safety profiles to become an automated administrative step only, without blocking other regulatory activities.



Chapter 6 – Lifecycle Maintenance – Pharmacovigilance

Nearly three years after the new EU Pharmacovigilance legislation became operational it is not clear if this major overhaul of the regulatory framework is delivering better protection of public health. The intended simplification and removal of duplication in community pharmacovigilance procedures with consequent efficiency gains for both pharmaceutical industry and medicines regulators is not visible. Numerous changes have been introduced, the biggest being moving from reactive vigilance to proactive investigation of potential safety issues in order to fill in knowledge gaps. In addition to better protection of public health, the major goals of the new legislation were simplification and reduction of duplicative activities.

6.1 Positive observations and 3-years experience

The legislation foresees various information systems to enhance pharmacovigilance related activities and some major deliverables are scheduled from 2015.

On-going dialogue on implementation

Closer cooperation between all stakeholders (National and European authorities plus industry) is taking place to make the “legislation work”. Increased cooperation is shown by the use of pilot processes, transparency and better communication

on experience gained and possible improvement.

Introduction of **quarterly Industry Stakeholder Platform meetings** is a step in the right direction to establish a strong communication channel between industry and regulators to openly discuss practical implementation options.

Move from routine to risk-based pharmacovigilance

The move from routine PSUR (Periodic Safety Update Report) submission to a risk based approach and to focus more frequent monitoring on those active substances which are associated with a higher risk is recognised as a positive step in optimisation of the pharmacovigilance activities. Successful establishment of the EU reference date (EURD) list, harmonised frequency of PSUR submissions and single assessment for all medicinal products containing the same active substance/ combination has been achieved. The next step which is welcomed is PSUR repository, a tool for simplified PSUR submissions.

For multisource generic medicines, it is of a great importance to assure an efficient way of dealing with pharmacovigilance activities without duplicating the assessment, avoiding multiplication of signals and assuring the consistency in assessment of medicinal products with the same active substance.

6.2 Room for further improvement

To build on progress already made, the EGA has identified some key areas of possible improvement:

Signal detection in the Eudravigilance database: When the Eudravigilance database is functional, every marketing authorisation holder (MAH) will be required to perform signal detection according to their level of access. This means that all MAH of the same active perform the same exercise in Eudravigilance as currently done by the EMA/ National Competent Authorities. This duplication was not intended by the legislation.

Single submission of PSUR per active substance: Generic medicines companies can hold multiple registration files for one active substance (or combination of active substances). In order to minimise the administrative burden on both the industry and competent authority side, a single submission of PSURs per active substance should be introduced. This requires the regulatory network to take out PSUR submissions from the lifecycle (eCTD) management.

Provision of simplified PBRER format for medicines with well known substances

A simplified PBRER format for medicines with well known substances, especially for products

authorised under Article other than 10(1), 10a, 14, 16a which are not exempted from the submission should be introduced . A simplified format would contribute to a risk-based approach to determine PSUR submission requirements.

Introduction of abbreviated Risk Management Plan (RMP) template with defined minimum data to be provided.

The new pharmacovigilance legislation introduced mandatory RMP for all new medicinal products, including generic medicines. The proposed universal RMP template does not take into the accounts the constraints on data available to the generic medicines industry, especially when the RMP for the reference product is not in place and/or if the safety concerns for the reference product are not available in public domain. An abbreviated Risk Management Plan (RMP) template with defined minimum data should be the norm for generic medicines.

Single assessment of RMPs

A single assessment of RMPs by adopting experience from PSUR work sharing to avoid further intra- and inter-agency assessment inconsistencies is recommended. Steps have already been taken by the EMA and CMDh to streamline the assessment process and ensure concise and focussed RMPs. The recent initiatives to establish a collaboration among interested parties to discuss practicalities concerning RMP through forums such as the ‘Working Party on Pharmacovigilance Procedures Work-Sharing’ is welcomed by industry.

Medical Literature Monitoring (MLM)

The EMA literature review service was seen as s promising step in reducing the multiplication of research for all companies possessing MAS with the same active substance.

This project shall bring a great benefit to regulators by avoiding duplication in assessment and signals coming in to the system. Due to being at the early stage of the implementation, experience is very limited. For generic companies only present in the EU, the EMA service will be partly beneficial although literature will still need to be reviewed for special situation reports and general safety issues which are not ICSRs. Workload may increase due to the manual downloading of ICSRs from the Eudravigilance database. Later benefit will come when ICSRs are automatically sent to the MAH on the basis of Article 57. For generic companies operating globally, benefits will be much lower since these companies will still need to provide the PSUR/ literature overview for non- EU markets.

Communications to patients and health care professionals

Increasing transparency and engagement of patients and healthcare professionals is needed, but with more emphasis on the benefits of medicines as well as the risks. All medicines can potentially cause unwanted effects and how this is communicated to patients and carers has to be tailored in an appropriate way. Starting in August 2014, EMA has published more than 80 RMP summaries with the aim of increased transparency

and public access to relevant information on medicines. Nevertheless, since they are not available in all EU languages and written with a focus on the risks their usefulness to patients in making informed decisions is limited.

Requests for the Post-Authorisation Safety Studies

The generic medicines industry faces increased complexity and costs, especially in terms of Post-Authorisation Safety Studies (PASS) and work-sharing models (e.g. consortiums). Several cases have been reported where a company choose to withdraw a product from the market rather than fund a PASS study. The EMA intention is to facilitate work sharing among all MAHs involved, but operational and legally-related difficulties remain an issue. The decision about triggering those studies needs to be well balanced between risk of public health and the unintended consequence of MAS being withdrawn.

Deliver the intended benefits from the 2012 Pharmacovigilance legislation

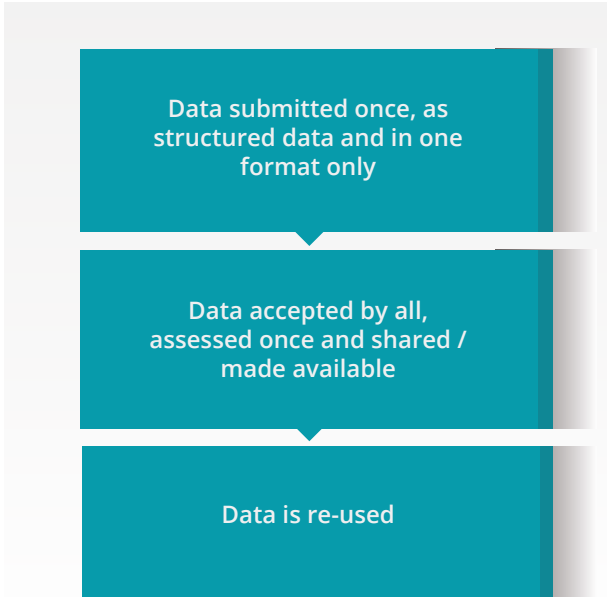
- 6.1** Stop duplication of signal detection in the Eudravigilance database.
- 6.2** Introduce the single submission of PSURS per AS
- 6.3** Simplify the PBRER format
- 6.4** Simplify the Risk Management Plan format for standard generic medicines and make just one EU assessment.
- 6.5** Streamline the content of Post Approval Safety Studies to avoid the unintended consequence of companies withdrawing from the market



Chapter 7 – Lifecycle Maintenance – Telematics

The effective use of IT systems can be a powerful enabling tool for regulatory efficiency across the European regulatory environment and participating stakeholders. In the last twenty years there has been an increase in the development of IT solutions to improve the EU regulatory environment. However in a number of cases, the solutions have been developed and implemented as a patchwork of IT solutions, not always being compatible with each other and more of a stand-alone solution. Some of these solutions were short lived and many appearing to only fulfil a specific legislative obligation, without taking a look at an improvement of the entire regulatory process.

7.1 EGA Vision
The EGA sees enormous opportunities in common information-technology services in order to add value and support the EU regulatory network. The ideal formula would be “capture once – use many”



With common data and information repeated data capture by different authorities and multiple reporting of the same or overlapping product data could be avoided. High-quality structured data gathered in one place is the objective.

7.2 Positive Observations
There are certain developments that have largely improved the efficiency of the network, e.g. implementation of the **Common European Submission Platform (CESP)**, which is demonstrating a precedent by providing a secure method of communicating with the Regulatory Agencies via one platform and allowing submission of an application once to reach all involved Agencies. The success of CESP could pave the way for national database systems to be scrapped or harmonised in the next few years. However, full implementation and close alignment between NCA’s is essential.

Another logical next step is that eCTD should mature from the current one way communication platform from applicant to regulator into a two way tool that functions equally in both directions .

Ongoing Dialogue

The generic medicines industry values cross stakeholder engagement: Industry platform meetings initiated by the EMA, as well as ad-hoc workshops between the industry and NCAs. Furthermore, regular working group meetings are essential for industry to positively contribute its knowledge and experience to process design & improvements.

7.3 Room for Improvement

On the other hand Industry is facing many projects for which the scope and implementation are challenging.

Article 57(2) database

This new telematics tool has come as part of the 2012 new pharmacovigilance legislation. Article 57(2) of Regulation (EC) No 726/2004 has required all marketing authorisations holders for medicinal products to submit exhaustive information to the European Medicines Agency (EMA) using an electronic format.

Three years after providing data to the so called “the Art 57 database” which engaged huge time and workload investment by all stakeholders involved, industry would like to see benefits from using this database to facilitate regulatory processes i.e. replacement of administrative variations with regular reference to data provided to this database.

Furthermore, in the process of the submission of data for Article 57, a major improvement could be achieved if the database would be part of the regulatory process (i.e. submitted by the MAH, validated, assessed and approved by the NCA´s and uploaded to the database). This would deliver a huge improvement over the current process and enable the set-up of an overview of all human medicinal products, which is valid, up-to-date and with data can be confidently reused for many purposes .

ISO IDMP standard implementation

Implementation of the ISO IDMP standards will be another challenge for industry. In view of the scope of data to be potentially provided to the EMA (significantly broader than in the scope of the Art 57), very deep reflection is needed on how to achieve it in a smart and efficient way. The process needs to be well defined and with a realistic timeframe for all involved partners (authorities, industry, vendors/ service providers). This points towards a stepwise approach as the practical solution.

EGA calls for very clear Road Map for ISO IDMP implementation, discussed and agreed with the industry as the provider of primary data. Establishing a EU Task Force with the role to provide recommendations and advice is a step in the right direction. All stakeholders need sufficient time for implementation, therefore a phased in approach is essential.

Industry’s role in Telematics governance

The European pharmaceutical industry acknowledges the positive evolution observed in the EU Telematics environment in recent years. The setting-up of the EU Telematics Governance in 2013 marked an important step in shaping the future of Telematics in the EEA. It will play a key role in promoting interoperability and cooperation between the EMA, European Commission and national Agencies IT systems. Through such strengthened collaboration, industry further expects decisions to be implemented in a more consistent and efficient way across agencies, while serving public health in a more transparent manner.

As the role of Industry is crucial in shaping the telematics environment, EGA looks forward to being given an official place in the governance model. This will enable co-operation at a strategic level (not only at the technical level of IT projects) to achieve interoperability of IT solutions between all partners.

7.4 Telematics’ Future

Given the complexity of the regulatory environment governing medicinal products within the EU and at international level, telematics tool shall be a very strongly support for simplification, efficiency and data sharing. Moreover, international data standardisation is essential to operate efficiently in a global environment. Master data technologies can break down system barriers but only

with appropriate harmonised data standards, compatible with each other.

Telematics tools as a support in electronic product information for medicines - e-leaflet

EGA fully recognises the importance of providing patients and health care professionals with accurate and up-to-date information on medicinal products. Such information must be easily accessible. Moreover, it needs to be adjustable to the need of the individual patient to provide the necessary level of detail for the most effective and safe use of the medicine.

Therefore, EGA sees necessity to start the process, together with other trade associations, of providing product information in more user-friendly structures and using modern technology tools.

In an era where the amount of electronic health information and applications are steadily growing, e-leaflet as a future option for disseminating health information is an interesting and promising avenue. In this context, a reliable, trusted source of authorised product information would be critical.

The concept needs to be further developed in greater detail but EGA sees this is a step in the right direction reflecting the evolution of society. This development might happen in a stepwise approach starting with countries with a higher IT literacy and better IT infrastructure. Some pilot projects would help to analyse the users’ reaction and to progress by designing out weaknesses.

Telematics and Information Management

- 7.1 Maximise the opportunity of the Article 57 database by using the single data collection to serve many purposes, including by connection to regulatory procedures
- 7.2 Utilise the Article 57 database for administrative and many Type 1A changes, instead of variations to maintain oversight but simplify procedures.
- 7.3 Build on the success of CESP to harmonise or make redundant national portals.
- 7.4 EGA should be a key partner in setting the road map for ISO IDMP implementation and for the long term EU regulatory telematics strategy
- 7.5 e-leaflet To explore e-leaflet as a future option for disseminating information on medicinal products to patients.



Conclusions

This report is the most detailed review of the European regulatory environment for generic medicines since 2010. The issues identified are many but in each case solutions are proposed. Some of these can be implemented quickly with little or no cost. Others will take longer to achieve, including legislative changes. Overall this report demonstrates that favourable interpretation of existing legislation can streamline regulatory systems at the same time as improving outcomes both in protecting public health and enabling more high quality generic medicines to be made available faster to patients, supported by a secure supply chain.

EGA calls for a deep analysis of the recommendations from this report as a contribution to strategic thinking for the further development and simplification of the EU regulatory environment.

The scope recommended for analysis and improvement covers research & development, new product approval procedures and lifecycle maintenance of generic medicines.

Raising efficiency and streamlining the regulatory processes will bring tangible benefits for all participants in the healthcare network of patients, governments, regulatory authorities and the generic medicines industry.



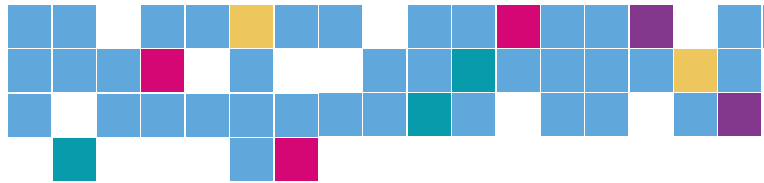
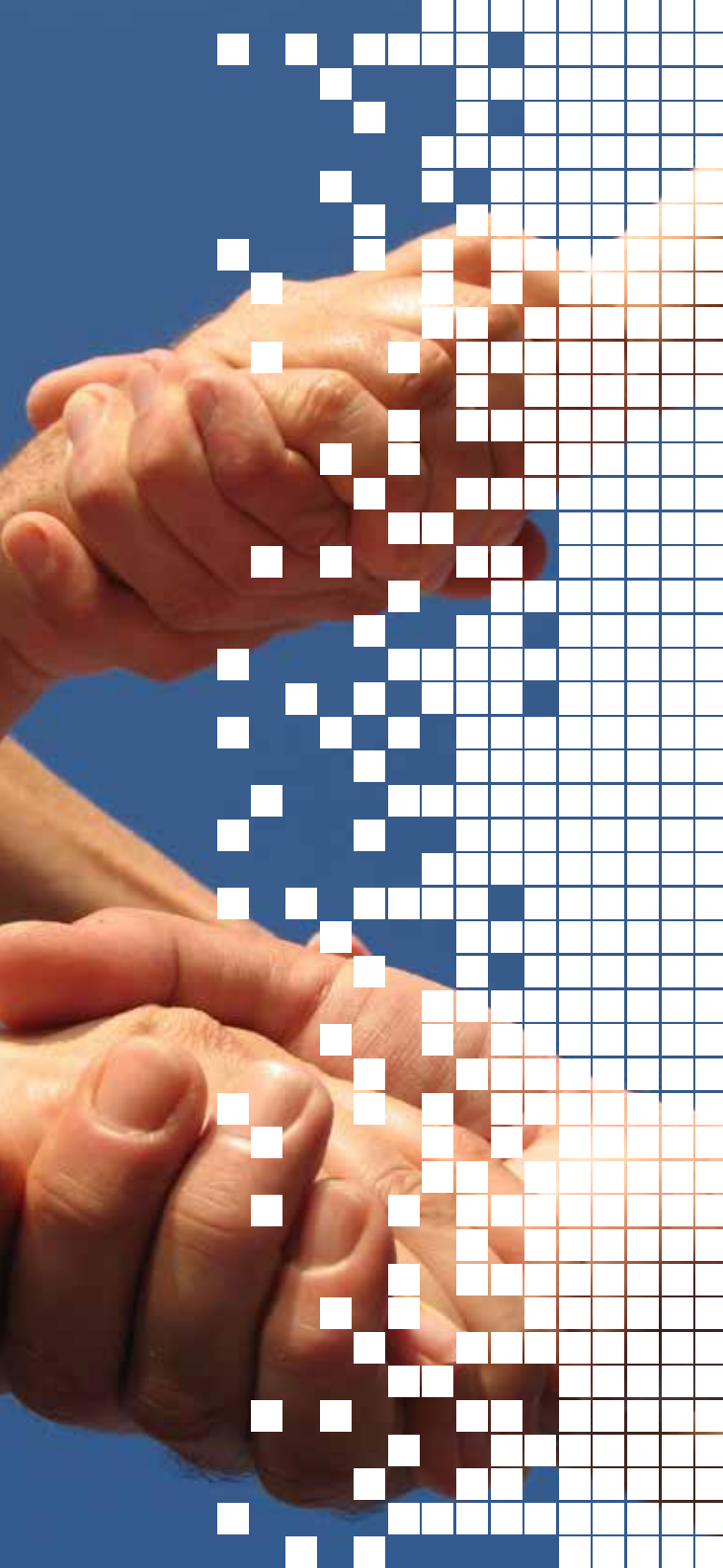
References

Vision 2015 The EGA's thoughts on how to improve the legal and regulatory framework for generic and biosimilar medicines (October 2010)

EU Guideline on the investigation of bioequivalence http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

CMDh best practice guides for DCP <http://www.hma.eu/91.html?&L=0>

The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective, June 2015



Glossary of terms

API Active Pharmaceutical Ingredient

AS Active Substance

ASMF Active Substance Master File

CEE Central and Eastern Europe

CEP European Pharmacopoeia Certificate of Suitability

CESP Common European Submission Platform

CHMP Committee for Human Medicinal Products

CMDh Coordination Group for Mutual Recognition and Decentralised Procedure – Human

CMS Concerned Member State

CP Centralised Procedure

CTD Common Technical Document

CTS Communication Tracking System

DCP Decentralised Procedure

DG Directorate General of the European Commission

DMF Drug Master File

eCTD electronic Common Technical Document

EDQM European Directorate for the Quality of Medicines of the Council of Europe

EEA European Economic Area

EMA European Medicines Agency

EPAR European Public Assessment Report

EURD European Reference Date

EWP Efficacy Working Party of EMA

FDA United States Food and Drug Administration

FP Finished Product

GCP Good Clinical Practice

GDP Good Distribution Practice

GMP Good Manufacturing Practice

HMA Heads of Medicines Agencies

ICH International Conference on Harmonisation

ICSR Individual Case Safety Report

IDMP Identification of Medicinal Products

INN International Nonproprietary Name

IP Intellectual Property

IPC In Process Control

ISO International Organisation for Standardisation

MAA Marketing Authorisation Application

MA(H) Marketing Authorisation (Holder)

MLM Medical Literature Monitoring

MRP Mutual Recognition Procedure

MS Member State

NCA National Competent Authority

NTA Notice to Applicants

PASS Post Authorisation Safety Studies

PBRER Periodic Benefit Risk Evaluation Report

PIC/S Pharmaceutical Inspection Co-operation Scheme

PIL Patient Information Leaflet

PSMF Pharmacovigilance System Master File

PSUR Periodic Safety Update Report

QWP Quality Working Party of EMA

R&D Research and Development

RMP Risk Management Plan

RMS Reference Member State

RUP Repeat Use Procedure

SANCO European Commission DG responsible for public health and consumer affairs

SOP Standard Operating Procedure

SPC/SmPC Summary of Product Characteristics

SPC Supplementary Protection Certificate

TSE Transmissible Spongiform Encephalopathy



EGA 2016 Events

9th EGA Pharmacovigilance Conference

27th January
Radisson Blu Portman Hotel, London

EBG Biosimilars 2016 14th European Biosimilars Group Conference

28th - 29th April
Grange Tower Bridge Hotel, London

15th EGA Regulatory & Scientific Affairs Conference

28th -29th January
Radisson Blu Portman Hotel, London

Joint 22nd EGA Annual Conference – 19th Annual IGPA Conference

8th - 10th June
Radisson Blu Dubrovnik, Croatia

12th EGA Legal Affairs Conference

8th - 9th March
The Hotel Brussels, Brussels



REGULATORY EFFICIENCY REPORT 2015

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