Attachment to EFPIA and Vaccines Europe's response to the European Commission's public consultation on the revision of the EU variation framework for medicines

September 2023

This document highlights joined position of European Federation of Pharmaceutical Industries and Associations (EFPIA) and Vaccines Europe (VE) and key recommendations on select topics within the proposed revision of the EU Variations Regulatory Framework.

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1. EXECUTIVE BRIEFING PROPOSAL FOR MAKING THE EU VARIATIONS REGULATORY FRAMEWORK STATE OF THE ART (12 March 2019)

INTRODUCTION

When the Variations Regulation (1234/2008) and the Variations Classification Guideline were implemented, they represented a leap forward in harmonisation and alignment of post-authorisation life-cycle management of medicinal products within the EU. Today, over a decade since they were first implemented, Industry, as represented by the various Trade Associations contributing to this Briefing Paper, believe that the time has come to review and reflect on its performance and look to the future.

The system needs to evolve in the light of that experience to: take account of technical advances in medicines development and in the process future proof the system; utilise the advances in digital technology which were not available when the Regulation was drafted; and better reflect the current needs of Manufacturers and Regulators alike. This targeted amendment of the EU Variations Regulation should be conducted under the mandate of the new European Commission.

PROPOSALS

1. Take into Account Technical Advances and Future Proof the System

1.1 Adopt principles and tools described in ICH Q12:

The intent to update the current Variations Framework to take account of technical advances in medicines development has not been realised. The pace of change has outstripped capacity and the system now needs to evolve to facilitate continual improvement of manufacturing processes in today's reality of global supply chains.

Companies are discouraged from attempting to secure a Design Space by the EU regulatory expectations associated with gaining approval and subsequent maintenance of a Design Space. Whilst companies see the potential benefit of post approval change management protocols (PACMPs), experience to-date suggests that there is a need to simplify requirements, introduce more mechanisms and to incorporate multi-product protocols in the Variations framework.

The additional flexibility and reduced post-approval change burden associated with the principles and tools described in ICH Q12 will be important in supporting the global availability and supply of medicines in EU in the future, particularly for those with long lifespans, broad geographical distribution and complex manufacturing processes.

1.2 Take into account the impact of ATMPs and MDR/IVDR

In addition, the impact of new medical technologies (e.g. Advanced Therapy Medicinal Products (ATMPs)) and recent scientific and regulatory developments (e.g. Medical Devices Regulation (MDR) and *In Vitro* Medical Device Regulation (IVDR)) on the Variations Framework needs to be considered. Adoption of the principles of ICH Q12 into the EU Variations Framework would provide flexibility for the management of changes in these areas to evolve over time, as experience is gained by Industry and Regulators, without the need for further revision of the Variations Framework.

1.3 Update the framework for well-characterized biological medicinal products

Advances in science and technology and decades of experience of the manufacture of well-characterized biological medicinal products makes the Variations Framework overly onerous for these products relative to the risk. Risk-based approaches to variation categorization should be extended to well-characterized

biological medicinal products by removing the default classification of manufacturing changes as major variations of Type II, and the specific exclusions that preclude the use of the Type IA variation category.

1.4 Update the framework for vaccine medicinal products

Vaccines, in particular, would benefit from revisions to the Variations Framework. The challenges due to the lack of worldwide harmonisation of data requirements, variation categories and review timelines, are of uppermost concern in the case of vaccines, given their long lifespan, broad geographical distribution and manufacturing complexities. This lack of harmonisation can result in significant delays before implementing changes in routine production, which may trigger supply issues. It is recommended that a new vaccine-specific Annex to the EU Variations Guideline modelled on the WHO "Guidelines on procedures and data requirements for changes to approved vaccines" be developed to promote international alignment of regulatory requirements for post-authorization lifecycle management. In doing so, the EU could play a key role in triggering more global alignment across variation systems, which would ultimately yield benefits in terms of sustainability of vaccine supply in EU and worldwide, and further underpin Europe's competitiveness in a global arena.

1.5. Update the framework for herbal medicinal products

There is an inconsistent approach to the variation classification across different product types, as demonstrated in the life cycle management of herbal medicinal products where the variation classification regime is generally higher than for chemically defined medicinal products. Minor changes in the manufacturing of herbal medicinal products generally require submission via a Type IB variation, compared to the less resource intensive Type IA variation for an equivalent change to a chemical compound and even a Type II if a minor change of the active substance of a herbal medicinal product is concerned compared to a Type IA variation for an equivalent change to a chemical compound. Revision of the Variation Regulation is needed to achieve the production of state-of-the-art herbal medicinal products and to enable further technical progress under proportionate regulation.

1.6 Move responsibility for future regular scientific update to EMA and/or HMA

The Annex to the Variations Classification Guideline needs to be revised regularly to reflect scientific progress and implement Article 5 recommendations. Around 50 recommendations have already been issued but the guideline has not been amended to reflect these. Whilst perhaps a challenge for the European Commission, faster updating could be achieved if responsibility for the Classification Guideline could be moved to EMA and/or HMA.

2. Take Advantage of Advances in Digital Technology to Reduce Administrative Burden

2.1. Disproportionate allocation of resources

At the current time, disproportionate levels of resources are allocated to the variations process in view of the overall benefit they provide to patients and the entire regulatory system. Data gathered from 2010-2018 indicates that the number of variations per MA and per year appears to have increased by about 75% since 2010 and over 50% of the total number of variations submitted to the Competent Authorities are minor changes (Type IA Variations and Notifications), engaging huge resources from both Regulators and Industry, in processing these minor, mainly administrative submissions that do not require scientific assessment. This use of resources does not add any value for patients and could be diverted to activities that would have a greater positive impact on public health in the EU.

While it is essential to provide full oversight and transparency of the supply chain and product flow to Competent Authorities, the current system for handling the maintenance of Active Pharmaceutical

Ingredient (API) related information discourages companies from registering several alternative API suppliers as a means to mitigate medicines supply shortages.

2.2 Digital solutions

Digital solutions offer enormous opportunities to notify minor, mainly administrative changes to the Marketing Authorization by the Marketing Authorization Holders directly into EU databases, with Competent Authorities having full access to the content. This processing change has already been realised for changes related to the Qualified Person for Pharmacovigilance (QPPV) and the location of the pharmacovigilance system master file (PSMF), and should be explored for use with other Type IA notifications, by optimising the opportunities of the SPOR database and the PMS Target Operating Model (TOM) concept already in development.

Regulation 1234/2008 was adopted at a time of relatively low digitalisation of Regulatory Operations and the pace of change in this field over the last decade has been significant and is accelerating all the time. The regulatory environment has evolved with the increasing availability of a range of IT tools and the future impact of on-going telematics projects (i.e. mandatory eCTD, e-Application Form, CESP, Art 57 database, SPOR/ISO IDMP; FMD and e-leaflet) will have a major impact on the way in which Regulatory Operations are conducted in the future.

The effective use of IT systems could also be a powerful tool for enabling regulatory efficiency in the processing of variations across the EU Network.

3. Better reflect the current needs of Manufacturers and Regulators

In addition to the above changes which reflect the current and future needs of Manufacturers and Regulators alike, there are a number of other changes that a review and update of the Variations Framework could enable.

Many concepts created in 2008, such as work-sharing procedures, grouping, and Article 5 recommendations, are of great benefit, but due to certain constraints, are not used to maximum effect. Grouping and Work-sharing approaches should be redefined to reduce time for review/approval of the change and its subsequent implementation, especially in cases where the same change affects multiple products.

In addition, the opportunity should be taken to ensure there is an appropriate level of risk-based review for post-authorization labelling changes.

CONCLUSIONS

Implementation of the Variations Framework was a significant innovation in 2008 that achieved a major step forward in harmonisation and alignment of post-authorisation processes across Europe. However, the Variations Framework has not be able to keep up with the pace of change in the external environment nor evolution in technology over the last decade.

With that backdrop in mind, Industry proposes a review of the Variations Framework to take account of technical advances in medicines and IT development, better reflect the current needs of Manufacturers and Regulators alike. Of upmost importance, a regulatory framework that is efficient, sustainable and able to continually improve is vital to ensure patient access to innovative and quality medicines is timely and unimpeded.

2. RESPONSE TO COMMISSION REQUEST FOR FURTHER INFORMATION: FOLLOWING THE CROSS-EU PHARMACEUTICAL TRADE ASSOCIATION MEETING (6 March 2019)

INTRODUCTION

The European Commission (EUComm) and members of the European Federation of Pharmaceutical Industries and Associations (EFPIA), Vaccines Europe (VE) and Medicines for Europe met on 6 March 2019 to discuss experience with the EU Variation Regulation (1234/2008).

- Some of the challenges, and possible solutions associated with the EU Variation Regulation, had been outlined in the EFPIA/Vaccines Europe/EBE Position Paper ('Reflection Paper on a Revision of the EU Variations Regulatory Framework') shared with the Commission in November 2018 (see **Annex I**).
- In order to provide the EUComm with the entire Industry perspective, Medicines for Europe and the Association of the European Self-Care Industry (AESGP) have also prepared a position paper ('Why is it now the right time to modernise the EU Variations system') outlining challenges and possible solutions with the EU Variation Regulation (see **Annex II**).
- At the conclusion of the meeting in March, the EUComm requested further information on several points. These are addressed as responses to the specific questions below in the annexes to this Executive Summary (**Annexes II** (Medicines for Europe and AESGP position paper) and **Annex III** (Application of Flexible Mechanisms).

Annex II provides a broad overview of the challenges with the EU Variation Regulation, but additionally addresses the following aspects related to the submission of post-authorisation changes:

- data on the number of EU post-approval changes over time;
- experience gained from the practical implementation of Regulation 1234/2008 and changes in GMP supervision of the supply chain; and
- the Industry burden associated with preparing dossiers for lifecycle changes.

Annex III covers aspects related to the application of flexible mechanisms, particularly in the areas of pharmaceutical quality and control and addresses:

- the potential under-utilisation of existing flexible mechanisms (e.g. Design Space and PACMP) by Industry;
- measures to maintain control of the end-to-end supply chain and further justification on the need for increased flexibility, with reference to the current Variation Regulation; and
- systems to allow continued regulatory oversight.

SUMMARY OF THE RESPONSES

- In the Vaccines space, the EU Region requires the largest number of CMC variations per product than any other region of the world and these are restricted in the main to variations of Type IB or Type II resulting in a huge administrative burden. The number of CMC variations specific to vaccines are also significantly higher compared to number of CMC variations for any other types of medicinal products (in EU and worldwide). This shows that vaccines are a medicine category that would benefit the most from changes to the Variations Regulation and such changes, if introduced, would help secure the future supply of vaccines around the globe (**for further details see annex I, addendum**).

- In the National/MR/DCP space, the number of variations per MA per year has increased by about 75% since 2010. Number of variations for centrally authorised medicinal products submitted annually

to the EMA by Industry has also increased significantly, supporting the case for a more efficient and flexible system to manage post-approval changes in the future (**for further details see annex II, page 9-11**).

- Factors influencing the maintenance of medicinal products over the last 10 years include (**for further details see annex II, page 8-25**):
    - Advances in science and technology
    - Globalisation of the Industry
    - Significant progress in digitalisation, including operational activities of the Regulators and the Industry
    - Increased efforts to protect public health though increased Pharmacovigilance
    - Unexpected political developments (i.e. Brexit)
    - Implementation of new legislation (i.e. Falsified Medicines Directive; Medical Devices Regulation and Veterinary Medicines Regulation) and new guidelines (i.e. Guideline on excipients)

- The disproportionate resources that need to be allocated to product maintenance discourage manufacturers from registering alternative API suppliers as a means to mitigate potential supply shortages, supporting the need for a streamlined, up to date system (**for further details see annex II, page 15-18**).

- The proportion of resources allocated to post-authorisation maintenance activities has substantial increased and in some sectors (i.e. Generics) costs over 3 years approximate to the invested R&D spend per year for new product development, resulting in the decisions to cease marketing or not apply for market authorisation in some countries with the consequent outcome of shortages and/or lack of availability of some medicines in some Member States (**for further details see annex II, page 7**).

- Some of these volume increases have been driven by specific events (such as Brexit and FMD) and have been compounded by the lack of flexibility in the Variations Regulation to allow handling of such changes in any other way than through the submission of huge numbers of Variations (**for further details see annex II, page 22-23**).

- Companies have become discouraged from attempting to secure a Design Space due to the EU regulatory expectations associated with gaining approval and subsequent maintenance of a design space and divergent regulatory expectations between Regions resulting from inconsistent implementation of ICH Q8-11 (**for further details see annex III response i)**.

- Companies see the potential benefit of PACMPs but experience to-date suggests that there is a need to simplify requirements, introduce more flexible mechanisms to change approved PACMPs, and incorporate multi-product protocols in the Variations Framework in order to fully realise the potential benefits in EU (**for further details see annex III response ii**).

- To ensure appropriate control of the end-to-end supply chain, medicine manufacturers have strict methodologies to evaluate which materials and ingredients may be at risk, and continuously evaluate the potential consequences of supply disruption for these raw materials. Measures employed include supplier information requests, audits and special contractual agreements (e.g. master supply

agreements, quality agreements and/or safeguard clauses) (**for further details see annex III response iia**).

- Increased flexibility is needed to foster continuous improvement and innovation, meet evolving regulatory requirements, and maintain manufacturing and operation in process (**for further details see annex III response iib**).

- The implementation of robust change management processes and quality management systems will ensure maintenance of quality and provide Regulators with assurance on the appropriate level of oversight (**annex III response iii**).

3. EFPIA/EBE/VACCINES EUROPE REFLECTION PAPER ON A REVISION OF THE EU VARIATIONS REGULATORY FRAMEWORK (9 November 2018)

The science behind how the biopharmaceutical industry researches, develops and manufactures new medicines is advancing rapidly. Our aim is to work with stakeholders across Europe, including the regulatory authorities, in order to contribute to the development of EU regulatory processes that deliver safe, effective new treatments to patients faster. It is vital to ensure that the assessment and management of changes to medicinal products during their lifecycle are governed by an approach to science and risk that is consistently interpreted, understood and agreed by all stakeholders. In parallel, there is also a need to adapt to advances in science and technology, whilst maintaining a clear, predictable and sustainable framework. This Reflection Paper includes specific examples (included in the Annex), provided by the industry, of challenges with the current EU variations regulatory framework in achieving these aims. Some of these examples highlight the rigidity of the current Variation Regulation and how this can impact on patients with significant medical needs by delaying access to medicines (either through issues of supply or by delaying access to improved medicines).

The examples provided in the Annex also serve as the basis for further discussion within this Reflection Paper on the potential to revise the EU variations regulatory framework to better meet the needs of patients, regulators and industry. Experience gained since the last amendment of the variations framework in 2012 presents opportunities to move to a more adaptable, proportionate and optimised approach for the management of post-approval changes. This has the potential to promote continual improvement and reduce manufacturing delays, mitigate supply issues, and free-up capacity to enable a greater focus on those changes that may impact on quality, efficacy or patient safety, with consequent benefits to public health. Furthermore, developments in new information technology (IT) systems provide the opportunity to incorporate efficiency and innovation in the variation management system, provided that their implementation is accompanied by a review of legislative provisions that give rise to repetitive submissions and assessments of changes by regulators. However, it is also important to acknowledge that proposals made in this Reflection Paper regarding improvements in efficiency through process optimisation are intended only to reflect a re-prioritisation of regulatory oversight and should not undermine the overall financial stability of Competent Authorities. Finally, any revision of the Variation Regulation and Guidelines should not only be able to accommodate recent advances in technology but also look further ahead to address the assessment of changes to *new* technological innovations in medicine for the full benefit of patients.

Whilst further discussion on these broader aspects is included in the body of the Reflection Paper, specific recommendations for areas within the EU Variations Regulation and Guidelines that may offer the opportunity for revision and improvement are as follows:

- Evolve the variations system to incorporate the principles and tools described in ICH Q12, thereby providing additional flexibility and reducing the post-approval change burden associated with continual improvement of manufacturing and supply, and the introduction of innovative manufacturing technologies. This evolution will be important in supporting the global availability and supply of medicines, particularly those with long lifespans, broad geographical distribution and complex manufacturing processes.
- Extend risk-based approaches to variation categorisation for well-characterised biological medicinal products by removing the default classification of manufacturing changes as major

variations of Type II, and the specific exclusions that preclude the use of the Type IA variation category.

- Develop a new vaccine-specific annex to the EU Variations Guideline modelled on the WHO "Guidelines on procedures and data requirements for changes to approved vaccines" to promote international alignment of regulatory requirements for post-authorisation lifecycle management. In doing so, the EU could play a key role in triggering more global alignment across variation systems, which would ultimately yield benefits in terms of sustainability of vaccine supply in Europe and worldwide, and further underpin Europe's competitiveness.
- Ensure there is an appropriate level of risk-based review for post-authorisation labelling changes.
- Assess the impact of new medical technologies (e.g. Advanced Therapy Medicinal Products (ATMPs)) and recent scientific and regulatory developments (e.g. Medical Devices Regulation (MDR)) on the variations framework. Adoption of the principles of ICH Q12 into the EU variations framework would provide flexibility for the management of changes in these areas to evolve over time, as experience is gained by industry and regulators, without the need for further revision of the variations framework.
- Re-evaluate the classification of changes with no impact on quality, safety or efficacy of the medicinal product to ensure that advances in IT can be utilised to optimise use of resources and enhance the efficiency of the variations regulatory system.
- Refine Grouping and Worksharing approaches to reduce time for review/approval of the change and its subsequent implementation, especially in cases where the same change affects multiple products.

INTRODUCTION: DRIVERS FOR CHANGE

In the ten years since the EU Variations Regulation[1] and Guidelines[2] were introduced as part of the "Better Regulation" initiative launched by the European Commission it has become clear that the goals to (i) simplify the system, through harmonising the categorisation, timelines and procedures as well as streamlining the procedures, and (ii) make it more flexible, have only been partly achieved and there is scope for further improvement. Such improvement is expressly envisaged by Articles 4 and 26 of the Variations Regulation that mandate regular updates of the Commission's implementing acts in light of scientific and technical progress, "*taking in particular account of developments regarding international harmonisation*". Indeed, such improvements are also part of both the EMA and HMA (Heads of Medicines Agency) multiannual work plans[3]. A revised Variations framework should also consider the emergence of new types of products, other EU legislation (e.g. Regulation 2017/745 on medical devices), and other EU activities (e.g. Regulatory Optimisation Group (ROG)).

The drafting of the Variations Regulation was strongly driven by the concept that variations need to be classified based on the level of risk to public health and the impact on the quality, safety and efficacy of the medicinal product concerned. It is also important to ensure that the Variations framework is proportionate, can facilitate innovation and is sufficiently adaptable to reflect the evolution of working practices and take account of the use of new developments in technology, thus contributing to EU competitiveness and growth.

[1] Commission Regulation (EC) No 1234/2008 (amended by Commission Regulation EC No. 712/2012) concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (the Variations Regulation)
[2] Variation Classification Guideline (Guidelines 2013/C 223/01: Commission Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 and on the documentation to be submitted pursuant to those procedures)
[3] https://www.ema.europa.eu/en/documents/work-programme/multiannual-work-programme-2020_en.pdf

The introduction of new paradigms in manufacturing such as continuous manufacturing, the development of advanced therapy medicinal products (ATMPs), and the growth of drug-device combination products are all examples of innovative developments where there may be challenges and limitations posed by the current Variations Regulation.

Globalisation of the pharmaceutical supply chain is also creating challenges that raise fundamental sustainability questions. There are increasing concerns regarding shortages of medicines and vaccines, both in the EU and globally [4], and facilitating post-approval changes globally is one of the approaches to help mitigate shortages.

Since 2008, information is increasingly handled in electronic formats and databases, rather than in printed documentation, and IT tools offer the opportunity to help further simplify and streamline working practices and reduce the regulatory administrative burden in this area.

This reflection paper outlines a set of proposals (with supporting examples) for revisions to the Variations Regulation and Guidelines that may be beneficial for patients, regulators, and the pharmaceutical industry.

PROPOSALS FOR REVISION OF THE EU VARIATIONS FRAMEWORK

1. Improving manufacturing and supply and introducing innovative manufacturing technologies

Recommendation:

Evolve the Variations system to incorporate the principles and tools described in ICH Q12, providing additional flexibility and reducing the post-approval change burden associated with continual improvement of manufacturing and supply, and the introduction of innovative manufacturing technologies. This evolution will be important in supporting the global availability and supply of medicines, particularly those with long lifespans, broad geographical distribution and complex manufacturing processes.

Issue statement:

The current Variations framework needs to evolve further to facilitate continual improvement of manufacturing processes and the adoption of innovative manufacturing technologies, especially in the context of global supply chains.

Discussion:

Industry continuously improves its manufacturing processes, and the majority of Chemistry, Manufacturing and Control (CMC) changes arise through activities linked to continuous improvement, capacity expansion and innovation. With globalisation of supply chains, the ability to continually innovate and make best use of emerging manufacturing technologies is becoming increasingly important for reliable supply of products, and this can also contribute to boosting EU competitiveness and growth. Currently, the total lead time for approval of critical variations worldwide can be extremely lengthy (up to several years) and represents a major supply chain bottleneck (N.B. Item 9 *in Annex, Part B* explains how the regulatory complexity may ultimately impact the availability of medicines to patients. This is also

[4] https://www.ifpma.org/wp-content/uploads/2023/01/i2023_IFPMA-ComplexJourney-2019_Stage-5_Web_High-Res.pdf

further illustrated under Examples 11 and 19 in *Annex, Part B*. Although data from vaccines have been used to illustrate this, many medicinal products other than vaccines are facing the same challenges). Although the current Variations framework incorporates some predictability and risk-based categorization through the elaboration of requirements for various changes in the guideline, there can be undesirable consequences. The current regulatory framework can result in detail which is included in the Quality module of the dossier that becomes subject to a Variation if it is changed, and this may lead to interruption of manufacturing activity. The need to manage this product supply issue across multiple countries (because of the global nature of supply chains) can delay, or even negate the business case for the introduction of manufacturing improvements or innovations. All changes are managed through a company's Pharmaceutical Quality system (PQS), which is subject to regulatory oversight through inspection, and there are opportunities to reduce the post-approval change management burden for industry and regulators by extending science- and risk-based approaches to focus Variations on the assessment of those changes with the greatest potential to impact patients.

The ICH Q12 Product Lifecycle Management guideline has been published as a draft Step 2 document for comment. It builds on recent ICH Quality guidelines (ICH Q8 to ICH Q11) to provide opportunities for a more science and risk-based approach for assessing changes across the lifecycle because the envisioned post-approval 'operational flexibility' from ICH Q8 to Q11 has not been achieved. Q12 aims to reduce the number of regulatory submissions for post-approval CMC changes by clearly distinguishing between major to moderate changes that need to be notified to Regulatory Authorities and minor changes to the product that can be managed solely within the PQS. This will enable companies to provide sufficiently detailed information in the dossier's Quality section to assist regulatory assessors, while the focus for Variations should be on the most critical product changes. Q12 also aims to accelerate the implementation of CMC changes through prior agreement mechanisms. A quicker implementation of CMC changes and a harmonisation of the basic principles upon which the different regional variations systems are based, should also help to reduce potential disruptions in supply chains to the benefit of patients in Europe and worldwide [see example 6 in the *Annex, Part A*].

Incorporating ICH Q12 into the existing EU Variations framework is readily achievable because the system already relies on a risk-based categorisation of post-approval CMC changes and includes the concept of Post Approval Change Management Protocols (PACMPs) - Q12 seeks to encourage greater use of PACMPs. Of the key features of the ICH Q12 Step 2 document, the Established Conditions concept and the Product Life Cycle Management Strategy ("PLCM") document would need to be included within the Variations framework. Incorporation of these concepts into the EU Variations framework will have a positive impact on the current practice by focusing requirements for submission and assessment of changes on those changes with the greatest potential to impact patients.

Conclusions:

Fully implementing the principles and tools described in the ICH Q12 Step 2 Product Lifecycle Management document in the EU Variations framework will promote continual improvement, the introduction of innovative manufacturing technologies, and proactive planning of supply chain adjustments. This will strengthen quality assurance and reliable supply of product. The EU is seen as a reference authority internationally, and by implementing the principles described in ICH Q12, the EU would give a clear signal and pave the way for further harmonisation of regulatory requirements across countries worldwide; encouraging the use of a science- and a risk-based approach to reduce lead times for post-approval changes.

2. Extending the risk-based approach to variation categorization for well-established biological medicines

Recommendation:

Extend risk-based approaches to variation categorization for well-characterised biological medicinal products by removing the default classification of manufacturing changes as major variations of Type II, and the specific exclusions that preclude the use of the Type IA variation category.

Issue statement:

Modifications in the manufacturing process or sites of the active substance for a biological medicinal product are all classified as major variations of Type II (Annex II point 2(e) of the Variations Regulation) that potentially impacts many biological variations and allows little scope for adaptation based on the risk to public health. In addition, certain minor changes are precluded from the Type IA category because of specific exclusions.

Discussion:

The experience of medicine developers and regulators with certain, well-defined biologicals, such as monoclonal antibodies (mAbs), vaccines and some recombinant protein products has increased considerably over the last decade to the extent that fewer changes are considered to require detailed assessment by regulators. In many cases, the level of experience with these well-defined biologicals is now in line with that of small molecules and thus the default Type II classification for changes is no longer proportionate, and we believe that this does not align with the original intention of the Regulation.

Furthermore, technological developments have led to an increase in the number of conjugated molecules such as pegylated medicines which combine a small molecule e.g. the polyethylene glycol (PEG) moiety together with a biological, resulting in an overall drug substance that has properties of both components. The current wording of the Variation Regulation does not adequately address the situation of conjugated molecules, including antibody-drug-conjugates.

We note regulatory developments such as the approach taken by the WHO "Guidelines on Procedures and Data Requirements for Changes to Approved Biotherapeutic Products" [6], and the proposals in the draft ICH Q12 Product Lifecycle Management guideline, are designed to facilitate post-approval changes by enabling companies to self-manage more CMC changes under an effective PQS, provided that certain criteria are met, and reflect increased product- and process-understanding for well-defined biological medicinal products.

Finally, in the current Annex of the Variation Classification Guideline (Guidelines 2013/C 223/01) several minor changes related to biologicals are precluded from the Type IA variation route due to the specific exclusion conditions listed. Consequently, manufacturers of biological medicinal products are obliged to follow the more prescriptive Type IB variation procedure or request further assistance for such changes which have minimal or no impact on quality, safety or efficacy.

Please refer to Example 3 and 4 in *Annex, Part A*, as well as to Examples 13 to 18 in *Annex, Part B* for illustrations of situations where the current Variation Regulation does not provide sufficient room for appropriate level of risk-based review, which would facilitate the assessment of post-authorisation changes and allow the introduction of improved and new technologies.

Conclusions:
There is an opportunity to more closely align the regulatory oversight of certain biologicals, particularly mAbs, vaccines and some recombinant protein products, with that of small molecules. This would take into account increased knowledge and experience of biological medicinal products that has accumulated since the last amendment of the regulation and enable better alignment of the level of risk associated with a change.

We believe that classifying all modifications in the manufacturing process or sites of the active substance for a biological medicinal product as major variations of Type II is no longer appropriate.
We also believe it is no longer justified to keep exclusion conditions that prevent several minor changes to be classified as Type IA Variations.

3. Vaccines: the complexity of life-cycle management in a global context

Recommendation:
Develop a new vaccine-specific annex to the EU Variations Guideline modelled on the WHO "Guidelines on procedures and data requirements for changes to approved vaccines" to promote international alignment of regulatory requirements for post-authorisation lifecycle management. In doing so, the EU could play a key role in triggering more global alignment across variation systems, which would ultimately yield benefits in terms of sustainability of vaccine supply in Europe and worldwide, and further underpin Europe's competitiveness.

Issue statement:
The long lifespan, broad geographical distribution and complexities in vaccine manufacturing highlight the challenges posed by the lack of worldwide harmonisation of Variations categories and can lead to delays introducing improvements for EU patients.

Discussion:
Vaccines are biological medicinal products with a long lifespan, during which many CMC changes are made to the marketing authorisation dossier, with many these changes categorized as Type IB or II variations. As with most products in large companies, vaccines are manufactured for worldwide supply, and any change must be approved in numerous countries before being implemented. This is even more pertinent in vaccine manufacturing due to composition (usually multiple antigens), the complexity of production (biological broth requiring high level of purification) and extensive testing schemes. For example, a vaccine company with a large portfolio submits typically an average of 6,000 to 8,000 Variations per year around the world.

The lack of worldwide harmonisation of data requirements, Variation categories and review timelines results in manufacturers having to wait for the last approval before implementing the change in routine production. Such delays may trigger supply issues because it is not possible in practice to concomitantly manufacture multiple variants of the same vaccine.

Vaccines are produced in different formulations for different countries, populations and age groups. Moreover, some products exist in standalone and combination formulations, which further increases the number of products that need to be manufactured. The complexity of vaccine production can be particularly challenging when marketing authorisation holders (MAHs) need to ensure continued supply to all markets worldwide in situations where marketing authorisation status of a product differs from country to country (i.e. change already approved in some countries but still pending in others); the vaccine

manufacturing complexity is such that it would be unmanageable for MAHs to keep several production lines running in parallel with different product versions. The situation is therefore complicated by the fact that a single CMC change typically affects several vaccines that are covered by hundreds of authorisations worldwide.[7] Around 60% of countries outside the EU require the EU approval as a reference at submission or at time of approval, and in some cases, it takes up to five years for the change to be approved worldwide. (See also *Annex, Part B* for vaccine-specific data, examples and case studies). For all these reasons, worldwide harmonisation of variations systems, with an efficient implementation of CMC changes would be of benefit for continuity of vaccines supply.
The WHO has adopted "Guidelines on Procedures and Data Requirements for Changes to Approved Vaccines" ('WHO Guidelines')[8] that illustrates the WHO's recognition of the specific characteristics and nature of vaccines. The EU is a well-recognised authority of reference at a worldwide level, and as such it is best placed to play a key role in initiatives and efforts towards more international harmonisation.

Conclusions:
We believe the EU should play a key role in leading more international alignment across variation systems. In a global supply context, sustainability of vaccine supply and Europe's competitiveness would strongly benefit from greater harmonisation of variation systems wherever possible. It would be helpful if the EU could ensure that revisions to the classification of Variations for vaccines and WHO technical recommendations are aligned.

4. Changes to product information: ensuring that the Variations Regulation and Guidance adapts with scientific progress and is proportionate for non-CMC changes to medicinal products

Recommendation:
Ensure there is an appropriate level of risk-based review for post-authorisation labelling changes.

Issue statement:
Experience with the implementation of the Regulation with respect to labelling changes has highlighted areas of misalignment between a proposed change and the default classifications applied by the regulation.

Discussion:
The Regulation defines a major variation of Type II as meaning "a variation which is not an extension and which may have a significant impact on the quality, safety or efficacy of the medicinal product concerned" and specifies that addition or amendment of an indication (C.I.6) as well as significant modifications of the Summary of Product Characteristics (SmPC) due to new quality, pre-clinical, clinical or pharmacovigilance findings (C.I.4) are to be classified as major variations of Type II. In practice this has the unintended effect of making all changes to an SmPC a Type II variation by default. Thus, a minor change to the wording of a single adverse event that arises from routine pharmacovigilance activities and requires minimal assessment is classified in the same way as the addition of a new indication potentially requiring a full review of substantial new clinical data and a full risk-benefit evaluation.

Furthermore, a default Type II categorisation (C.I.13) for submission of studies when no changes to the product information are proposed equally does not reflect on the workload of different Type II variations. The application of the same Type II category for a single, short (e.g. 50 pages) clinical study report (CSR) submitted as a Post Approval Measure with no impact on the SmPC should not attract the same categorisation as a variation to add a new indication incorporating many CSRs in the submission package.

There are examples of new data being supplied with a Type IB categorisation such as studies submitted in the context of an environmental risk assessment (ERA).

Conclusions:
Some adaptation of the Regulation to better stratify changes to the SmPC and/or labelling according to the potential impact on public safety and level of assessment would make the regulation classification system more proportionate in relation to safety and efficacy changes. Equally, some stratification of requirements for data submissions not requiring change to the SmPC and/or labelling would improve proportionality in the variation classification system.

5. Adapting to the impact of the introduction of new regulations and medical technologies

Recommendation:
Assess the impact of new medical technologies (e.g. ATMPs) and recent scientific and regulatory developments (e.g. MDR) on the Variations framework. Adoption of the principles of ICH Q12 into the EU Variations framework would provide flexibility for the management of changes in these areas to evolve over time, as experience is gained by industry and regulators, without the need for future revisions of the Variations framework.

Issue statement:
Introduction of new medical technologies and other scientific and regulatory developments may not be fully encompassed within the current variations framework.

Discussion:
There have been several developments in technology and regulatory science since the last update of the Variations regulation in 2012. A revision of the variations framework would allow full consideration of these developments and assessment of impact on the Regulation.

One such example would be the recent entry into force of the Medical Devices Regulation (MDR; Regulation (EU) 2017/745). It is understood that the MDR requires that proposals to change an already approved product may trigger the requirement for a Notified Body (NB) Opinion to be filed, and that this will require additional guidance. However, the Variation Guideline does not provide an extensive list of classifications for device-related changes for integral drug/device medicinal products. Often, the categorization of a change depends on the fact that the device component may also be classed as a container closure system rather than a device, e.g. the syringe barrel of a pre-filled syringe (PFS) product, but invariably this does not suit all possible device types. Therefore, a review of the Variations framework would provide the opportunity to fully evaluate if there is further impact of the MDR and other developments in regulatory science on the Regulation, and if there are further opportunities for efficiency in the management of changes. As part of this, consideration should be given to aligning with the principles of ICH Q12 and utilising a risk-based approach for evaluating what changes would qualify within scope of a variation.

A further consideration in the context of technological developments, would be to consider ensuring that the variations framework is able to embrace innovation in medicinal technologies e.g. ATMPs and beyond. At present, with these technologies there is less experience and consequently there may be a need for greater scrutiny of changes: the extent of operational and regulatory flexibility should be subject to product and process understanding and application of risk management principles e.g. as outlined in ICH Q8-12. Principles and tools presented in ICH Q12 e.g. the "Established Conditions" concept and PACMPs,

could also be applied to these newer technologies, enabling the categorization and approach to management of these changes to evolve over time, reflecting the product and process understanding gained by the company and experience of the regulators, without needing to change the variations framework.

Conclusions:
A revision of the variations framework would allow full consideration of recent scientific and regulatory developments and assessment of impact of these developments on the regulation. Adoption of the principles of ICH Q12 into the EU variations framework would provide flexibility for the management of changes to new technologies such as ATMPs to evolve over time as experience is gained by industry and regulators, without the need for revision of the variations framework.

6. Optimise the classification and management of administrative and other changes

Recommendation:
Re-evaluate the classification of changes with no impact on quality, safety or efficacy of the medicinal product to ensure that advances in information technology can be utilised to optimise use of resources and enhance the efficiency of the Variations regulatory system.

Issue statement:
The management of changes which do not impact on the safety, efficacy or quality of the medicinal product, and which are currently submitted as variations of Type IA or Type IA_{IN} consume significant industry and regulator resources that would be better applied to managing those changes requiring deep scientific understanding and carrying a risk to the patient.

Discussion:
Currently the management of administrative and minor changes that are submitted as variations of Type IA or Type IA_{IN} consumes significant industry and regulator resources. Such changes do not impact on the safety, efficacy or quality of the medicinal product, and provide an opportunity to re-establish the appropriate balance for time and resources spent on minor versus major variations.
Examples of such minor/administrative changes include MAH name/address changes and minor changes to the SmPC. Hence, reducing the requirements for submission by industry and for verification and time spent on routine changes by regulators could help optimise the efficiency of the Variations system.

There are currently some examples of purely administrative changes that have the option of being made via a route other than a Type IA variation. These include those in category C.I.8 'introduction of, or change to, a summary of pharmacovigilance system for medicinal products for human use' which offers the opportunity to submit changes to the QPPV and location of the pharmacovigilance system master file via the Article 57 database without the need for a variation. These few examples illustrate that managing simple administrative changes outside of the standard variation route is already possible, and an expansion of this approach to more broadly encompass other simple Type IA variations would be helpful.

Reducing the average time spent on Type IA notifications and lowering the volume through a combination of process interventions and making optimal use of IT systems (including substance, product, organisational and referential (SPOR) master data in the medium term and electronic product information in the longer term) could possibly lead to a reduction in FTE requirements associated with these activities; indeed it has been estimated that up to a 65% reduction in FTEs within the European network may be

achievable by combining these reductions in time and volume associated with processing these Type IA variations.

Further incorporation of the concepts of efficiency and innovation in the variation management systems will only have a positive impact on the current practice if their implementation is accompanied by a review of legislation that results in repetitive submissions and assessment of changes by regulators. The technology upon which future solutions are built needs to be robust and yet flexible to enable fast adoption of new technology and changes in legislation and should aim to remove redundancy/duplication of data, and to switch to the submission, management and evaluation of data without the need for paper documentation. A move in this direction entails the development of the Target Operating Model (TOG) as the business process to optimise the exchange of application data between regulators and applicants for new products and variations, allowing to progressively replace document-based submission by electronic data exchange and allowing the EU to become a key driver of the digitalization of the regulatory world. This should further align with the EU Telematics strategy 2025, which intends that all new projects use SPOR data, and that the vision for information management and technology is both clearly described and embraces the many opportunities afforded by innovative technology to meet the European Medicines Regulatory Network's business needs.

By moving towards an electronic data notification approach together with a series of process interventions, the EU would also pave the way for more international harmonisation. This would indeed be aligned with the approach adopted for instance in the two following WHO guidance documents: "Guidelines on Procedures and Data Requirements for Changes to Approved Vaccines" and "Guidelines on Procedures and Data Requirements for Changes to Approved Biotherapeutic Products" i.e. these two guidance documents recommend that all changes with no (or minimal) impact on the quality, safety and efficacy of the medicinal product are not to be formally submitted for assessment to the relevant regulatory authorities.

Conclusions:
Reducing the volume of Type IA variations associated with minor/administrative changes through a combination of re-evaluation of the classification, process interventions, and use of IT systems should lead to a significant reduction in resources associated with these activities. This will enhance the efficiency of the European network without impacting the quality, safety or efficacy of medicinal products.

7. Simplification of groupings and worksharing

Recommendation:
Refine Grouping and Worksharing approaches to reduce time for review/approval of the change and its subsequent implementation, especially in cases where the same change affects multiple products.

Issue statement:
The grouping and worksharing approaches are very helpful in life-cycle management operations for medicinal products, especially in cases where the same change affects multiple products (e.g. combined vaccines). However, some adjustment would bring significant benefit to Public Health by further reducing time for review/approval of the change and its subsequent implementation.

Discussion:
For administrative and some CMC changes (e.g. deletion of non-significant specification parameters) it is common to have multiple changes requiring submission of several variations under the same category of

change, resulting in very large groupings of applications with increased complexity at submission, as well as longer validation and assessment timelines by the regulators. The requirement for submission of a specific category of change for each specific change proposed should be clearly defined in the Classification Guideline for those changes where this approach is relevant, otherwise, unnecessary complexity for both the industry and the regulators is introduced. An example of simplification in this context was the CMDh recommendation regarding submission of variations under category A.7. Deletion of manufacturing sites, which allows deleting several sites with one single Type IA variation.

With respect to the notification of minor Type IA variations, the EU Regulation allows for a great deal of flexibility in grouping possibilities (e.g. grouping by type of change, grouping by product, grouping across products). Additional simplification of the process for reporting Type IA variations could be considered for "super-grouping" procedures in order to allow submission of a "super-grouping" application encompassing multiple types of procedures and multiple countries. This type of submission is currently restricted to CP, or to MRP/DCP (combining MAs of more than one RMS in one grouped application if needed) or to purely national MAs within one single MS. Alignment between worksharing and "super-grouping" procedures in that respect would bring a significant improvement to the current system.

Furthermore, non-fulfilment of one or more conditions of a Type IA variation automatically converts it into a Type IB variation in the same category of change. The fulfilment of the applicable conditions should be assessed scientifically, based on justification provided by the applicant, and not applied as a default. This is especially important when a grouped variation is being submitted. In the case of a variation application for a minor change in manufacturing process, one of the conditions that is required to be fulfilled to classify the variation as Type IA is that there should be no change in finished product specifications. However, there could be cases where the change in finished product specification is completely unrelated to, and is not resulting from, the change in the manufacturing process for example removal of an insignificant parameter.

Conclusions:

Grouping and Worksharing approaches should be refined further to reduce time for review/approval of the change and its subsequent implementation, especially in cases where the same change affects multiple products. Opportunities for refinement are in the areas of administrative and some minor CMC changes, simplification of 'super-grouping, and fulfilment of applicable conditions for Type IA variations.

ANNEX: IMPACTS OF THE CURRENT VARIATION SYSTEMS AND THE LACK OF ALIGNMENT FROM A WORLDWIDE PERSPECTIVE

A – Data and illustrative examples

1. Administrative burden of minor variations

An estimate of the administrative burden associated with the processing of Type 1A variations across the EU network was made using data gathered by the Regulatory Optimisation Group (ROG) through CMDh, CMDv and EMA. Although the figures derived are approximate, due to the different ways of working and systems within the National Competent Authorities it is estimated that the processing of Type 1A variations across the EU network required approximately 191 FTEs over a 12-month period.

Authorities	Process	Average time spent (minutes)	Volume 2016	FTE[2]
	CP as EMA	148	1.852	3
	CP as NCA	46	16.668[3]	8
	MRP as CMS	103	71.635	73
	MRP as RMS	205	15.912	32
	National	153	49.704	75
	Total		**155.771**	**191**

Industry	Human/ veterinary	Number of Type IA variations[4]	Time to prepare Type IA variation/MA (minutes)[5]	FTE
	Human	143.309	102	143
	Veterinary	12.462	212	25
	Total	**155.771**		**168**

From slide presentation entitled Regulatory Optimisation Group (ROG) Update - Presented at DIA, Basel, 2018

2. Consequences of not meeting Type 1A criteria

When one or more of the conditions or criteria established in the Variation Classification Guideline for a Type IA variation are not met, then a default Type IB(z) must be submitted. Some examples of default IB (z) applications include: B.II.b.3 (z) Type IB Removal of overages: and B.II.d.1 (z) Type IA Change in Description of finished product in release and stability specifications (removal of odour test). However, in some cases, the changes are considered minor and should be classified as a Type IA(z). Therefore, reconsideration of the categories and conditions in the Variation Classification Guideline, to make sure that such changes are appropriately classified at the outset would be welcomed.

3. Further alignment for biologicals and small molecules

With reference to section 2.2 of the reflection paper, there are opportunities to align changes for biologicals and small molecules. For example, under manufacture of an active substance (B.I.a.1), changes to quality control testing arrangements and replacement or addition of a site where batch control/testing takes place for biologicals (currently Type II, B.I.a.1 (J)) could be combined with the same change for small molecules (Type IA, B.I.a.1 (f)) as the same control of site selection and method transfer should be conducted for small molecules and biologics alike.

Regarding minor changes to an approved change management protocol (B.I.e.4/ BII.g.4), it should be feasible for the change to be maintained as Type IB, even if it is not strictly within the approved ranges, as long as it does not fundamentally change the strategy defined in the protocol *.

** additional footnote: See note 1 (BI.e.4/BII.g4): 'Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products'*

4. Minor variation categories for which the exclusion conditions related to biologicals should be removed (Annex of the Variation Classification Guideline - 2013/C 223/01)

In the current Annex of the Variation Classification Guideline (Guidelines 2013/C 223/01) several minor changes related to biologicals are precluded from the Type IA variation route due to the specific exclusion conditions listed. Consequently, manufacturers of biological medicinal products are obliged to follow the more prescriptive Type IB variation procedure (listed below) for such changes which have minimal or no impact on quality, safety or efficacy. We believe it is no longer justified to keep these exclusion conditions for several minor variations categories; for example, the following (non-exhaustive list):

- Change in the manufacturer of a starting material/ reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance/ (B.I.a.1)

    - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer
    - Changes to quality control testing arrangements for the active substance- replacement or addition of a site where batch control/testing takes place
    - Changes to quality control testing arrangements for a biological active substance: replacement or addition of a site where batch control/testing including a biological/immunological/immunochemical method takes place- Type II shall be deleted
- Changes in the manufacturing process of the active substance / a) Minor change in the manufacturing process of the active substance (B.I.a.2)
- Change in the qualitative and/or quantitative composition of the immediate packaging of the active substance (B.I.c.1)
- Addition of a new in-process test and limits applied during the manufacture of the active substance (B.I.a.4) or of the finished product (B.II.b.5)
- Any minor adjustment of the quantitative composition of the finished product with respect to excipients (B.II.a.3)
- Replacement or addition of a manufacturing site for the finished product (B.II.b.1)
- Change to importer, and batch release arrangements of the finished product (B.II.b.2)
- Minor change to an approved test procedure (B.I.b.2.a)
- Minor change in the manufacturing process of the active substance (B.I.a.2) or of the finished product (B.II.b.3)
- Changes to batch size (up to 10-fold increase or decrease) of active substance or intermediate used in the manufacturing process of the active substance (B.I.a.3) or of the finished product (B.II.b.4)

5. Small molecule active substance manufacturing site transfer

The example in this case relates to a transfer in active substance manufacturing from a Third Country site to an EU site for an oncology injection medicine (EU Centralised product). The global assessment began in 2010 and submission in the EU occurred in 2013 as grouping of Type IA and Type IB variations.

After approval in the EU, submissions were made in global markets. To date (2018) there are still a number of Third Country markets where the EU site is not approved (e.g. South Africa, Brazil, Turkey) due to long approval timelines or supplemental requirements, and for these markets the Third Country API source is still being used in the finished product. However, the Third Country site has now stopped manufacturing and the above markets are now at risk of stock-out in markets pending approval of the new EU source of active substance.

Thus, in this example the consequences for protracted approval times for post-approval changes outside of the EU are:

- Loss of economic activity at the EU active substance manufacturing site because of inability to supply certain global markets.
- A major supply chain bottleneck for the EU-based site, with potential for shortages of this oncology medicine in Third Country markets that have not approved the site change.

6. Post-approval Variation Requirements Inhibiting the Adoption of New Technology

Adoption of new technologies in manufacturing can enhance the assurance of quality and facilitate access to medicines. However, the Variations framework may inhibit the adoption of these innovative

manufacturing approaches, as was discussed in the meeting between EFPIA experts and the EMA NIR drafting team (7 June 2018).

This example relates to the adoption of modern analytical technology, such as online NIR process analysers, to generate information about the manufacturing process and product quality in real time. The requirements to submit variations for changes to, for example, model maintenance activities associated with the use of online NIR process analysers can result in the manufacturing site reverting to a traditional offline analytical method, if one is available, while waiting for approval of the updated online NIR analytical method. Consequently, a manufacturing site supplying global markets needs to manage the compliance and scheduling complexity related to multiple processes with the different analytical methods being used to make the same product. This complexity may negate the business case for adopting the modern analytical technology. In the case of continuous manufacturing, where it is essential to use online process analysers, it is not possible to revert to a traditional method, and thus manufacturing operations must be suspended until the Variation is approved in all countries where it has been submitted.

7. Regulatory reporting requirements for device-related changes in the EU

(*Ref. Appendix 2 EBE Reflection Paper 15 January 2018*)

The Variation classification guideline does not provide sufficient classifications for device-related changes for human medicinal drug-device combination products. Currently there is a lack of a suitable framework to manage device changes efficiently because the categorization of a change may treat the device component as a container-closure system or as a device, e.g. the syringe barrel of a Pre-Filled Syringe product. Therefore, there is a possibility of crossover or uncertainty between the two categories and this could also result in a higher classification being applied. This may require companies to consult with regulatory agencies to determine the appropriate approach for a Variation submission, leading to inefficiency and lack of predictability in the Variation process. Examples of these uncertainties are given below:

Summary of the change	Variation category	Submission strategy - Classification
Introduction of a new Pre-Filled Pen presentation (same pharmaceutical form, same route of administration)	B.II.e.1.b).2. Change in immediate packaging of the finished product, Change in type of container or addition for sterile medicinal products.	Type II variation
Prefilled syringe (PFS) with staked-in needle, where only the needle dimension changed.	B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging) b) The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product.	Type IB variation B.II.e.4.z (Unforeseen change)

Change in needle shield system to make it 'safe-sharp'. There was no change to the design of the device/needle or the delivery aspect of the device. There is no contact with product and no change to the IFU or product literature	B.II.e.6 - Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)	Type IA change

In this context, review of the following variations categories to include device-related changes, for example, would be beneficial:

- **B.II.e.1:** Change in immediate packaging of the finished product; composition of packaging material or change to/addition of a new container. This variation may apply to changes to a syringe-based container closure system that would also be classified as an integral administration device.
- **B.II.e.2:** Changes in the specification parameters and/or limits of the immediate packaging of the finished product.
- **B.II.e.3:** Change in test procedure for the immediate package of the finished product.
- **B.II.e.4:** Change in shape or dimensions of the container or closure (immediate packaging).
- **B.II.e.6:** Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)).

Furthermore, the implementation of ICH Q12 should offer further opportunities for the implementation risk-based approaches to the management of changes to Drug-Device Combination products.

8. Further Examples of Minor Challenges with the Current Variations Regulation

- Some changes that are not foreseen in the Classification Guideline are required to be submitted as Type IB – z) other variation by default. Some examples of default IB (z) applications include *B.II.b.3 (z) Type IB Removal of overages* and *B.II.d.1 (z) Type IA Change in Description of finished product in release and stability specifications (removal of odour test)*. In some cases, the changes are considered minor and should perhaps be classified as a Type IA(z), which is currently only possible further to a specific recommendation under Article 5 of the Regulation. Therefore, reconsideration of the categories and conditions in the Variation Classification Guideline, to make sure that such changes are appropriately classified at the outset would be welcomed.

- The revised regulation could also address handling minor Type IA changes previously implemented but which are not submitted to the regulator immediately or within a year, as applicable. In practice, these changes are generally upgraded to Type IB, which is not specifically foreseen in the regulation and introduces additional complexity in handling of minor, sometimes administrative changes.

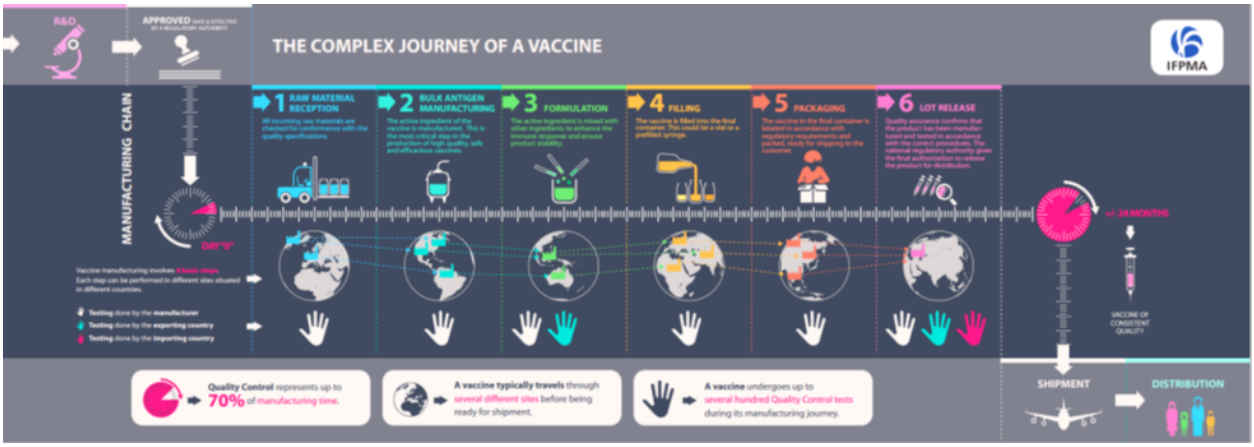
- The current timeline for assessment of a Type IB variation is 30 days. When a Type IB variation is submitted through a worksharing procedure, the timeline is 60 days. As described on the EMA

website, the total time for a worksharing variation can be reduced in case of safety emergency. We therefore also propose that the assessment of a Type IB in worksharing is reduced to 30 days in case of potential supply impact.

B - Vaccine-specific data, examples and case studies

9. Overview: The complex journey of a vaccine - how does the regulatory complexity (and lack of worldwide alignment) impact the supply and availability of medicines to patients?

Major vaccine manufacturers are global in nature, however many of their research and development (R&D) activities are based in Europe as well as the majority of their critical manufacturing operations. The complexity of vaccine manufacturing requires highly technical facilities, equipment and controls; vaccine production sites are therefore limited geographically and usually used for worldwide supply. The total lead time for the production and shipment of a vaccine dose is approximately 24 months on average.



Source: IFPMA 2016 Paper "The complex journey of a vaccine Part One"

Usually, the same production line is used to supply a large number of different markets (within and outside the EU) and before an improved vaccine (i.e. a vaccine including the variation) can be distributed, the variation must be approved by each regulatory authority in the countries of destination within and outside of the EU. There are significant differences in approval timelines worldwide: from 6-month timelines in a 1st group of countries – i.e. those with the most advanced regulatory systems and agencies (corresponding to 10% of the target population), to 24 months in a 2nd group of countries (corresponding to 40% of the target population), up to 48 months in countries with the least advanced systems and agencies (corresponding to 50% of the target population).

These approval differences can have serious consequences on patient access to medicines and security of supply. Indeed, due to the length and complexity of the production process of vaccines, and the limited production capacity, manufacturers often cannot simultaneously maintain two (or more) separate manufacturing processes (one for the original vaccine and one for the improved vaccine).

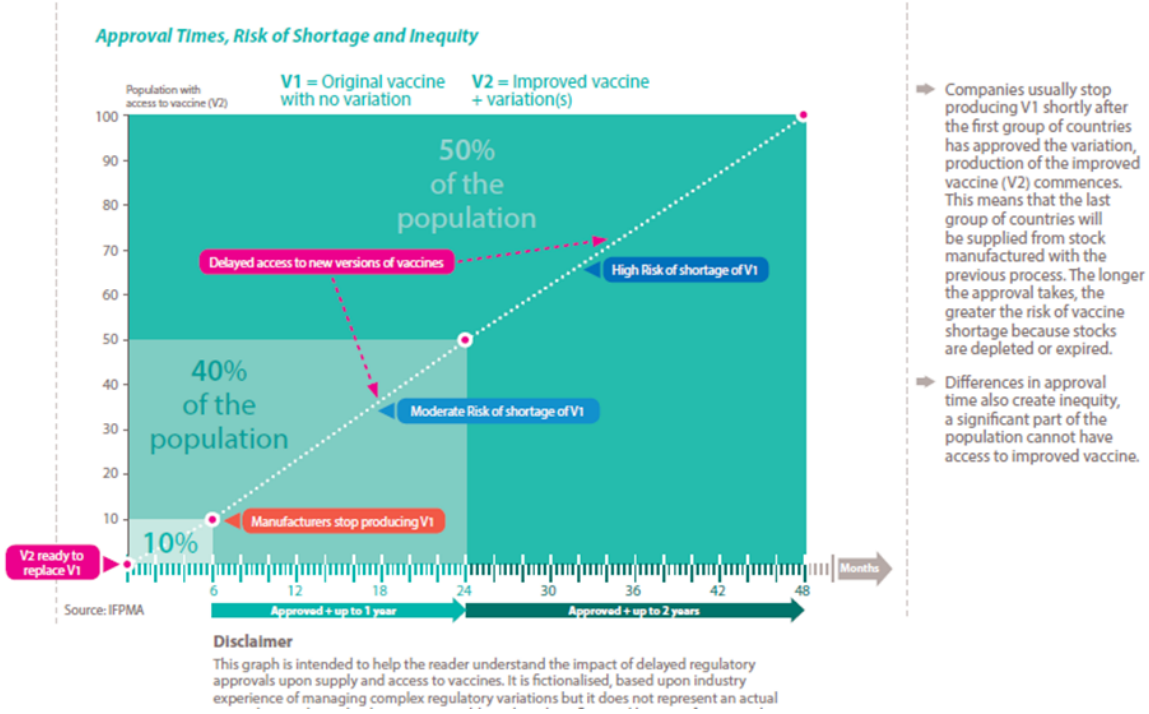
Vaccine manufacturers are therefore faced with the following options, none of which is ideal nor possible in all circumstances:

- **Option 1:** Stop production of V1 (original vaccine prior to variation) and implement vaccine V2 (improved vaccine including the variation). Vaccine V2 can only be made available in the countries where it is approved. There is a risk of shortage for people in countries where the variation is not

approved when stocks of V1 run out. This option is the one most often followed, but it does not support fair and equitable access to vaccines on a worldwide scale.

- **Option 2:** Continue production of V1 until the variation is approved worldwide, even though this means delaying access to an improved vaccine for the entire global population. Option 2 is not always possible; if the variation has been developed to meet new standards, manufacturers cannot (and are not allowed to) wait for all countries to have approved the variation as they may undergo inspections of their site that will verify that the variation has been implemented. Option 2 may also not be feasible in situations where regulatory agencies require the variation be implemented immediately upon approval in their country.

- **Option 3:** Continue the production of V1 and V2 at the same time. This can put the supply chain at risk due to the increased complexity of maintaining more than one process and the need to restrict V2 to the countries where it has been approved. This option is typically not feasible for vaccines, because manufacturers do not have the capacity to operate two separate production lines.



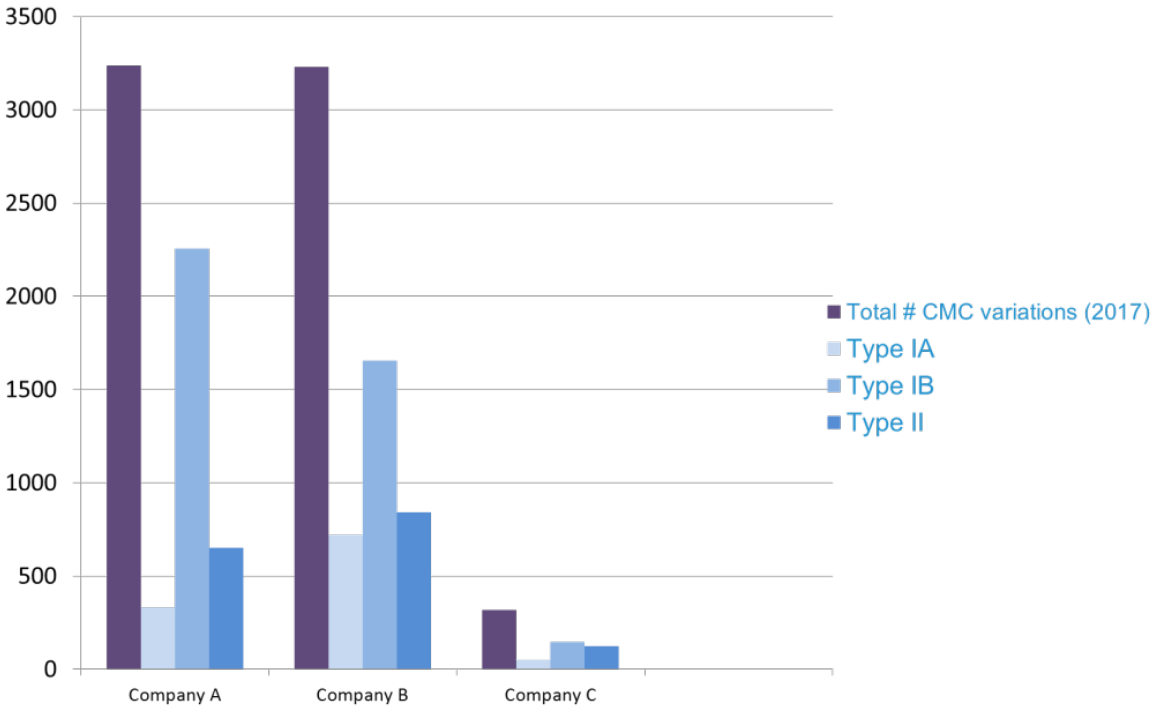
Source: IFPMA 2016 Paper "The complex journey of a vaccine Part One"

The overview given above uses data from vaccines to illustrate the point. However, a number of medicinal products other than vaccines are facing exactly the same challenges.

10. Case study: Snapshot on 2017 statistics:

- 6,000 to 8,000 worldwide variations / year / company
- 40-60% of World-Wide variations are submitted in the EU
- About 60% of countries outside the EU require the EU approval as a reference at submission or at time of approval

- Classification of vaccine-related CMC variations in the EU (see graph below):
  - In general, 80%-90% of variations are greater than Type IA
  - Most variations are Type IB
  - In lot of situations, variations on biologicals are upgraded to Type II
  - Approximately 30% of submissions are related to analytical changes.



Source: PDA EU conference on Vaccines in Malaga in April 2018

- Post-Approval Change Management Protocols (PACMPs) are useful, but do not reduce the number of Variations that companies and regulatory agencies must process
- Established Conditions would be a key enabler in Q12 to reduce this effort and complexity for post-approval changes
- Please note that the overall differences between companies A, B and C represents the differences in the size of the vaccine portfolios at each of the companies, respectively.

The case study given above uses data from vaccines to illustrate the point. However, exactly the same issue arises with medicinal products other than vaccines.

11. Example on the impact of Worldwide approval of a variation on the Implementation Date in the EU:

- In this example, a Type II variation was submitted in the EU in November 2013 (and approved in the EU in February 2014) to accommodate a change in an analytical procedure of a conjugated Hib (*Haemophilus Influenzae* Type B) vaccine in bulk and final container.
- The objectives of the proposed change in the test procedure were:
  - reduce result variability and 'false' risk of out of specifications results
  - increase reproducibility of results generated by the National Control laboratory

- Maintaining two tests in parallel is complex and even not possible when many analytical methods are changed: not practical, long release times, more costs, and ultimately potentially impacts supply
- The only solution is to delay implementation until the change is approved in the majority of countries of destination (i.e. February 2016), including for the EU.

The above example uses data from vaccines to illustrate the point. However, exactly the same issue arises with medicinal products other than vaccines.

12. Example of the complexity in the management of type IA variations impacting multiple vaccines:

In 2017, in the context of 4 minor analytical Type IA variations impacting multiple vaccines, a company had to submit the same series of grouped changes through multiple groupings and via different procedures depending on the different marketing authorization statuses and countries, as follows:

- Products under CP: submission of 43 Type IA variations
- In 2 countries under MRP/DCP: submission of 46 Type IA variations
- In one country under national procedure: 177 Type IA variations
- In 29 other countries under national procedures: submission of 182 Type IA variations

It was not possible for the MAH to avoid this huge number of Type IA variations due to the current EU regulatory framework. A system, similar to the worksharing procedure (not applicable to Type IA today), would have significantly streamlined the submission process and avoided such a regulatory burden for minor Type IA changes (with no or minimal impact on quality, safety or efficacy), which ultimately could be easily managed through the company's internal PQS.

13. Example of how a minor change in the manufacturing process of a vaccine Antigen have to be handled as a Type II variation due to item 2(e) of Annex II of Reg. (EC) No 1234/2008 and the exclusion condition in the Guidelines

The company proposed to put in place a reprocessing step during the inactivation process performed as part of the manufacturing of IPV Inactivated Polio Virus) monovalent bulk antigens. In case of an exceptional technical event justifying the need for an additional filtration, the proposed change is meant to allow one repeated filtration at any of the three successive filtrations performed during the inactivation step. The change is foreseen for production of the three types of IPV monovalent bulk antigens (Types 1, 2 and 3) and for all registered facilities.

In accordance with what is foreseen in the EU Classification Guideline, the change must be submitted under category B.I.a.2 ["Changes in the manufacturing process of the active substance"]; sub-category c) ["The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol"]; for which the only variation procedure foreseen is a Type II.

This is a clear example of a minor change with no or minimal impact on the Quality, Safety and Efficacy of the final vaccine, which has to be submitted under the major variation procedure category (Type II). This is a consequence of item 2(e) of Annex II of Reg. (EC) No 1234/2008, which does not allow for more granularity in the EU Variations classification guideline (i.e. Type II classification in any circumstances). A Type II results in longer review timelines and in the need for extensive assessment by regulatory authorities, hence increased resources.
It should be noted that in contrast, the reporting category according to the WHO guidance for the introduction of such a reprocessing step is Type N, which corresponds to a minor change that must be notified immediately to WHO (N stands for "immediate notification").

14. Example of a minor change concerning the manufacturing facilities of a biological active substance (a vaccine antigen) which has to be handled as a Type II variation due to item 2(e) of Annex II of Reg. (EC) No 1234/2008 and the exclusion condition in the Guidelines

In this example, a virus stock seed is a process input to the manufacture of a virus antigen bulk. Currently, all stock seed batches are produced in one facility. In order to ensure supply of the antigen bulk, another facility is being added as an alternative source of virus stock seed. This additional facility is already licensed for the manufacture of the antigen bulk. No diagram or facility changes are required with the addition of the virus stock seed manufacturing process. The virus stock seed manufacturing process has been designed to be comparable to the manufacturing process in the current facility. Nevertheless, subtle process changes will need to be implemented to align the stock seed process with the virus antigen bulk facility procedures (example: use of Cell Culture Stacks instead of T-flasks, use of larger volumes of Stock Seed Media, the pooled virus would be dispensed into sterilized PET bottles instead of glass bottle). Of note, no changes are made to the current virus stock seed release specifications and procedures because of the facility addition. According to the Variation Classification Guideline, the addition of the new facility for the manufacture of the stock seed and the related minor adaptations to the manufacturing process would be considered as Type IA(IN) variations for small molecules (B.I.a.1.a and B.I.a.2.a, respectively) but, as the active substance is a biological/immunological substance, they theoretically must be submitted as Type II variations (B.I.a.1.e and B.I.a.2.c, respectively), except if a downgrading of the categorization may be pre-agreed with the Reference Member State (this vaccine being registered according to the Mutual Recognition Procedure). Of course, there might be some variability in the appreciation of the categorization, depending on the RMS and on the procedure manager, which in turn makes the timing for approval and implementation hardly predictable, with a possible impact on supply, not only in the EU but also in all countries outside the EU which rely on the approval in the source country.

15. Example of how a minor change in the manufacturing process of a vaccine Antigen must in principle be handled as a Type II variation due to item 2(e) of Annex II of Reg. (EC) No 1234/2008 and the exclusion condition in the Guidelines

Below, two examples of variations submitted in 2016, and related to minor changes in the manufacturing process of biological active substances (Antigens) of two vaccines approved under Mutual Recognition Procedure (MRP):

i. In the case of a meningococcal vaccine, the MAH wanted to register a new type of filter (disposable encapsulated filter), as an alternative to the Cartridge filters currently used for the medium preparation and the in-depth filtration steps in the manufacturing process of two antigens. In accordance with Commission Guideline 2013/C 223/01, this type of change should be submitted under category B.I.a.2 ["Changes in the manufacturing process of the active substance"], sub-category c) ["The change refers to a biological / immunological substance or use

of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol"]; for which the only variation procedure foreseen is a Type II. This is again an obvious example of a minor change with no or minimal impact on the Quality, Safety and Efficacy of the final vaccine, which must be submitted under the major variation procedure category, because of item 2(e) of Annex II of Reg. (EC) No 1234/2008. As already said in previous examples, a Type II results in longer review timelines and in the need for extensive assessment by regulatory authorities, hence increased demand in resources.

ii. In the case of a rabies vaccine, the MAH wanted to register an additional filter system for the filtration of rabies virus suspension. The additional filter system was identical to the one already described in the initial dossier and was only meant to be used for a second filtration in case of need, to complete the filtration within the maximum filtration time. Similar to the example (i.) this type of change should in principle be submitted under category B.I.a.2.(c) in accordance with Commission Guideline 2013/C 223/01; which requires a Type II variation procedure.

Of note: *in these two examples (i) and (ii), it was agreed in negotiations with the respective RMSs (UK and Germany), that the variation could be submitted under B.I.a.2.a [N.B. sub-category (a) "Minor change in the manufacturing process of the active substance"] and processed as a Type IB due to condition 5 ("The active substance is not a biological / immunological substance"). This shows that when scientifically justified, certain authorities in the EU have become open to some pragmatism, even though this is not strictly in line with Annex II of the Regulation. Indeed, such interpretations deviating from the law carries a risk for the company to be confronted with a different regulatory decision by another EU authority which would apply the law more "stricto sensu". Misalignment among different agencies could lead to complications and potentially further delays for the approval under MRP.*

16. Example of how minor changes in the manufacturing process of the finished product has to be handled as Type IB variation for biologicals and vaccines (instead of 1A) due to the condition excluding biologicals product *(variation category B.II.c.4 "Change in synthesis or recovery of a non-pharmacopoeial excipient")*

The company sought EMA regulatory advice on the classification of an upcoming change to a purified immunoenhancer derived from an aqueous extract of the bark of the tree *Quillaja saponaria Molina*, which is a component of adjuvant systems manufactured by the company and is also included in the adjuvant system used for several other vaccines.

The company wanted to notify the replacement of a filtration membrane and a chromatography resin used in the purification process of this immunoenhancer (i.e. change from current suppliers to new suppliers, because the current suppliers have stopped producing the filtration membrane and the chromatography resin used in the purification process of the immunoenhancer). The Company intends to submit a Type IB (B.II.C.4.a.) variation by default as Condition 2 is not met (i.e. Adjuvant are excluded).

17. Example of how a minor change, unforeseen in the current EU classification guideline has to be handled as Type IB variations for biologicals and vaccines (instead of 1A):

The company is proposing to implement the use of a closed system for sampling/distribution outside of isolator. The aim is to reduce the use of isolators during formulation operation and align with practices for the other formulations operations performed in the same facility. The manufacturing process remains unchanged and there is no additional validation data required. The sampling for testing in scope of this change pertains to the antigen final bulk, the adjuvant final bulk and the concentrated liposomes bulk (CLB) intermediate; the distribution procedure in scope of this change pertains only to the CLB

intermediate. The manufacturing process and the facilities where the different operations take place will remain the same.

The Company's proposed to submit a Type IA variation to submit the impacted CTD sections even if the change is covered under the Company's quality management system and does not require a variation as such. However, the EMA requested for the submission of a Type IB B.II.z as the Variation is not classified in the variation Classification Guideline or Article 5.

18. Example of how minor changes in test procedure used in the manufacturing process of a vaccine Antigen have to be handled *as Type IB variations (instead of 1A) for biologicals and vaccines according to the EU classification*

The example relates to a change in the validity criteria for a QC Release testing of antigen content (ELISA test) in the Drug Substance and Product levels.

According to the Annex of the EU Guidelines, the change should in principle be classified as Type IA under sub-category (a) *"Minor changes to an approved test procedure"* if all conditions are met. However, Condition 4 can never be met in the case of a vaccine *("4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance…").*

As a consequence, the change is classified as Type IB (by default) for an antigen/vaccine in the EU, and the company has to follow the *"tell-wait-and do"* submission procedure, which results in a supply delay of at least one month (and potentially more if authorities have any questions during their assessment), due to the waiting period prior to being authorised to implement the change in the production line.

A one-month delay in the supply chain could potentially lead to significant concerns from a public health perspective, not only in the EU but also in all countries outside the EU which rely on the approval in the source country.

19. Example of how minor changes to an approved test procedure have to be handled in the EU, and the impact at worldwide level:

The change relates to a test procedure aiming at confirming the absence of infectious agents using an animal model. This test is performed on cell banks, intermediates and bulks, depending on the product (this test is performed on 6 different vaccines).

A change in the analytical assay procedure to align with existing EU, US-FDA and WHO guidance as well as Ph.Eur. and USP, with a view to reducing the number of animals used. There were no changes to the specifications.

The company introduced the change at global level, with submissions in the EU, Latin America, Middle East and Asia Pacific countries and including:

- Method update
- Current CoA and declaration explaining what would change
- Justification and rationale for change
- Comparison of guidance documents for proposed change

The change was submitted in the EU as a Type II variation (under category B.I.b.2.d), in accordance with the EU guideline on variations. [Of note: the same change for a small molecule would have been classified as Type IA (B.I.b.2.a), according to the EU guideline].

According to the WHO guideline (specific for the vaccines), this change would be considered as a "Minor" variation *(category 18.f: "Change from an in-house analytical procedure to a recognized compendial/pharmacopoeial analytical procedure")*.

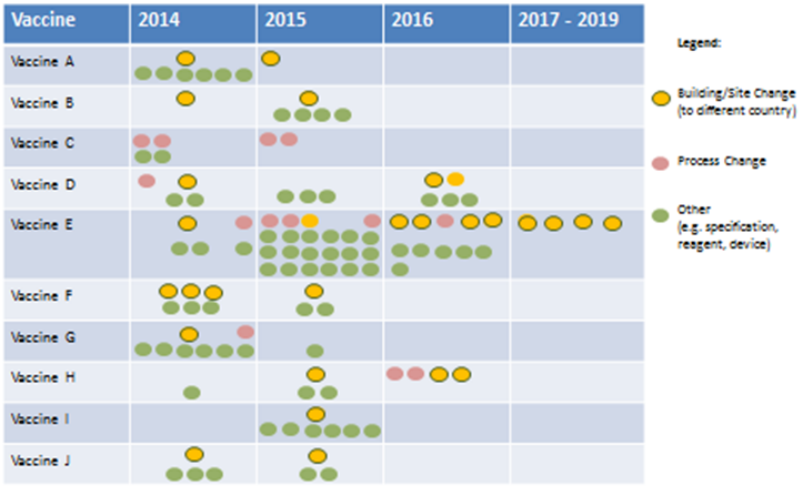
The stringent EU classification has also global impact outside the EU: in this example, the same submission package as for the EU was submitted in Brazil. The approval by the Brazilian Health Authority, ANVISA, was granted after 8 months for 3 products (out of 6), after 18 months for 2 of the remaining products, and is still awaiting approval for the last one (after more than 3.5 years).
As a consequence, the company has not been able to implement the change yet, and the old test method is still used in the EU, pending approval for one product in Brazil.

20. Case Study: Multiple Post-Approval Changes to Vaccine Products submitted at a worldwide scale:

This case examines how vaccines can undergo a significant number of Post-Approval Changes (PACs) submitted worldwide. In the long run, vaccines journeys become very complex and unsustainable.

The case study shown below is a snap-shot from 2013/2014 projecting the PACs needed for a range of vaccine products over 3-4 years. The PACs are broadly classified into those impacting buildings/sites, the manufacturing process, and others (such as specifications, reagents, devices).

Multiple and overlapping technical changes
(examples of Vaccine Products – a view from 2013/2014)



This case study shows that many vaccines (often combinations) have multiple PACs in one year. Given that each change can potentially impact 50-100 licences worldwide (as vaccine products are often registered widely) it is easy to understand how a vaccine company can file for thousands of PACs each year.

This case study shows that many of the PACs involve manufacturing site and building PACs. As millions of doses of vaccines are produced to supply large immunisation programs, new sites of manufacture are often introduced to ensure supply of these doses and to maintain state-of-art processes. In total, across all the products, twenty-six building/site PACs are shown (though many will be the same site, as the same building is used for multiple products). Given that such PACs often impact many licences, this represents approximately 1300-2000 building licence PACs alone around the world (based on 50-75 licences per

product). As each new manufacturing site change can take around 5 years to be approved globally, in some countries patients won't have access to the product from the new site for at least the first five years after its first registration. This 5-year period is long enough for other PACs to be filed for maintaining state-of-the-art processes and innovation.

The result of this is that vaccine companies submit multiple PACs to many licences worldwide that are overlapping or partially overlapping in time. A single change can be assessed numerous times by different authorities globally, each of them taking different times to assess and approve (in some cases, between 24 to 36 months). This requires high levels of supply chain management to track PACs in the product to ensure that the product released matches its registered details in a given country. It also means that multiple variants of the same product need to be produced and handled to ensure supply of vaccine products worldwide. This case study illustrates the significant number of PACs being submitted worldwide. A single regulator only sees a fraction of these PACs but the global picture is complex with multiple PACs at different stages. Ultimately, the regulator and the vaccine manufacturer aim to supply high quality, well tolerated and effective vaccines, manufactured using processes that are continuously improving to keep up to date.

The current systems and approaches of submitting multiple PACs worldwide that are assessed repeatedly during a period of 3-5 years is not sustainable.

3.1 ANNEX 1 Addendum. Vaccines are the medicines category that would benefit the most from changes to the EU Variations Regulation

Vaccines are the medicines category that would benefit the most from changes to the EU Variations Regulation.

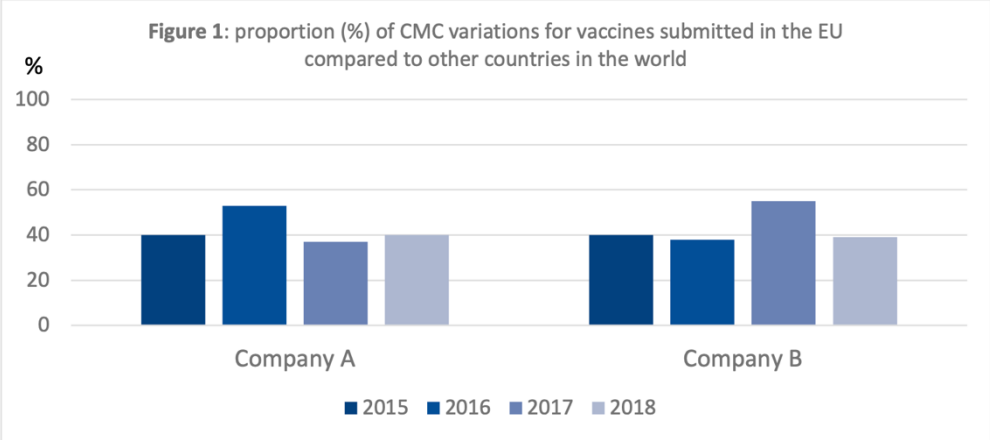
The analysis hereafter is based on metrics from 2 major European Vaccine companies ("Company A" and "Company B") which are distributing large portfolios of vaccines around the world for many decades. *[N.B. Companies A and B, are both operating multiple types of medicinal products (small molecules, biologicals and vaccines)]*

This analysis shows that the EU Region requires the largest number of CMC variations per vaccine than any other region of the world and these are mainly variations of Type IB or Type II resulting in a huge administrative burden. The number of CMC variations specific to vaccines is also significantly higher compared to numbers of CMC variations for any other types of medicinal products (in the EU and worldwide).

This is why we believe that Vaccines are the medicinal product category that would benefit the most from changes to the Variations Regulation and such changes, if introduced, would help secure the future supply of vaccines in the EU and worldwide.

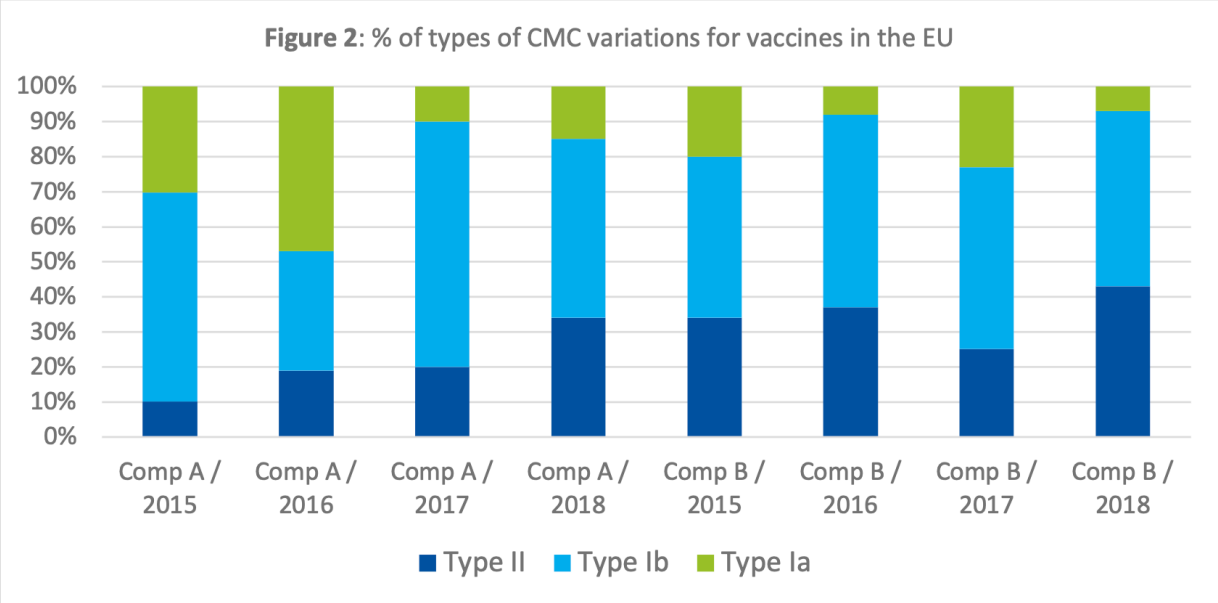
VARIATIONS IN THE EU VS REST OF THE WORLD

Approximately 40% to 50% of worldwide CMC variations for vaccines are submitted in the EU compared to other countries in the world. This represents about 2000 to 4000 variation dossiers submitted in the EU depending on companies and years.



VARIATIONS TYPES FOR VACCINES IN THE EU

Figure 2 below, based on metrics from the two major vaccine companies (A and B), shows that the vast majority (70% to 90%) of CMC variations in the EU are Type IB and Type II variations.



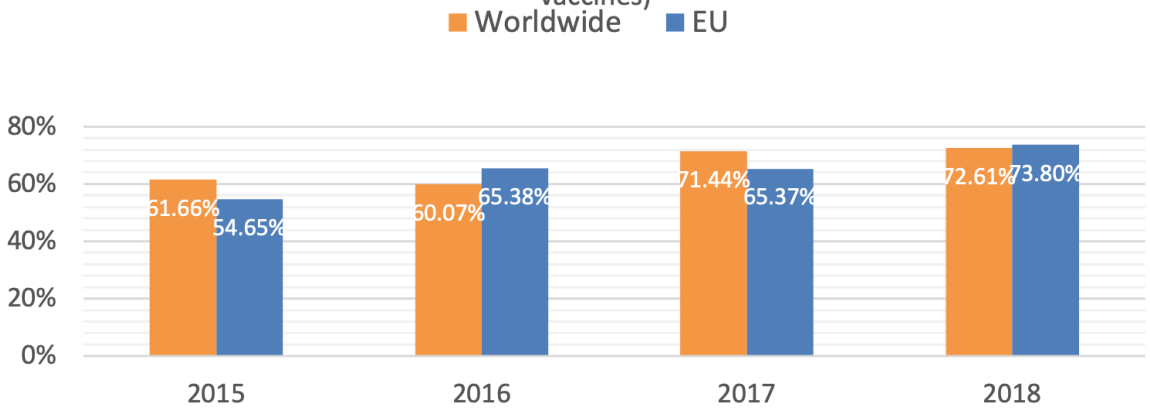
PROPORTION OF VACCINE-RELATED VARIATIONS VS OTHER TYPES OF PRODUCTS

Figures 3.a and 3.b below, show the proportion of CMC variations specifically related to vaccines in comparison to other products submitted on a yearly basis by Companies A and B, which are both operating multiple types of products (small molecules, biologicals and vaccines).

[Of note: whilst the number of vaccines operated by both Companies (A and B) represents only 10-15% of their total number of products respectively, it is obvious that these vaccine portfolios alone generate most CMC variations for both companies.]

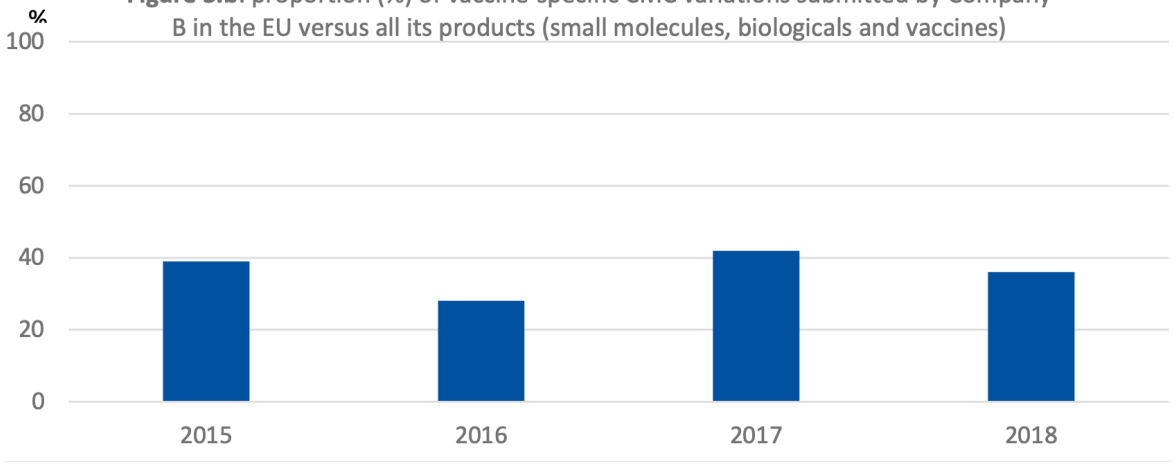
- For Company A (see Figure 3.a), vaccine-specific CMC variations represent 55% to 75% of the total number of CMC variations submitted every year in EU and worldwide across all products operated by the company (small molecules, biologicals and vaccines).

Figure 3.a: proportion (%) of vaccine-specific CMC variations submitted by Company A versus all its products (small molecules, biologicals and vaccines)



- For Company B (see Figure 3.b), vaccine-specific CMC variations represent 30% to 40% of the total number of CMC variations submitted every year in the EU across all products (small molecules, biologicals, vaccines)

Figure 3.b: proportion (%) of vaccine-specific CMC variations submitted by Company B in the EU versus all its products (small molecules, biologicals and vaccines)



In addition, Table 1 below shows that, out of the top 5 medicinal products which generated the largest number of CMC variation submissions worldwide for Company B, 3 were vaccines. Out of those 3 vaccines, the first one (vaccine A) has first been licensed more than 20 years ago. Those data illustrate that CMC variations are not driven by the most recently licensed vaccines but well-established products are also generating huge number of CMC variations.

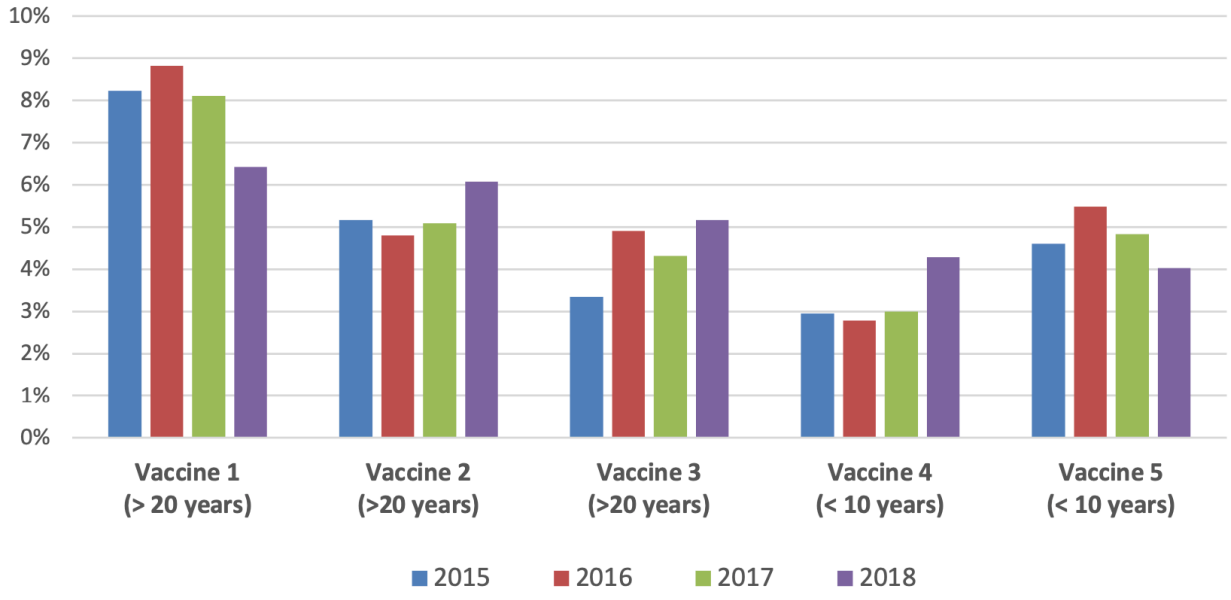
Table 1: top 5 products generating the highest number of worldwide CMC variations for Company B

Top 5 submissions in 2018	No. Of variation dossiers (WW)
Bio drug	846
Vaccine A	447
Small mol drug	385
Vaccine B	356
Vaccine C	352

WELL-ESTABLISHED VACCINES VS RECENT VACCINES

Figure 4 below shows a comparison of % of CMC variations submitted worldwide for 3 well established vaccines (> 20 years on the market) Vs 2 more recent vaccines (< 10 years on the market) for Company A. These data show that all vaccines, irrespective of whether they have been recently licensed or not, are generating a large proportion of CMC variations every year.

Figure 4 : Comparison % CMC variations (for Company A) per year for well established vaccines (> 20 y) **Vs** recent vaccines (< 10 y)



SUMMARY AND CONCLUSIONS

In summary, the above vaccine-specific metrics show that:

- Vaccines represent a very significant proportion of all CMC variations submitted in the EU and Worldwide, compared to any other types of medicinal products (small molecules or biologicals).
- EU is the Region with the largest number of CMC variations for vaccines compared to in the rest of the world.
- In the EU, Type IB and Type II variations represent the vast majority of CMC variation types compared to type IA variations for vaccines.
- All vaccines, irrespective of whether they have been recently authorized or are well-established ones (>20 years on the market), are generating a large number of CMC variations every year.

Hence, revising the EU regulatory framework for variations is expected to significantly decrease the burden resulting from the huge number of CMC variations for vaccines. Considering the high degree of complexity and timing for manufacturing, controlling and releasing vaccines, we assume that vaccines likely represent the category of medicinal products which would benefit the most from a revision of the EU variations system. Such a revision would help securing the supply of vaccines to populations who need them in the EU and worldwide.

3.2 ANNEX 2 Why is now the right time to modernise the EU variations system (link)

INDUSTRY ASK

The pharmaceutical industry calls to modernise the current variations system to reflect the evolution in technology and regulatory needs. The targeted amendment of the EC Variations Regulations 1234/2008 and Variations Classification Guideline shall be considered under the mandate of the new European Commission 2019- 2024.

EXECUTIVE SUMMARY

The current regulatory framework for maintaining products on the market needs to continue evolving to better reflect the scientific progress and operational efficiency in line with the spirit of Better Regulation which aims to balance regulatory objectives with the need to reduce administrative burden for companies and authorities. Raising efficiency and streamlining regulatory processes will bring tangible benefits for all participants in the healthcare network of patients, regulatory authorities and the industry.

After over 10 years of experience of the Variations Regulation (Commission Regulation (EC) No 1234/2008), it now appears appropriate to assess how far the objectives of Better Regulation have been achieved and what has changed, and to reflect on possible improvements of the variations' framework.

The following experience has been gained by the Industry over last 10 years:

- Disproportionate resources are allocated to the variations process in view of the overall benefit for patients and the entire regulatory system:
  - Based on data gathered from 2010-2018[5], the number of variations per MA and per year appears to have increased about 75% since 2010.
  - Over 50% of the total number of variations submitted to the Competent Authorities are minor changes (Type IA Variations and Notifications), engaging a lot of resources from both regulators and the industry, to process these minor, mainly administrative submissions without scientific assessment and without any real added value for patients.
  - By reducing the average time spent on the type IA notification process in general, as well as lowering the volume by changing the way of reporting, approx. 65% of the current

[5] *Data collected among the members of Medicines for Europe*

effort could be saved/resources could be used differently on activities more meaningful for public health[6].

- While it is essential to provide full oversight and transparency of the supply chain and product flow to the competent authorities, the current way of handling the maintenance of API related information discourages companies from registering more alternative API suppliers to mitigate shortages.
- The Regulation 1234/2008 was adopted at the time of relatively low digitalisation of the regulatory operations. Over the last 10 years, the regulatory environment has evolved significantly with regards to available IT tools and on-going telematics projects (i.e. mandatory eCTD, e-Application Form, CESP, Art 57 database, SPOR/ISO IDMP; FMD and e-leaflet).
    - The effective use of IT systems can be a powerful enabling tool for regulatory efficiency in the processing of variations across the EU Network.
    - Digital solutions offer enormous opportunities to report minor, mainly administrative changes to the Mas by the MAHs directly to the databases, with the Competent Authorities having full access to the content. The example of changes related to the QPPV and the location of the PVSMF, which can be submitted to the Art 57 database only, is to be followed and explored for other situations.
- Optimisation of the EU regulatory variations could be achieved by maximising the opportunities of the SPOR database and the PMS Target Operating Model (TOM) concept.
- Many concepts created in 2008, such as work-sharing procedures, grouping, Article 5 recommendations, are of great benefit. However due to certain constraints, are not yet used to maximum effect.
- The current Variations framework needs to evolve further to facilitate the continual improvement of manufacturing processes and the adoption of innovative manufacturing technologies, especially in the context of global supply chains (i.e. ICH Q12).
- The Annex of the Variations Classification Guidelines should be revised regularly to reflect scientific progress and to implement the Art 5 recommendations:
    - To consider the Variations Classification Guideline to be the EMA/HMA (CMDh) guideline, instead of the EC guideline in view of more regular/frequent updates (around 50 recommendations to Art 5 have already been issued but the guideline has not amended).
    - To extend risk-based approaches to variation categorisation for well-characterised biological medicinal products or herbal medicines by removing the default classification of manufacturing changes major variations of Type II, and the specific exclusions that preclude the use of the Type IA variation category.
    - To develop a new vaccine-specific annex to the EU Variations Guideline modelled on the WHO "Guidelines on procedures and data requirements for changes to approved vaccines" to promote international alignment of regulatory requirements for post-authorisation lifecycle management.
    - To ensure the new Medical Devices Regulation requirements are properly reflected in the Variations Classification guideline.

3.3 ANNEX 3: Application of Flexible Mechanisms

[6] *ROG BUSINESS CASE Business Case No. 1 Optimisation of selected type IA variations, Feb. 2017*

FOLLOW-UP RESPONSE TO THE EUROPEAN COMMISSION'S REQUEST FOR FURTHER DETAILS AND BACKGROUND INFORMATION FOLLOWING THE CROSS-EU PHARMACEUTICAL TRADE ASSOCIATION MEETING ON 06 MARCH 2019

Question i):

Are existing mechanisms that offer some flexibility in the EU such as Design Space Mechanisms and post-approval change management protocols (PACMPs) currently under-utilised by Industry, and if so, why?

Industry Response:

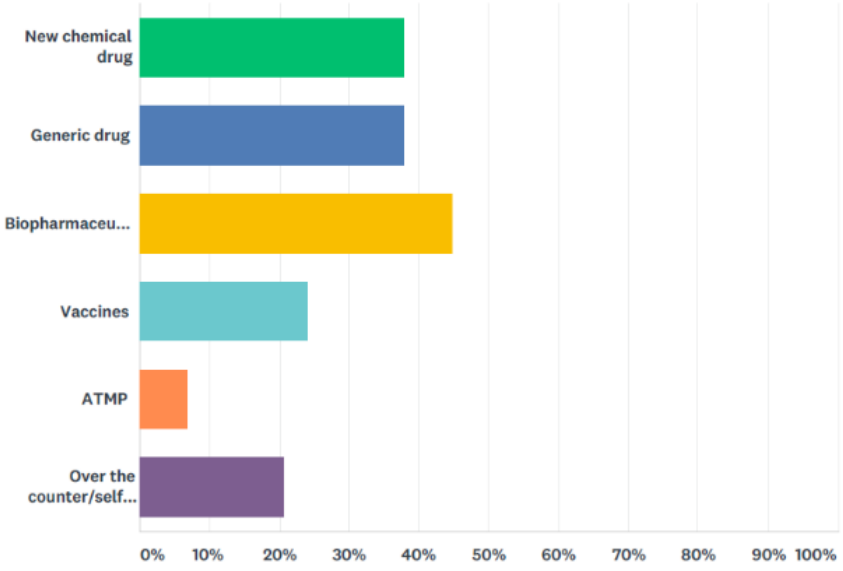
Industry welcomes the opportunity to address the EU Commission's questions on the use of Design Space and PACMPs and to provide data from companies supplying innovative, generic and over-the- counter medicines, vaccines and advanced therapies.

In order to address the Commission's questions, EFPIA completed a survey of the views of companies who submit marketing authorisation applications (MAAs). Two short surveys were organised by EFPIA to establish the experience and viewpoints of EFPIA, Vaccines Europe, Medicines for Europe, and AESGP member companies with Design Space and PACMPs This is a short summary of the outcomes of that survey and includes recommendations from EFPIA/Vaccines Europe and Medicines for Europe for the Commission's consideration.

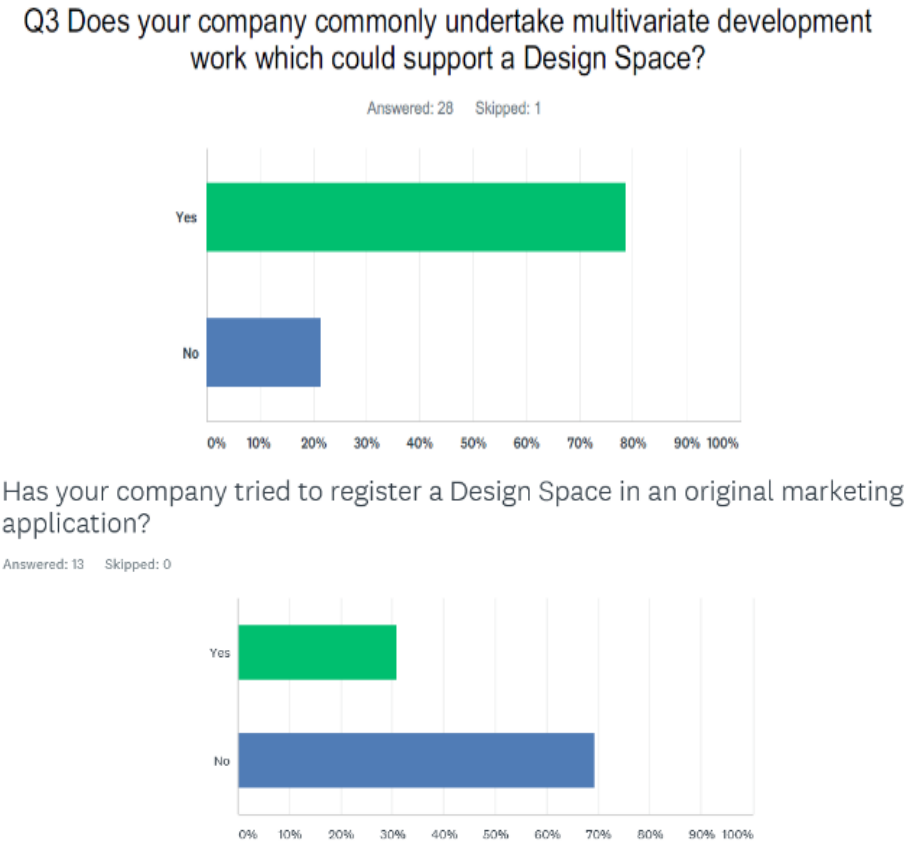
In order to allow for the fact that some companies may have different experience with both design spaces and PACMPs for the different products they supply, companies were able to answer separately for the different product types (e.g. new chemical drugs, vaccines, biopharmaceuticals, ATMPs etc).

i. Design Space Survey

In total, for the Design Space survey, there were 29 responses to the survey from 20 companies. As shown in the figure below, the responses received covered new chemical drugs, biological drugs, vaccines, ATMPs, generic and over the counter medicines.



In summary, the survey showed that the majority of the 29 respondents (79%) commonly undertake multivariate development work which could support a Design Space. However, only 31% of respondents had tried to claim a Design Space in an MAA and only 10% (one response) claimed a Design Space in a variation.



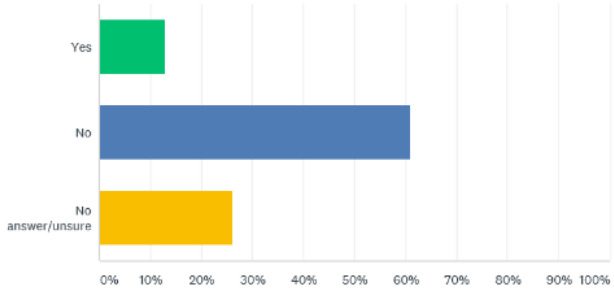
The data indicated that Design Spaces were most likely to be claimed for new chemical drugs, with 63% of responses indicating that a Design Space had been claimed in an MAA.

Respondents were also asked to explain why they had not claimed Design Space and to comment on what might make them more likely to do so. Only 13% (1 response) felt that expectations for design space in EU were clear, with 61% of responses stating that requirements are unclear.

Equally, 83% of responses indicated that companies feel that the use of the term Design Space brings additional complexity to review of the application, and no responses indicated the view that EU assessors had been consistent with expectations for Design Space over the last 5-10 years.

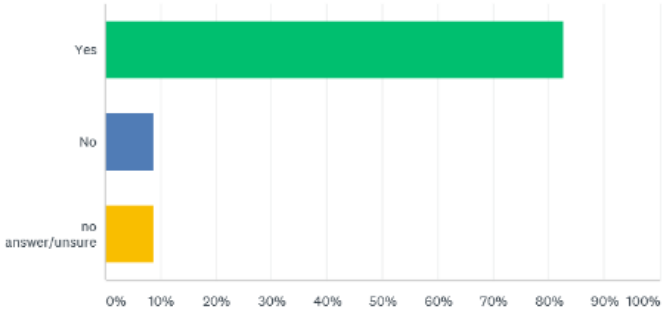
Does your company feel expectations for justification of design space in EU are clear?

Answered: 23 Skipped: 6



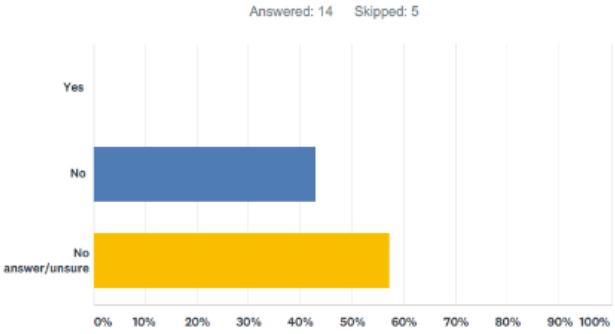
Does your company believe that the use of the term Design Space brings additional complexity to review and approval of the application?

Answered: 23 Skipped: 6



Q15 Has your company seen consistency in regulators' (EMA and/or member states') expectations for design space over the last 5-10 years?

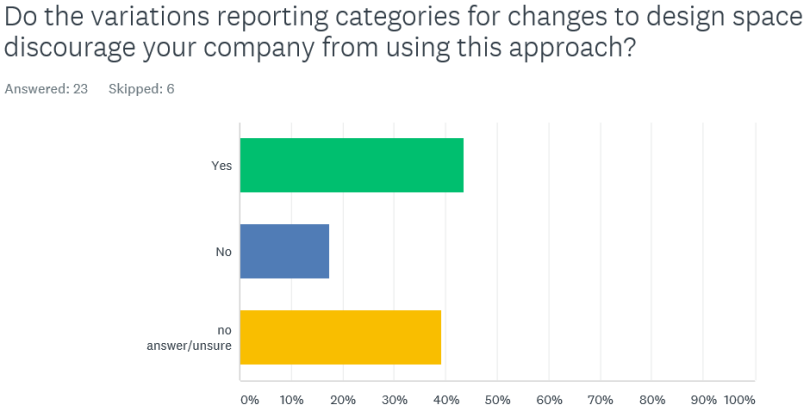
Answered: 14 Skipped: 5



Respondents were evenly matched between those who felt that the development of Design Space was worth the resource required and those who felt that it was not (35% versus 39%).

In a separate question, respondents were asked to select those benefits that registration of the Design Space by an applicant can bring. The answers were mixed, with companies seeing a mixture of positive benefits and no significant benefit.

In addition, 43% of responses stated that the variations reporting categories for changes to Design Space discourage companies from using it.



Companies were asked to comment on the survey questions and to explain what was discouraging them from using Design Space overall. The following recommendations are made by industry based on the information generated by the survey:

- Expectations for justification of Design Space are unclear in EU, and not aligned with expectations in ICH guidance or in other regions. Respondents were particularly concerned with EU regional expectation, citing the example of *EMA/CHMP/CVMP/QWP/354895/2017 Improving the understanding of NORs, PARs, DS and normal variability of process parameters"* where EU specific considerations for Design Space and PARs (Proven Acceptable Ranges) are not aligned with ICH guidance provided in ICH Q8, Q9, Q10 (e.g. IWG Q8, Q9, Q10 (R4) Q&A 8, or IWG Q8, Q9, Q10) or the expectations of other regions. Several respondents also highlighted concerns with EU expectations for commercial scale data to verify design spaces.
- The EU variations guidance (sections B.I.e.1. and B.II.g.1.) categorizes all changes to Design Space as Type II, regardless of the risk to quality. This discourages the use of Design Space and does not align with the concepts of quality risk management in ICH Q8-11. It is recommended that the Variations legal framework is updated to address this point.
- Industry respondents recognised that updating the Variations legal framework for changes to Design Space to align more fully with consideration of risk to product quality will also enable implementation of concepts described in the draft ICH Q12 guideline on Pharmaceutical Product Lifecycle

Management. In particular, enabling changes to Design Space to be handled via Type IA or Type IB Variations will support wider usage.

In addition to the survey responses, some further perspective on the use of Design Space in the context of vaccine manufacturers is also provided. Consistent with the survey feedback, there is not yet full implementation of Design Space in the end-to-end manufacturing process by vaccine manufacturers and some of the reasons for this are as follows:

- While there is the potential for a return on investment, definition of Design Space for vaccines may be time- and resource-consuming, due to the complexity and diversity of these products. Furthermore, there is little guidance on how to document, submit and validate Design Space. In addition, sophisticated statistical analysis is needed especially for multivariate studies and modelling.
- For legacy products not developed according to Quality by Design (QbD) principles, processes were developed in a univariate way, varying one factor at a time, and the sum of PAR (Proven Acceptable Range) does not constitute a valid Design Space by definition. Defining process ranges in such a way overlooks cumulative effects and interactions. Design Spaces are very difficult to establish 'a posteriori' with sufficient precision using only CPV (Continued Process Verification) data. Moreover, in multivariate analysis of historical data, parameters are often aliased.
- Even if the ranges of the parameters were identified with multivariate approaches (e.g. Design of Experiment - DoE) as proposed in QbD, the level of scrutiny that will be requested for both the scale down model applied and the mathematical model behind may be perceived as a risk. Also, companies might be expected to provide data from commercial scale, which would be an additional challenge.
- Applying PAT (Process Analytical Technologies) would help to monitor and provide feedback control to the Design Space. The use of PAT in vaccine development is only just starting in R&D and many operations are still manual, hence the use of PAT in large scale manufacturing (industrial production) is extremely limited. As Design Spaces are largely asymmetrical, for manual operations it is not very practical for the operators to have to constantly apply an equation to check if the level of parameters is still acceptable in moving ranges. So, it is often preferred to provide only a subset of the Design Space, under the form of individual PAR, as would have been done with a more classical development approach.
- Some elements of QbD are being utilized for new products but it is too early to see the full benefit of this approach. The use of ICH Q12 tools to simplify lifecycle management will ensure full exploitation of QbD benefits, as risk-based approaches for development set the grounds for definition of Established Conditions and post- approval management.

Conclusions and Recommendations on Design Space

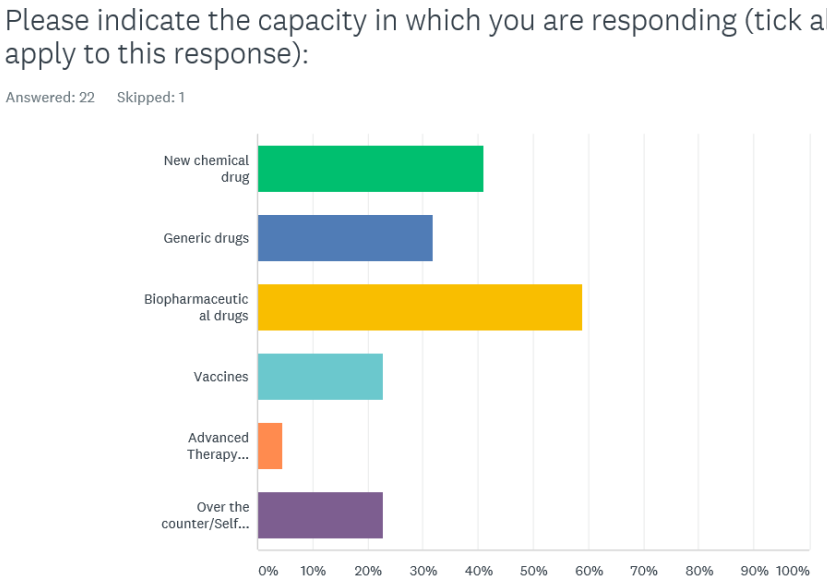
In summary, most companies are routinely undertaking enhanced development aligned with ICH Q8-11 and are developing process understanding that could support design spaces. However, companies have become discouraged from attempting to secure a Design Space by the EU regulatory expectations associated with gaining approval and subsequent maintenance of a design space, and divergent regulatory expectations between regions due to inconsistent implementation of ICH Q8-11.

Furthermore, whilst the implementation of ICH Q14 and ICH Q2(R2) is also expected to clarify opportunities for enhanced approaches to method development and lifecycle management, Industry recommends that the EU Commission sponsors a revision of the EU Variations legal framework and associated regulatory guidelines (in particular, the problematic EU-specific guidance provided in *EMA/CHMP/CVMP/QWP/354895/2017)* with respect to the categorisation of Variations for changes to

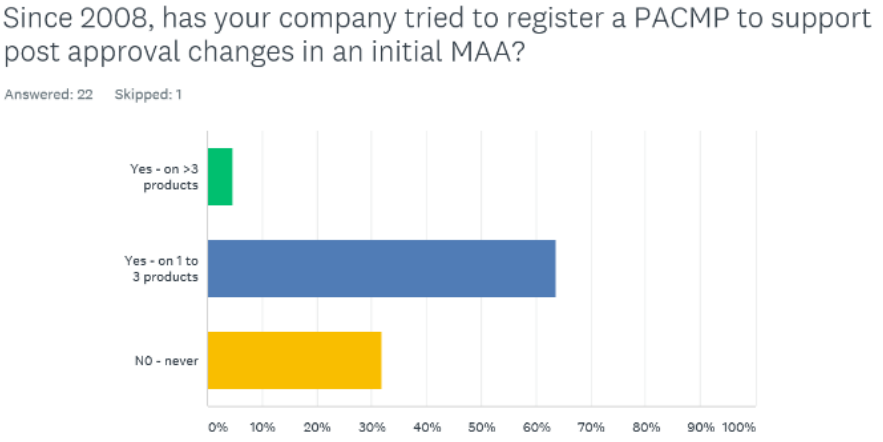
design space, and supports further harmonisation activities within ICH to ensure consistent global regulatory expectations for design space.

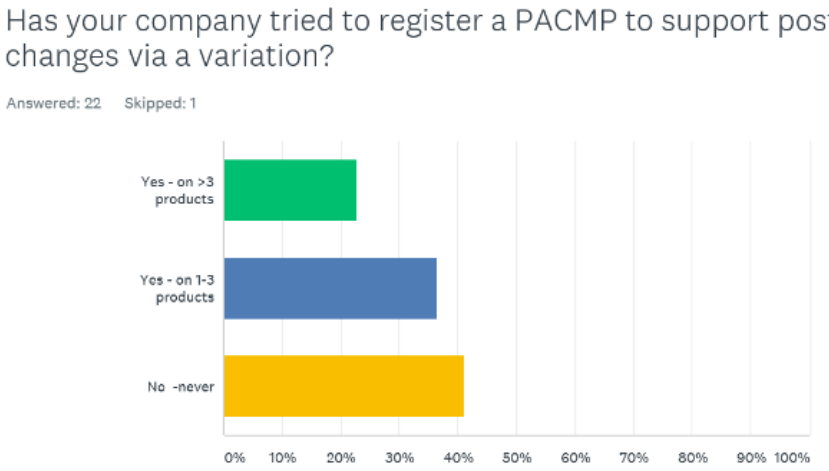
ii. PACMP Survey

In total for the PACMP survey there were 23 responses to the survey from 16 companies. The responses received covered new chemical drugs, biological drugs, vaccines, ATMPs, generic and over the counter medicines.



Respondents were asked to identify whether they had used PACMPs in an MAA or variation in the last 10 years. The majority of respondents had used PACMPs 1-3 times since 2008. Further analysis of the data showed that respondents were most likely to use PACMPs for biological drugs, with 85% of respondents on biopharmaceutical drugs having submitted a protocol with the MAA and 77% as a variation since 2008.





Companies were also asked to indicate what they had used PACMPs for. The most common use was for a change to a manufacturing process or site (76%).

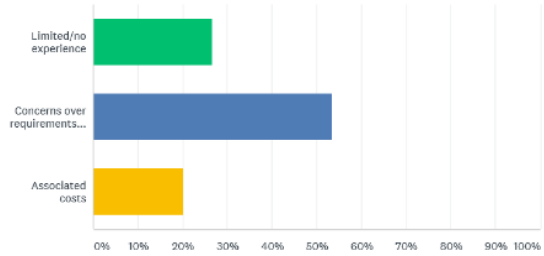
ANSWER CHOICES	RESPONSES	
Managing a change to a single product?	80.95%	17
Managing a change to group of products?	4.76%	1
Changes relating to Manufacturing process/sites?	76.19%	16
Changes relating to Analytical procedures?	14.29%	3
Changes relating to Excipients?	0.00%	0
Changes relating to Specifications?	4.76%	1
Changes relating to Container Closure?y	14.29%	3
Changes relating to Stability?	4.76%	1
No experience of PACMPs	19.05%	4

Respondents were also asked to comment on the uses of PACMPs. Generally, greater predictability of outcomes (68%), reduced reporting categories (64%) and predictable timelines (73%) were considered as positive benefits. 40% of applicants felt that PACMPs support more rapid registration of new medicines by facilitating post approval changes.

ANSWER CHOICES	RESPONSES	
Greater predictability/certainty of outcomes for changes	68.18%	15
Reduced reporting categories for changes to Chemical Drugs	40.91%	9
Reduced reporting categories for changes to Biological Drugs and Vaccines	63.64%	14
Greater predictability/consistency between regions (where PACMPs are accepted)	36.36%	8
Support more rapid registration of new medicines by facilitating post approval changes	40.91%	9
More predictable timelines for implementation of changes	72.73%	16
No experience/no answer	22.73%	5
Total Respondents: 22		

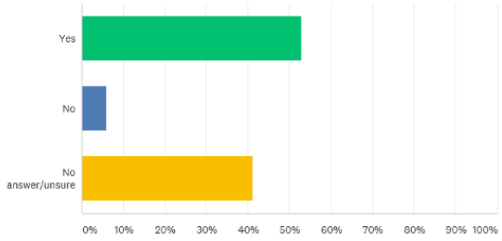
Please indicate any blockers that your company feels discourage the use of PACMPs (tick all that apply)

Answered: 15 Skipped: 3



Would your company use more PACMPs if they could be applied to multiple products?

Answered: 17 Skipped: 1



Respondents were also asked to comment on any blockers which discourage the use of PACMPs. 47% cited concerns over requirements or complexity.

In addition to the options in the survey, a number of comments on elements which discourage the use of PACMPs were made by respondents. The following points and recommendations were made in the survey and have been subsequently endorsed by industry:

- There is little flexibility to change a PACMP once it has been agreed, since any change requires prior approval via a Type II variation. There is a need in EU for more flexible mechanisms in the Variations framework to amend or augment approved protocols.
- Because submission of a PACMP for a marketed product is via a Type II variation it can be faster to simply submit the change as a Type II variation. Hence use of PACMPs by companies is likely to be limited to more complex post-approval changes where the greater predictability of outcomes outweighs concerns over requirements or complexity.
- Development of multi-product protocols, to support changes across similar product types, could significantly contribute to consistent use by applicants, and review and approval by assessors, and thereby enhance the effectiveness of PACMPs as a tool to facilitate post-approval changes.
- There is an opportunity to make better use of PACMPs to support common types of change, with similar protocols describing how types of change will be handled, without requiring significant product-specific justification for common types of change (e.g. updating a specification limit once additional manufacturing experience has been acquired).
- There is an opportunity to use PACMPs to support rapid implementation of changes associated with acceleration/access to new medicines.
- Implementation of ICH Q12 should encourage greater use of PACMPs across ICH regions, and perhaps beyond, and industry encourages the EU to continue to lead in this area and share its experience of the use of PACMPs with other regions.

In addition to the survey responses, some further perspective on the use of PACMPs in the context of vaccine manufacturers is also provided. This feedback illustrates that there has been mixed experiences with the use of PACMPs with only some companies using this mechanism. Those who are using it are running a thorough analysis of the potential advantages and disadvantages of this approach prior to launching this process, which involves evaluating the potential for time-saving compared to submitting variations in the conventional way. The main reasons for not using PACMPs are:

- No significant gain compared to the "conventional" process in terms of timing; in particular, for biological products, which include vaccines, a type Ib variation by default is still needed for submitting the results obtained with the previously agreed protocol, which does not represent a strong incentive; and in these cases where a worksharing procedure is being used, a type II variation is required. Hence, the 2-step approach (type II / type IB or type II / type II) does not provide a significant benefit compared to submitting only one type II variation.
- While the vast majority of vaccines are licensed in numerous international countries including EU, the PACMP process is currently not used in all other countries in the world (except Switzerland, and US where a similar mechanism exists: "comparability protocols"); as Post Approval Changes (PACs) are managed on a global worldwide basis, there is then currently no advantage using PACMPs if no other countries than EU are using them. It may even be considered as an additional layer of complexity compared to preparing one single variation dossier which fits all destinations, including the EU.
- In some cases, a PACMP may be perceived to reduce flexibility and increase risk. For example, the requirement to submit the PACMP before the PPQ (Process Performance Qualification) lots means that any adaptation of the parameters (for whatever reason) will lead to those PPQ lots no longer being covered by the PACMP. In this case, a new PACMP (Type II variation) will have to be submitted when the results of the PPQ lots are available.

Conclusions and Recommendations on PACMPs

In summary, most companies that responded to the survey have some experience of the use of PACMPs and clearly see the potential benefit. However, companies' experience suggests that there is a need to simplify requirements for PACMPs, introduce more flexible mechanisms to change approved PACMPs, and incorporate multi-product protocols in the Variations framework in order to fully realise the potential benefits in Europe.

Industry therefore recommends that the EU Commission sponsors both the modernisation of the expectations for PACMPs through an update in the EU Variations legal framework and further harmonisation activities with other regions, particularly through the implementation framework of ICH Q12 to ensure consistent global regulatory expectations for PACMPs.

Question iia):
How do Companies currently ensure appropriate control of their own end-to-end supply chain?

Industry Response:

Fundamental controls in the pharmaceutical supply chain are designed to ensure that resources are allocated, and manufacture is planned, so that release and distribution of medicinal products meets the needs of patients. This requires detailed monitoring and control of the supply of starting materials, assessment of alternative sources or distribution channels (such as market to market transfers) for medically critical medicines, adaptability to face fluctuations in demand and unforeseen events impacting supply routes as well as patient populations, and short- medium- and long-term forecasting of product

demand. The pharmaceutical industry is also conscious that particular attention is needed with respect to its own:

- suppliers of starting materials for manufacturing,
- customers receiving finished goods for further distribution,
- contracted service providers performing operations in the supply chain between suppliers of raw materials and sites manufacturing medicinal products, and between sites manufacturing, importing and/or releasing finished goods, downstream supply chain operators and customers,
- application of the requirements of the Falsified Medicines Directive to ensure product authenticity.

Current EU GDP (2013 C/ 343/01) outlines the obligations for distributors of finished goods, which includes manufacturers distributing the pharmaceuticals that they produce, to have procedures in place for qualification of suppliers (Ch 5.2) and customers (Ch 5.3), and for quality oversight of outsourced activities in distribution (Ch 1.3). This latter requirement includes specifically the extension of quality management principles, and the application of risk management, performance monitoring and review to any outsourced service providers. EU GDP (2015 C/ 95/01) outlines similar requirements for active substance distribution.

Regarding control of manufacturing and importation operations performed by multiple sites within and outside the EU, the detailed responsibilities of the Qualified Person are laid out in Annex 16 of EU GMP. For the control of suppliers of starting materials including APIs for manufacture, especially for certain specific raw materials purchased in limited quantities and for which alternative suppliers may be difficult to find, manufacturers of medicinal products have put methodologies in place to evaluate which materials and ingredients may be at risk, and they continuously evaluate the potential consequences of supply disruption for these raw materials. In some instances, where identified risks are not considered sufficiently mitigated, alternative sourcing may be employed and should be considered in drug regulatory filings.

In some cases, increasing stock ("stockpiling"/ safety stock) of raw materials or of medically critical finished goods may be the appropriate strategy for mitigation of potential supply risk, but requires regulatory flexibility to avoid obsolescence and write-off. For example, solutions such as e-labeling should be implemented to avoid wasteful write-off due to labelling updates; a regulatory obligation to maintain safety stock should be accompanied by flexibility regarding the use of outdated labelling text so that inventory which is already allocated to a market but for which the labelling has subsequently been revised, may be used.

Moreover, in the last two to three decades, increased globalisation has meant that the international supply and flow of products, often at intermediate stages of production, has increased significantly. More than ever, industry is looking for appropriate flexibility and proactivity in order to facilitate such global supply chains, while continuously ensuring compliance to cGMPs. This includes the use, where possible, of multi-country shared packs, and the adoption of innovative manufacturing and distribution technologies such as modular, local small scale production for certain dosage forms, or late stage "postponement" packaging at regional, local level, to take place as close as possible to the end-user / patient, allowing agility in allocation of inventory to meet fluctuating demand. These measures have to be balanced against the additional complexity that they introduce to the supply chain and its management.

To ensure appropriate control of the end-to-end supply chain, and quality-oversight of actors contracted to perform operations on behalf of the Marketing Authorisation Holder (MAH) or manufacturer, methodologies are in place for:

- requests for information or proposals by potential partners to operate as contractors in distribution,
- due diligence, quality assessment and audit for selection, ongoing performance and compliance oversight, based on risk-assessment that considers product type and potential impact of the operation on product quality,
- specific contractual agreements including master supply agreements for materials, and
- quality agreements for suppliers of materials and suppliers of distribution services, including standard elements required in the contractor's QMS

The contract giver that takes the responsibility for oversight will typically in global pharmaceutical companies, be an intercompany supply chain operations group for distribution between manufacturers, importation and supply to market affiliates. The contract giver for in-market operations and distribution to first paying customers will typically be the market affiliate who is usually also the MAH. In global organisations, a Quality group responsible for supporting the Supply Chain operations group, spanning contract manufacturing/ external supply, intercompany operations, and in-market affiliates typically have responsibility for ensuring implementation of the above processes. Each entity is duly authorised by Health Authorities through a MIA or WDA with associated named individuals having ultimate responsibility as Qualified Person (MIA) or Responsible Person (WDA). Application of global pharmaceutical quality standards ensures commonality of approach.

Regarding controls for product authenticity, industry has in 2019 implemented unprecedented changes in the supply chain to comply with the Falsified Medicines Directive for unit pack serialization and tamper-evidence. Collaboration with EMVO and NMVOs in managing alerts provides a robust control against counterfeits entering the supply chain. While this could be considered a means of control of the product itself, rather than control of the supply chain, compliance by all players will allow secondary uses of FMD data to further enhance supply chain controls, such as in the mitigation of shortages.

Finally, parallel distribution of medicinal products in the EU is one specific area where the MAH is not able to maintain full oversight and control of its own supply chain. In this case parallel distributors will open and re-seal packaging to include patient information leaflets in the national language of the destination EU Member State and ship the medicinal product without MAH oversight of adherence to any specific requirements e.g. maintenance of cold chain distribution.

The above methodologies are based on close collaboration between pharmaceutical manufacturers, MAHs and their suppliers, customers and distribution/logistics service providers, as well as between pharmaceutical companies, and with Health Authorities, ensuring that the necessary level of control is maintained in the end-to-end supply chain, to minimize the impact of operations on product quality, safety and efficacy, to ensure only legitimate product is supplied to patients, and to meet the MAHs obligation for continuous supply of medicines.

Question iib):
The European Commission would like to better understand why increased flexibility is needed, with reference to the current variation regulation.

Industry Response:

There are essentially three main drivers for lifecycle and post-approval CMC changes:

- First, to foster continuous improvement and innovation in terms of:
    - manufacturing processes (to ensure process optimization and update them to the newest available technologies),
    - increased production scale to meet market demand and ensure continued supply of medicinal products and vaccines (e.g. necessary changes to introduce new manufacturing facilities),
    - analytical testing in order to cope with latest technology improvements and moving towards more reliable methods (*in vitro* vs *in vivo*),
    - Product stability (i.e. changes to improve storage conditions)
- Second, to meet the requirements of an evolving regulatory system (i.e. to comply with new regulatory guidance / pharmacopoeia standards) such as the EMA's Implementation Strategy of the ICH Q3D guideline in 2017.
- Third, to maintain manufacturing and testing in operation (e.g. managing changes in facilities and equipment, supplier changes, change in reference standards, anticipate seed lots and cell banks depletion).

In addition, there is a need for regulatory mechanisms to be sufficiently flexible to accommodate post approval changes in line with the current environment that medicine developers and vaccine manufacturers are facing. For example, in the case of some vaccine manufacturers, the reality is that for some suppliers of raw materials this is a niche business. Despite contract agreements and close relationships with their suppliers (see response to question iia, previously), vaccine manufacturers may face issues with their manufacturing supply chain if suppliers take unilateral and sudden business decisions to stop supplying their raw materials. Whilst vaccine manufacturers take precautions with their suppliers, it is not possible to have multi-sourcing solutions for all materials. Hence, having the possibility to change suppliers without the need to report this type of change, providing that there is appropriate comparability between the raw materials, would represent a very significant improvement.

Moreover, dossiers do not always bear the same level of details depending on products and companies. This is due to the history of the marketing authorisation of each individual product of the company portfolio, the evolution of regulatory requirements over time, the licensing in and out of products between companies with different practices, etc. As a consequence, depending on products, within the same company, the same type of information is present in some dossiers and not in others. Given that the provision of information in dossiers is the basis for submitting life cycle management variations, then this situation creates divergent reporting for identical changes instead of submitting variations only based on risk and scientific-based approaches. Acknowledging that reporting changes must only be based on scientific risk-based approaches would provide more flexibility for implementing changes with no risk, instead of reporting them based on the information provided into the dossier.

A real-life example to illustrate the above concerns the following. One of the 2 molecular weight (Mw) standards used in an SDS-PAGE analysis was no longer commercially available. Because a very old dossier mentioned the commercial reference of this Mw standard, the company had to submit the change of supplier as a B.I.b.2.a variation (Type IB because immunological), while this variation would not have been submitted for a more recent product because this level of detail is not requested and included into more recent dossiers.

Lifecycle changes should be handled in a more effective and efficient manner and categorized based on a robust scientific and risk analysis. Where risk is low, for example a change to a reference standard, this could be handled internally, without the need to submit a variation.

Another obvious example of a low risk variation is the reporting of changes to "European Pharmacopoeia (TSE) Certificate of Suitability", for instance when the Certificate is updated. Today, even if this type of change requires only a Type 1A submission, it is a burdensome administrative activity for marketing authorization holders and for competent authorities (indeed, in the case of vaccines, in most instances such changes impact several vaccines registered via different EU procedures - CP, MRP, National), without any real added value since the Certificates of Suitability (and their updates) are initially reviewed and approved by EDQM. The handling of such minor or purely administrative changes internally within companies' quality systems would enable a quicker and more straightforward implementation with company oversight, and with the possibility for regulators to review during audits.

For greater risks such as change of method or production process, such changes would be submitted with authorities for their approval. Innovation could be fueled by focusing regulatory resources on these latter changes, and quality resources on prior ones.

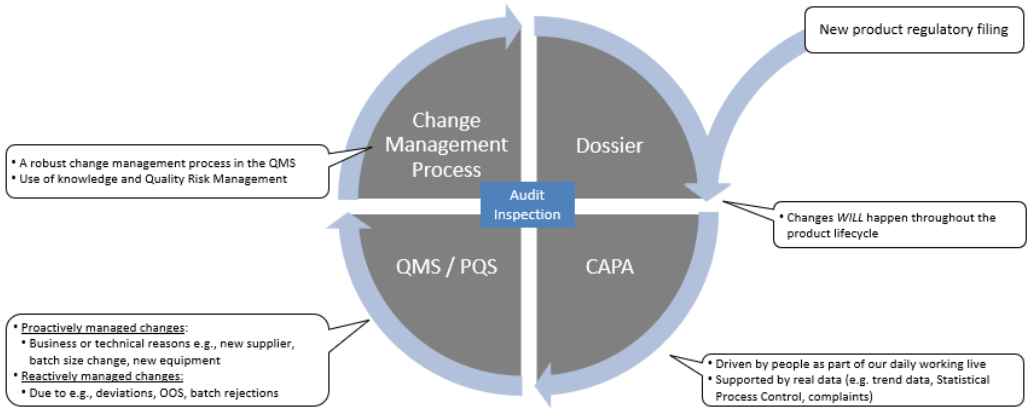
Question iii)
Proposed changes, including with the implementation of ICH Q12 trigger the impression of decrease of regulatory oversight by regulators. How could regulators be reassured?

Industry Response:
Whilst the ICH Q12 draft guidance indicates that effective implementation of the guideline should result in "less need for regulatory oversight prior to implementation" of post-approval changes this will not lead any decrease in the quality of medicines delivered to patients. The overall intention is to continue providing patients with medicines of the highest quality whilst accommodating innovation. The bases of any change management process are the principles as described in ICH Q9 (Quality risk management), ICH Q10 section 3.2.3 and 3.2.4 and in chapter 6 of the draft Q12 guidance. These are required in the EU GMPs as described in chapter 1.4. All changes are managed within the company's Quality Management System (QMS), under the supervision of the Quality Unit, in a change management system. Change management is a systematic approach to proposing, evaluating, approving, implementing and reviewing changes. Change management is a multi-disciplinary activity and the system will describe clear accountabilities for each of the steps:

- Evaluation of a change
- Approval to proceed with the change
- Implementation of the change
- Review to ensure that the change has been effective
- Reviews effectiveness of overall system

An important part of the evaluation of the change is consideration of the need for regulatory submissions to update the Marketing Authorisation. The introduction of the Established Conditions (ECs) concept with implementation of Q12 will facilitate this process because ECs clearly define those elements of the regulatory dossier that are subject to regulatory action if changed. Quality risk management tools and product & process knowledge (development data, manufacturing experience, first principles etc.) are used to support the evaluation of the impact of the change and effectiveness after implementation. As with all GMP elements this workflow will be available for inspection or as part of a remote (desktop) review (see PIC/S guidance on GMP-Inspection reliance, PI 048).

Stimuli for a change can come from the Corrective Action and Preventive Action (CAPA) process, part of the QMS described in ICH Q10 section 3.2.2. The CAPA process is supported by assessment of trends in deviations, complaints and recalls, annual product review/product quality review (APR / PQR), and management reviews Increased process understanding, knowledge gained from other manufacturing processes, and continuous improvement activities can also drive changes. Post-change monitoring activities need to be included in the CAPA process (see also ICH Q10, section 3.2.1).



Regulatory change management as a product of continual improvement

Aside from ICH Q12, companies also leverage other ICH guidelines and the Quality by Design (QbD) approach to ensure a holistic approach to change control, take increased responsibility to determine category of change and PQS effectiveness. Good Manufacturing Practice (GMP) (e.g. according to ICH Q7) and related regulations recommend appropriate oversight of the QMS. Internal oversight will be through the company's self-inspection and audits programme. Such processes will assess effectiveness of the quality management system, including the change management and CAPA systems, and also the capability of the manufacturing processes, the adequacy of production and control procedures, the suitability of equipment and facilities, etc. Finally, for vaccines specifically, OMCLs are analysing each of the batches produced (in addition to the manufacturer's testing) to ensure they meet the specifications approved by the regulatory authorities.

4. CROSS-TRADE KEY PROPOSALS – VARIATION FRAMEWORK (16 July 2021)

GENERAL INTRODUCTION:

Regulatory efficiency, as a prerequisite for a modern regulatory system, is recognised in the Pharmaceutical Strategy for Europe (published 25 Nov 2020) and as such the need to revise the variation framework through changes in legislation and guidelines is listed as a flagship initiative.

Revision of the Variation Regulation (1234/2008) and the Classification Guideline (C(2013) 2804) is required to provide for simplification, efficient life-cycle management (including addressing challenges relating to the interplay of medicines and devices and for novel and more complex therapies) and to adapt to digitalization. There is an opportunity here for the EU to play a leading role in driving international alignment across variation systems thereby improving lifecycle management at a global level.

Increased responsiveness of the framework is needed to foster continuous improvement and innovation. Changing the Variations Classification Guideline to an EMA/HMA guideline would allow for more frequent updates thereby facilitating continual improvement.

The key proposals build on those developed in the EFPIA/EBE/Vaccines Europe Reflection Paper sent to the European Commission on 9 Nov 2018, complemented 6 Dec 2019. This includes, but is not limited to, reviewing the classification of multiple changes, alternatives to the current options for submission (such as direct database notification, or "no submission" handling within the Pharmaceutical Quality System), classification of changes to vaccines, ATMPs and guidance for specific processes. A series of 6 appendices relating to the key proposals are also included to provide further context and specific recommendations for advancement.

KEY PROPOSALS:

1. Build on experience and technical advances to deliver a variation framework that enables the efficient lifecycle management of medicines and vaccines today and can be readily adapted for rapid technological advances in the future.

a) Implement a more flexible framework using a risk-based approach applicable across all types of active ingredients and pharmaceutical products. This would be supported by legislation that describes principles, while guidance supporting the legislation would be used to describe the detailed approach and provide examples. The European Medicines Agency, in conjunction with the European Medicines Regulatory Network, would take primary responsibility for revisions or updates to the guidance based on accumulated learnings.

b) Accommodate innovation and emerging science through classifications which incorporate all elements of ICH Q12 and are included in regulatory guidance (Appendix 1). Ensure the future variation regulatory framework can minimise stresses within the system by enabling a streamlined approach to the lifecycle management of manufacturing and control of processes and labelling changes, implementing learnings and experience from the COVID-19 pandemic where applicable.

c) Implement a risk-based approach for effective change management of drug-device combinations that is aligned with modernization of the EU variations framework. Acknowledge Notified Body involvement for drug-device combinations where appropriate, consistent with ICH Q12 implementation overall (Appendix 2).

d) Establish an ATMP specific variation classification that accounts for their specificities and enables continuous product, analytical and/or process improvements (Appendix 3).

e) Establish a dedicated regulatory mechanism ("Platform Technology Master File" - PTMF) for the registration and lifecycle management of new platform technologies such as mRNA-based manufacturing platforms, ATMP viral vectors, recombinant protein technologies, devices etc. to allow the review and implementation of post-approval changes in a coordinated manner across all impacted therapies and vaccines. Such prior and platform knowledge-based evolution of the regulatory framework in Europe will offer a significant benefit to innovation as well as enabling product evolution and improvements (Appendix 4 for applicability to vaccines). Appendix 4 also suggests exploring the potential implementation of a vaccine specific variation classification.

2. Capitalise on advances in digital technology to reduce administrative burden and increase transparency between regulators and industry.

a) In the near-term, further develop EU databases to maintain administrative information associated with the marketing authorisation which have no impact on safety, efficacy or quality (former Type IA/IA^{IN}) and can be routinely updated (Appendix 5).

b) In the longer-term, utilise advances in cloud-based technology such as Accumulus Synergy to enable real-time oversight of the dossier by regulators, thereby removing the requirement to submit individual changes for review.

3. Better reflect the current and future needs of Regulators and Manufacturers through simplification, standardization and acceleration to ensure optimal delivery of medicines to patients at a global level and minimize drug shortages.

a) Fully implement science and risk-based approaches to variation categorization for well-characterised biological medicinal products by removing the default classification of manufacturing changes as major (Type II) and the specific exclusion that preclude the use of the Type IA variation category.

b) Redefine existing concepts such as work-sharing procedures and grouping to reduce time for review/approval of the change and its subsequent implementation, especially in cases where the same change affects multiple products and procedures (Appendix 6).

c) Include the concept of worksharing and regulatory reliance with other regulatory agencies outside of EU into the Regulation. These processes provide multiple benefits including faster overall approvals, reduced regulator & industry resources and can drive regulatory harmonization, resulting in a more rapid global implementation of changes, including in the EU.

APPENDIX 1: INCORPORATION OF ICH Q12 PRINCIPLES AND TOOLS IN THE EU REGULATORY FRAMEWORK

Introduction

The ICH Q12 Product Lifecycle Management guideline is currently in step-5 (implementation) of the ICH process. The Guideline provides a framework to facilitate the management of post-approval Chemistry Manufacturing Controls (CMC) changes in a predictable, science- and risk-based, efficient manner, and applies to pharmaceutical drug substances (i.e., active pharmaceutical ingredients) and pharmaceutical drug products, including marketed chemical, and biotechnological/biological products. The guideline is also applicable to drug-device combination products that meet the definition of a pharmaceutical or biotechnological/biological product.

Some aspects of the ICH Q12 tools already exist within the EU regulatory framework , but a revision of the Variation Regulation and Classification guidelines will be necessary to incorporate new concepts such as 'Established Conditions (ECs)' and the 'Product Lifecycle Management (PLCM) Document' so that the full benefits of ICH Q12 can be realised.

Incorporation of Q12 Principles and Tools within EU Legal Framework

The main tools incorporated in ICH Q12, supported by ICH Q9 and ICH Q10, to facilitate post-approval changes within the regulatory framework are:

a. **Established Conditions**
b. **Post Approval Change Management Protocols**
c. **Product Lifecycle Management document**

In addition to the above tools, in accordance with ICH Q12 Chapter 8, a simplified approach to accomplish certain CMC changes is possible for products whose original marketing authorization submission did not involve identification of ECs with associated reporting categories.

To meet the ICH overall objective of harmonisation, EFPIA and Vaccines-Europe strongly support incorporation of all Q12 tools in a consistent manner across all ICH regions.

a. Established Conditions (ECs)

ECs are legally binding information considered necessary to assure product quality. Consequently, any change to ECs necessitates a submission to the regulatory authority to update (or vary) the marketing authorization.

Supportive information in regulatory dossiers is not considered to be ECs, but provided to share with regulators the development and manufacturing information at an appropriate level of detail, and to justify the selection of ECs and their reporting category.

Established Conditions are not defined in the current EU regulatory framework but mirror information and quality characteristics that are subject to a variation, as described in the EU Variation Regulation (EC) No 1234/2008 (as amended) and associated EU Variation Classification Guidelines.

EFPIA and Vaccines-Europe consider it important to further clarify that ECs represent the legally binding information in module 3 of the Common Technical Document (CTD) that forms the compliance commitment of the Marketing Authorization Holder (MAH), and consequently we agree on the need to revise the EU Variation regulation and categorisation guideline as per EU Note on ICH Q12 Implementation and recent Commission communication on a pharmaceutical strategy for Europe.

ICH Q12 also makes provisions for changes that do not require reporting to regulatory authorities but can instead be appropriately managed and documented through the change management process within an effective Pharmaceutical Quality System (PQS) by applying ICH Q10 (Annex 1). These changes may be verified during routine or other inspection, based on the recommendation published by PIC/S on 15 July, 2021 GROUP 2: (picscheme.org).

Our understanding of ICH Q12 implementation is as follows:

- Established Conditions – The concept instituted by ICH Q12 should be understood as follows: when a company submits an application, it may ask the regulatory authority(s) to agree (i) that specific CMC information in the MAA dossier qualifies as an Established Condition, i.e. information that relates to the elements impacting the product quality (product, manufacturing process, elements of associated control strategy); and optionally (ii) on the variation category for changes to that information defining the Established Condition. The Established Condition and its reporting categorisation can be mentioned in the PLCM. Only changes to the Established Conditions would be reported as variations and be subject to the variation rules (i.e. according to

the pre-agreed variation category between HA and applicant or, in the absence of such pre-agreement, according to the category defined in the Variations Guidelines); other (supportive) CMC information would be changed only through the MAH's change management system operating within an effective Pharmaceutical Quality System as per ICH Q10.

- Established Conditions and their associated variation categories may be presented in the PLCM (see below). They can also be removed from the PLCM (and elsewhere in the dossier) if they no longer meet the criteria for qualifying as Established Conditions. Both an Established Condition and its categorisation (and supporting documentation) can be modified. ICH Q12 foresees that such changes could occur (i) by application of the rules on variations (which presupposes that corresponding entries are added to the Annex to the Variations Guidelines), including through a PACMP or a post-approval CMC commitment, and (ii) in accordance with the variation category indicated in the PLCM.

Applicants may propose ECs in their original application or during product life cycle management through a variation submission. During product life cycle, applicants may propose to add, eliminate, or make changes to approved ECs or revisions to their associated reporting categories through the submission of a variation.

Therefore, we propose that:

- The Variations Classification Guidelines detail the general concept of Established Conditions and provide examples, if appropriate. New entries would be added to the Annex to the Variations Guidelines to cover the introduction or the deletion of an Established Condition, as well as a modification of an Established Condition and/or of the variation category of a change to an Established Condition (Annex 1).

- In parallel, the EMA could issue a new, more detailed implementation guideline on Established Conditions and the PLCM document, which would be based on ICH Q12. Industry also believes that ultimately the current Commission Variations Classification Guidelines should be replaced by relevant Guidelines issued by EMA and the European Medicines Regulatory Network in order to make the EU Variations Framework more adaptable to future needs and competitive to foster European innovation.

b. Post Approval Change Management Protocols (PACMPs)

The EU regulatory framework has already incorporated the use of PACMPs. ICH Q12 seeks to facilitate the use and broaden the scope of changes that can be made through PACMPs. Therefore some revisions may be needed to the EMA Q&As for PACMPs from 2012, e.g. to fully accommodate for the "broader protocol" concept including changes affecting multiple sites/products as outlined in the Annex document to ICH Q12 and to remove default variation categorisations for the PACMP step-2 submission.

c. Product Lifecycle Management Document (PLCM)

ICH Q12 proposes that the PLCM document outlines the specific plan for product lifecycle management that is foreseen by the MAH, and includes the ECs, proposed reporting categories for changes to ECs, PACMPs (if used) and any post-approval CMC commitments.

Industry considers that the EU regulatory authorities will need to establish expectations for the submission of updates to a PLCM document in the Variations Regulation and Guidelines (see above).

Applicants may propose ECs in their original applications or during product lifecycle through a variation submission. Applicants may also propose reporting categories for changes to ECs.

An increased understanding of the risk to product quality posed by a change to an EC may support reduced reporting categories.

A complete list of proposed ECs, their reporting categories (if proposed), and the eCTD locations for their scientific justification as well as a reference to PACMPs (if used) and any post-approval CMC commitments can be included in the Product Lifecycle Management (PLCM) document in eCTD section 3.2.R.

Creation of a Product Lifecycle Management section within the Variation Categorisation guideline?
The new features set forth by ICH Q12 not currently included in the Variations classification guideline (i.e. Established Conditions and PLCM) could be added to sections B.I.e and B.II.g containing the existing tools of PACMP and design space.

However, the importance of these tools for product lifecycle management could be reinforced in the EU Variations regulatory framework by grouping them in a new section in the Variations Regulation and in the classification part of the Variations Guidelines.

The objective would be to set out general principles for prior approval by the regulatory authority of the company approach to management of future changes that have no, or minor-to-moderate, risk to impact product quality, and ultimately on safety and efficacy. More detailed examples could be provided in the Variations Classification Guideline to explain how use of these tools accelerates implementation of changes by the MAH and thereby supports product improvements as well as continuous supply.

APPENDIX 2: DRUG-DEVICE COMBINATIONS

Introduction

Since the implementation of Article 117 of Regulation (EU) 2017/745, which amends Directive 2001/83/EC, the current EU regulatory framework for post-approval variations no longer aligns with the regulatory expectations. Specifically, the acknowledgement a Notified Body opinion maybe required when seeking regulatory approval for certain change types for drug-device combinations, depending on the significance of the change.

Furthermore, the change types within the current classification guidance are somewhat limiting when it comes to considering typical changes for drug-device combinations, and aren't necessarily well-positioned for the future, given the advancement of technology now being introduced. e.g. integrated electronics and software. The guidance currently defines classification categories but does not recognise a 'substantial change' which was introduced by EMA in the Q&A on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746) (EMA/37991/2019) in conjunction with requiring a Notified Body Opinion as part of a variation submission.
Management of changes relating to the device-constituent of a drug-device combination and the consideration as to whether a Notified Body opinion is required as part of the variation should be commensurate with management of changes for the overall medicinal product.

Not all changes require the same level of regulatory oversight prior to implementation. It should be recognised that other regulatory agencies view the significance of changes to the device constituent of a drug-device combinations within the overall medicines change guidance, given the continued guidance

we see being made available. In preparing a revision to the EU medicinal product change framework, the same considerations should be given to ensure adequate guidance is available to facilitate effective change management in the future.

Recommendations

- Implement a risk-based approach for effective change management that is aligned with the overall approach to advancements being proposed to the EU variations framework. Ensure the guidance and framework developed is commensurate with principles and approaches for all aspects of the medicinal product (i.e. API or DP changes), including ICH Q12 Product Lifecycle Management guideline, which utilises ICH Q9 Risk Management within a framework based on ICH Q10 Quality Pharmaceutical Systems.

- Consistent with ISO 13485 and design and development considerations, those functions and characteristics that are considered essential for safe and effective use of the delivery presentation are the 'primary characteristics' of the device constituent and could be used to define ECs for the device-constituent, e.g. design features and characteristics essential to achieve the delivered dose or functions essential for safe use. This includes manufacturing process requirements that need to be controlled to ensure a defined primary characteristic.

- The identification and consideration of the primary characteristics can facilitate the effective change management such that if a change is shown to impact the safe and effective performance/use of the device constituent (primary characteristics), these are changes that would require greater regulatory oversight to implement. Similarly, the level of risk associated with a primary characteristic could require greater oversight before implementation. This level of regulatory oversight could extend to the MAH requiring a Notified Body opinion to also support the change, dependant on the evidence gathered that supports the outcome and associated risk of the change.

- The approach defined within ISO 20069:2019 *Guidance for assessment and evaluation of changes to drug delivery systems* aligns with the framework suggested above and is compatible with ICH Q12. This guidance could be used by MAHs to assess changes and consider process and product understanding, prior evidence and impact to the primary characteristics. It could also be the foundation for creating enhancements to the variations framework and used to develop conditions for variation IA/IB/II, line extensions, specifically as it relates to drug-device combinations and considering when a supportive Notified Body opinion might be required.

- The use of platform device technologies would enable device and drug-device combination developers to leverage the prior knowledge gained from a particular device platform and apply this to other products. The concept of a Device Platform Master File also might enable the review and implementation of such platforms in a coordinated manner across all impacted products and support rapid innovation in new product development. It would streamline and accelerate the review and approval by Health Authorities in the subsequent use of device platforms for other products and/or for post-approval changes to already approved platform technologies.

APPENDIX 3: ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPS)

Introduction

The field of ATMPs is still nascent, and the analytical and manufacturing technologies are rapidly evolving providing opportunity for production process changes during development or post approval. Due to the

unique properties of ATMPs, and the rapid evolution of technologies, the variation guideline designed for chemical and "traditional" biological medicinal products creates a rigid framework that may block innovation, continuous improvements and potentially patient access.

Post approval changes for ATMPs follow the EU Variation regulation for biological medicinal products but the manufacturing paradigm differs considerably. The complexity of ATMPs is often much greater than that of traditional biopharmaceuticals, but whilst the analytical methodology for characterizing ATMPs is still evolving, there is the potential to generate batch data for ATMPs much more quickly than for biologics thereby enabling rapid assimilation of process understanding. It is also particularly challenging to define quality attributes that have meaningful linkage to safety and efficacy and other clinical outcomes (such as duration of response). Furthermore, the patient populations being targeted are usually small in number, which limits the supply of testing materials and the possibility to perform extensive analytical characterisation or have a statistical comparison.

In case of a personalized ATMP (e.g., autologous), which is produced for a specific patient, each batch has unique quality properties that are not comparable (either by design or by their inherent natural variability) and there is no traditional reference standard.

Recommendations

- Establishment of ATMP specific variation classification that accounts for their specificities and enable continuous product-, analytical and/or process improvements.
- Consider adaptable timelines that can ensure timely access to treatment. The current timeline for variations for biological products is appropriate for large production scale medicines. Depending on the modality (e.g., personalized ATMP) and treatment specifics, following traditional timelines may be a barrier for process changes that require customization of the product/process to each patient (e.g., urgent treatment need, storage not compatible with regulatory procedure).
- Consider approaches for ATMPs that could potentially be applied to enable incremental updates, such as iterative improvements used already for devices, or annual updates to vaccines for infectious diseases (analogous to the annual updates process for flu vaccines).
- Consider situations where data analytics are being used in the production process for quality control purposes, with the intent of having ongoing improvement (issue similar to process model updates for "traditional" medicines).
- Consider how the use of platform (e.g., in-vivo gene therapy using the same vector but individualized gene) and lifecycle management of such platform could be leveraged in future variation framework (point not exclusively applicable to ATMPs; valid also for other modalities).
- Apply ICH Q12 and develop guidance on how to implement Q12 tools for ATMPs (e.g., Established Conditions are an important tool to have clarity on what would require reporting when changed, PACMPs could enable rapid implementation with reduced reporting).
- Clarify conditions for variation IA/B/II, line extension, and new MAA, specifically in the ATMP context. Process/product changes, that are intended to improve the product quality, accessibility and/or safety, can result in better medicinal products. This can raise issues related to the boundaries of the product sameness, and their regulatory impact (i.e., variation vs line extension vs new MAA).

APPENDIX 4: VACCINES

Introduction

The revision of the EU Variations Framework, as recommended under the EFPIA/VE key proposals and appendices, is expected to benefit all types of pharmaceuticals. Vaccines represent a specific category of medicinal products which deserves specific attention on certain aspects, as described below, and may require the implementation of a vaccine-specific variation classification.

Recommendations

- **Need for specific categories of variations adapted to vaccines**

Vaccine manufacturers believe that there would be a value in reviewing the current Commission *"Guidelines on the details of the various categories of variations and on the operation of the procedures" (C(2013) 2804)*, with a view to better reflecting the specificities and particular needs of vaccines development, manufacturing and lifecycle.

This was already highlighted in the *"EFPIA/EBE/Vaccines Europe Reflection Paper on a Revision of the EU Variations Regulatory Framework"* sent to the European Commission (EC) in November 2018, and complemented with additional evidence and data sent to the EC in December 2019.

One chapter in these documents highlighted the specificities and complexities in the lifecycle management of vaccines. The recommendation in the reflection paper was to foresee dedicated variation categories for vaccines and/or (if relevant) a new vaccine-specific Annex to the EU guideline on variations classification, which would be more aligned with the approach recommended by the WHO *"Guidelines on procedures and data requirements for changes to approved vaccines"*. This would also be a step forward to foster more international alignment of regulatory requirements for post-authorization lifecycle management for vaccines, and to a larger extent for all pharmaceuticals.

- **Platform Technology Master File (PTMF)**

For several years, vaccine developers have worked on alternative technologies with a view to accelerating the development and availability of new vaccines. Some of these alternative technologies include among others: mRNA-based platforms, bacterial vector vaccines, recombinant protein technologies.

The use of such platform technologies enables to shift production quickly from one antigen (i.e. one active substance) to another by leveraging the prior knowledge gained from a particular technological platform, and this without having to restart lengthy development activities from scratch.

The concept of Platform Technology Master File (PTMF) would enable the review and implementation of such technological platforms in a coordinated manner across all impacted products. It would streamline and accelerate the review and approval by Health Authorities of subsequent use of technological platforms for other antigens, and/or for post-approval changes to already approved platform technologies: Health Authorities could leverage their initial assessment of particular technologies, instead of having to re-assess the data every time the same technology is used to manufacture a new vaccine, or every time a change is made to the initial platform technology.

Besides the active substance (or antigen), this PTMF concept could also be applied to ingredients which enter into the composition of multiple products (e.g. adjuvants for vaccines).

On January 2021, the Committee for Medicinal Products for Veterinary Use (CVMP) has released for comments a draft "Concept paper for the development of a guideline on data requirements for vaccine platform technology master files (PTMF)" (EMA/CVMP/IWP/582191/2020). Vaccine manufacturers welcomed this initiative and recommended that a similar concept be applied to human vaccines, whilst

taking into consideration the lessons learned from the "Guideline on requirements for vaccine antigen master file (VAMF) certification" (EMEA/CPMP/4548/03/Final/Rev 1), issued by EMA in 2005, but rarely used by vaccines manufacturers.

APPENDIX 5: DATABASE NOTIFICATIONS

Introduction

At the current time, disproportionate levels of resources are allocated to the variations process in view of the overall benefit they provide to patients and the entire regulatory system. Raising efficiency and streamlining regulatory processes is a prerequisite for a modern regulatory system that can respond to the changes in the environment.

More than ever, recent experience of the COVID-19 pandemic serves to underline the need for a flexible and agile regulatory system in Europe that can respond to the needs of patients quickly by ensuring the optimization of life-cycle management to deliver safe and effective treatments to patients faster.

Recommendations

Developments in new information technology (IT) systems and ICH Q12 Product Lifecycle Management (see Appendix 1), provide the opportunity to incorporate efficiency and innovation into the variation management system enabled by a review of the legislative provisions. The introduction of a proportionate and optimized approach for the management of post-approval changes has the potential to promote continual improvement and reduce manufacturing delays, mitigate supply issues and free-up capacity to enable greater efficiencies and focus on those changes that would have a greater positive impact on public health in the EU.

Digital solutions offer enormous opportunities to maintain administrative details associated with the marketing authorization directly in an EU database, with Competent Authorities having full access to the content. This processing principle has already been realised for changes related to the Qualified Person for Pharmacovigilance (QPPV) and the location of the pharmacovigilance system master file (PSMF) via the Article 57 database, and is now further recognized in the Commission Implementing Regulation (EU) 2021/17 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 on Veterinary medicinal products.

Lowering the volume of submissions and thereby reducing the average time spent on Type IA notifications through a combination of processing changes and optimal use of IT systems (including substance, product, organizational and referential (SPOR) master data) could lead to a substantial reduction in the manpower currently engaged in these largely administrative tasks. The technology upon which the solutions are built needs to be robust yet flexible to enable fast adoption of new technology along with changing legislative requirements. SPOR, and its Target Operating Model (TOM) provide a platform and process by which data-only submissions (following the FHIR data standard) are possible; the use of this mechanism should be established to enable simplified processing of Type IA notifications.
It is important to acknowledge that the proposed improvements in efficiency through process optimization are intended only to reflect a re-prioritisation of regulatory oversight and should not undermine the overall financial stability of Competent Authorities. Industry supports an expanded annual maintenance fee that includes all Type IA/IB variations.

Conclusion

Regulation 1234/2008 was adopted at a time of relatively low digitalisation of Regulatory Operations and the pace of change in this field over the last decade has been significant and is accelerating all the time.

The effective use of IT systems is a potentially powerful tool for enabling regulatory efficiency in the processing of variations, thereby reducing the volume of Type IA notifications associated with minor/administrative changes. This will enhance the efficiency of the European network with an optimized life-cycle management approach to enable increased efforts on activities more meaningful for public health.

APPENDIX 6: PROCEDURAL ASPECTS: WORKSHARING, GROUPING AND GLOBAL RELIANCE

Introduction:

Grouping and worksharing approaches within the current variation framework are valuable processes that can support improved efficiency in life-cycle management operations for medicinal products, especially in cases where the same change affects multiple products (e.g. combined vaccines). However, some simplification of the variation guidance, together with significantly reducing the requirement to submit type IA/IA^{IN} variations and reflecting these details in an EU database (see principle 2a) would bring significant benefit to public health by further reducing time for review/approval of these multiple changes and their subsequent implementation.As illustrated in several publications and position papers, the worldwide regulatory management of post approval changes is highly heterogenous. This triggers delays in the implementation of post-approval changes (PACs) by manufacturers, also in countries with more mature and faster regulatory systems such as the EU.

The COVID-19 experience has illustrated the importance of developing global reliance mechanisms across countries, to enable equitable and timely access to vaccines for all populations worldwide. The same philosophy should apply not only to initial reviews and approvals, but also to post-approval changes.

Recommendations

Grouping and worksharing

Through using worksharing procedures it is possible to have multiple changes requiring submission of several variations included under the same category of change. These changes could possibly be the same Type IB or Type II variation, or the same group of variations affecting more than one marketing authorisation from the same MAH in one application; in some cases, it is also possible within the current variation framework to include type IA/IA^{IN} in these worksharing procedures. This approach has been widely used to handle changes to marketing authorisations, particularly for administrative and some CMC changes (e.g. deletion of non-significant specification parameters), but sometimes results in very large groupings of applications. This increases the complexity of the submission, sometimes resulting in lengthy validation and assessment timelines by the regulators. This issue of complexity could be addressed to a certain degree by significantly reducing the requirement to submit type IA/IA^{IN} and reflecting these details in an EU database, together with revisions to the guidance to clarify the requirement for submission of a specific category of change and examples of where this approach may be applied. This will reduce unnecessary complexity for both the industry and the regulators.

For grouped submissions, whereby multiple minor Type IA/IA^{IN} variations may be submitted together, the EU variation framework currently allows for a great deal of flexibility in grouping possibilities (e.g., by type of change, by product, and across products). However, it would also be beneficial to simplify this approach across the different authorisation routes in Europe (centralised, mutual recognition, decentralised and national). In moving to a future state where information is updated in a database with Regulator access and oversight (i.e. SPOR) rather than submitting type IA/IA^{IN} variations for review, the specific conditions and requirements around grouping these simple variations would no longer be necessary. This would alleviate some of the workload and complexity associated with this type of grouping, particularly with submissions that under the current variation framework constitute very large (*e.g.* so called "super-group"

for MRP/DCP) applications. The variations notified via a database update should also allow for individual changes that impact multiple products e.g. updating the name or address of the Marketing Authorisation Holder should be made with a single update applicable to all impacted licenses for all types of authorisation routes.

Global reliance

As illustrated in several publications and position papers, the worldwide regulatory management of post approval changes is highly heterogenous. This triggers delays in the implementation of post-approval changes (PACs) by manufacturers, also in countries with more mature and faster regulatory systems such as the EU.

The COVID-19 experience has illustrated the importance of developing global reliance mechanisms across countries, to enable equitable and timely access to vaccines for all populations worldwide. The same philosophy should apply not only to initial reviews and approvals, but also to post-approval changes.
While the EU Legislation does not prevent reliance mechanisms across countries, we believe that the importance of global reliance should be reflected and encouraged in the EU Variation Regulation, if not in the Pharmaceutical Legislation as a whole, with some concrete illustrations such as the possibility to share assessment reports and to take into consideration assessment reports issued by other non-EU regulatory authorities.

Some recent examples of this have been shown by the project ORBIS[7], the ACCESS[8] consortium and more recently the EMA "OPEN" pilot and WHO Emergency Use Listing procedure which has included PACs to support Covid vaccines and therapeutics. In addition to these approaches, the WHO has published a guidance on "Good reliance practices in regulatory decision making" (TRS 1033, Annex 10, March 2021). Reference to the use of worksharing approaches or regulatory reliance practices within the EU legislation and guidelines would also help promoting these practices more broadly amongst National Regulatory Authorities, with a view to accelerating global access to medicines and vaccines and reducing risks of shortages.

Conclusions

Worksharing approaches should be further developed to reduce time for review/approval of the change and its subsequent implementation, especially in cases where the same change affects multiple products. These changes should also be considered in the context of significantly reducing the requirement to submit simple type IA/IA^{IN} variations for review (Appendix 5) which will remove some of the complexities associated with very large groupings of simple variations. Finally, the importance of global reliance should be reflected and encouraged.

[7] Project ORBIS
[8] ACCESS Consortium

5. VE RESPONSE ON THE OPEN PUBLIC CONSULTATION ON THE REVISION OF THE GENERAL PHARMACEUTICAL LEGISLATION (19 December 2021)

Contribution ID: 39a01f7e-4dd9-422b-9d6c-e1b6343a33ed
Date: 20/12/2021 12:40:26

Open Public Consultation on the revision of the general pharmaceutical legislation

Fields marked with * are mandatory.

Is there any other aspect you would like to mention, for example on the potential economic, social, environmental or other impacts of the outlined measures, or would you like to justify/elaborate your replies?
800 character(s) maximum

VE believe that there would be a value to review the Variation Regulation (1234/2008) and the Classification Guideline (C(2013) 2804) to better reflect the specificities and particular needs of vaccines development, manufacturing and life cycle management. EFPIA/VE letter was submitted to EC on 16 July 2021 as a follow up of submission in Nov 2018 & Dec 2019. More details could be find here: *"EFPIA/EBE/Vaccines Europe Reflection Paper on a Revision of the EU Variations Regulatory Framework"*
There is an opportunity here for the EU to play a leading role in driving international alignment across variation systems thereby improving lifecycle management at a global level.

6. REVISION OF THE VARIATION FRAMEWORK (9 May 2022)

By e-mail: Florian Schmidt,
Cc: Olga Solomon, Tina Engraff

Brussels, 9 May 2022

Subject: revision of the European variation framework for human medicines

Dear Florian,

Further to previous communications on this topic we would like to reiterate our view that modernisation of the variation framework for human medicines is an essential element underpinning future innovation in medicine development and manufacture within the EU.

Despite the inclusion of the revision of the variation framework as a flagship initiative on regulatory efficiency in the EC's Pharmaceutical Strategy, there appears to have been little movement forwards on this in the past few months, in contrast to some of the other elements included in the Strategy. Whilst we acknowledge that there are several important competing initiatives advancing along similar timelines, and that these are understandably taking time and resources to progress, we would propose that revision of the EU variation framework is now elevated within the list of priorities.

We feel that this is the right time to again raise this topic for the following reasons:

• Firstly, we continue to observe and experience challenges due to resource constraints within the EU regulatory network. Implementing a streamlined variation framework with accompanying advances in Information Technology to reduce the administrative burden for variations could also release resources for use in other areas such as scientific advice and assessment of new medicines;
• Secondly, the full incorporation of risk-based approaches to lifecycle management, together with potentially embedding some regulatory flexibilities adopted during the pandemic would support innovation in the EU, particularly in manufacturing and quality where advances in this area are often implemented via the variations framework;
• Thirdly, learnings from the pandemic and other programs such as PRIME have demonstrated that post approval changes remain a crucial bottleneck;
• Fourthly, on-going work on digital projects, portals, digital infrastructure and databases of the EMA and National Authorities serving as a building block for the future operational support to regulatory processes;
• Finally, raising the priority of the modernisation of the variation framework now would allow development of a future-state which could be aligned with other changes to the pharmaceutical legislation and would also provide the opportunity to consider how the revised framework might operate with increasing utilisation of reliance pathways and regulatory worksharing models, such as the EMA's OPEN pilot.

On behalf of the EU Trade Associations, we would therefore like to request a meeting to discuss the topic in more detail. From our perspective, the anticipated scope of such a meeting would build on the EFPIA/Vaccines Europe document submitted in July 2021, the Medicines for Europe and AESGP Report 2019 1and the previous cross trade association papers submitted in 2019, but primarily focus on some

definitive next steps for a future variation framework. At this stage, we believe that a meeting would be beneficial for both parties since a clearer understanding of the EC's vision for the variation framework will help to ensure the successful implementation of any future changes. Therefore, we would value discussion on the following points:

• Insight into the extent of changes that the EC is anticipating with the revision of the variation framework. As previously stated from the industry side, we believe that to achieve improved efficiency and support innovation then significant revisions to the framework are necessary. An indication of the direction of thinking in this area will allow all parties to develop a plan to meet the overall aims.
• The impact and relevance of the new veterinary regulation and the potential application of the variation framework as a model to human medicines. Whilst progress made with the veterinary regulation is noted, it would be good to understand if there are learnings that may be applied to human medicines moving forwards.
• How to link operational elements (Information Technology, reliance, business processes) with the legislative changes and the different stakeholders across the EU network that would need to be involved to ensure successful implementation of a new future-state for variations. We should seek to capitalise upon the development of data services such as SPOR and introduce a mechanism for changes to the data that avoids time-consuming and unnecessary temporary conversion of that data to documents for assessment.

To conclude, on behalf of the Cross-Trade Industry Association, we are incredibly keen to see this initiative progress and believe that to maximise the potential benefits an active engagement on this topic must start as soon as possible.

We thank you for considering our request and look forward to your response.

Sincerely,

Pär Tellner
Director – Regulatory Affairs
EFPIA

Beata Stepniewska
Deputy Director General
Head of Regulatory Affairs
Medicines for Europe

Christelle Anguez-Traxler
Regulatory and Scientific Affairs
Manager
AESGP

Anna Czwarno
Director, Regulatory & Science,
Vaccines Europe

7. A MODERNISED EU VARIATION FRAMEWORK FOR ENHANCING THE LIFE OF EUROPEAN PATIENTS (16 March 2023)

''*After more than 20 years since the last major revision, now is the time to update the regulatory framework for variations to simplify and adapt it to keep pace with scientific development. This will benefit patients by decreasing the risk for shortages and ensuring swifter access to innovative medicines and optimise life-cycle management to ensure the availability of safe, effective and innovative treatments to patients in a timely manner*.'' - Pär Tellner, Simon Bennett & Markus Goese

BACKGROUND

The submission of information to regulators does not end with a medicine being approved. Medicine developers are required to continuously update the terms of their marketing authorisation to reflect the current understanding of the quality, safety and efficacy of a medicine. The current EU legal framework for managing these updates, the EU Variation Regulation and Classification Guideline[9], is inflexible, outdated and is associated with a very high administrative burden both for industry and for regulators. Therefore, there is a pressing need to modernise the variation framework for human medicines in order to support future innovation in medicine development and manufacturing within the EU. Moreover, it should be a priority to revise the EU variation framework in the light of recent experience with the COVID-19 pandemic which underlined the necessity for a flexible and agile regulatory system in Europe that can rapidly respond to the needs of patients by guaranteeing the optimization of life-cycle management to deliver safe and effective treatments of high quality to patients[10].

THE TIME IS NOW

A comprehensive revision of the Variation Regulation (1234/2008) and the associated Classification Guideline (C(2013) 2804) is essential to deliver simplification, well-organized life-cycle management and to adapt to latest technological developments such as digitalization. This also includes addressing challenges that link to the increasing number of medicines associated with devices, as well as for novel and more complex therapies, such as cell- and gene/ advanced therapies (ATMPs). Meanwhile, for the EU, there is an opportunity to continue playing a leading role in driving international alignment across variation systems thereby improving lifecycle management at a global level. The time for action is now and we are pleased to see this on the Commission Workplan for Q4 2023, because:

- There are many challenges due to resource constraints within the EU regulatory network. Implementing a streamlined variation framework with accompanying advances in Information Technology to reduce the administrative burden for variations could release resources for use in other areas such as scientific advice and assessment of new medicines.
- The full incorporation of risk-based approaches to lifecycle management, together with potentially embedding some regulatory flexibilities adopted during the COVID-19 pandemic would support innovation in the EU, particularly in manufacturing and quality where advances in this area are often implemented via the variation framework. A very important modality to benefit from such full incorporation of a risk- and science-based approach would be well defined biologics (e.g. monoclonal antibodies), where industry has made significant progress over the last decades in terms of understanding the products and their manufacturing processes. The risk-based approach may also be extended beyond quality topics to include updates to labelling under certain circumstances.

[9] *https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:334:0007:0024:EN:PDF*
[10] *https://www.medicinesforeurope.com/wp-content/uploads/2020/01/ESE_2019_Medicine-for-Europe_AESGP_Variation_WEB.pdf*

- Lessons learned from the pandemic and expedited programs like PRIME have also demonstrated that post-approval lifecycle management continues to be a critical bottleneck under the current variation framework.
- On-going work on digital projects, portals, digital infrastructure and databases of the EMA and National Authorities serve as a building block for the future operational support to regulatory processes.
- Raising the modernisation of the variation framework as a priority now facilitates progress towards a future-state which could be aligned with modifications to the general EU pharmaceutical legislation.

GOING FORWARD

Going forward, it will be essential to build on experience and technical innovations to provide an EU variation framework that allows for efficient lifecycle management of medicines and vaccines today and which can also include future technological advances. Furthermore, revision to the EU change classification should incorporate all elements of the important international guideline ICH Q12 and accommodate developments of innovation and science to be "fit for the future". This should preferably happen via regulatory guidance, to allow for regular review and updating, rather than embed the detailed provisions in a regulation.

In parallel, advances in digital technology should be exploited to reduce the administrative burden associated with the oversight of minor variations that have no impact on safety, efficacy or quality of a medicine. In the near-term this may involve the development or extension of EU databases to maintain administrative information. In the longer term, advances in cloud-based technology could be employed to enable real-time maintenance and oversight of the dossier by regulators, thereby negating the requirement for any type of additional submission or data entry by regulators and industry. The present variation regulation needs however to be revised to fully benefit from such rationalization.

Lastly, the current and future needs of Regulators and Manufacturers should be reflected in a future variation framework through simplification, standardization and acceleration to certify optimal delivery of medicines to patients at a global level and reduce drug shortages. This can be achieved by redefining existing concepts such as work-sharing methods and grouping to decrease time for review and approval of the change and its subsequent implementation. Additionally, the concept of work-sharing and regulatory reliance with other regulatory agencies outside of EU, should be considered. These processes offer several benefits involving faster overall approvals, reduced regulator and industry resources and can support regulatory harmonization. This could result in rapid global implementation of changes, including in the EU[11].

CONCLUSION

EFPIA recommends that the EC and EMA fully implement the principles and tools described in ICH Q12 guidance in the future EU variation system and legislation. In addition, the future variation framework should assist a lifecycle management of medicines in being more efficient and tailored to new important modalities (e.g. ATMPs) and drug-device combination products as well as accommodate for the latest IT technological advances and digitalisation. In order to nurture European innovation, a revision of the EU variation framework needs to be tackled now. We owe it to European patients to ensure optimal and faster delivery of life-changing medicines throughout their lifecycle.

[11] https://www.medicinesforeurope.com/wp-content/uploads/2020/01/ESE_2019_Medicine-for-Europe_AESGP_Variation_WEB.pdf

8. **HOW TO ACCELERATE THE SUPPLY OF VACCINES TO ALL POPULATIONS WORLDWIDE? PART I: INITIAL INDUSTRY LESSONS LEARNED AND PRACTICAL OVERARCHING PROPOSALS LEVERAGING THE COVID-19 SITUATION - SCIENCEDIRECT (SEE PAGE: 1218-1221) (23 February 2022)** (link)

9. **HOW TO ACCELERATE THE SUPPLY OF VACCINES TO ALL POPULATIONS WORLDWIDE? PART II: INITIAL INDUSTRY LESSONS LEARNED AND DETAILED TECHNICAL REFLECTIONS LEVERAGING THE COVID-19 SITUATION - SCIENCEDIRECT (SEE PAGE: 1227) (23 February 2022)** (link)

10. **ADDRESSING VACCINE SUPPLY CHALLENGES IN EUROPE: EXPERT INDUSTRY PERSPECTIVE AND RECOMMENDATIONS (SEE PAGES 38-39) (January 2022)** (link)

11. **JOINT POSITION FROM EFPIA, IFPMA, AND VACCINES EUROPE: "PATH FORWARD TO OPTIMISE POST-APPROVAL CHANGE MANAGEMENT AND FACILITATE CONTINOUS SUPPLY OF MEDICINES AND VACCINES OF HIGH-QUALITY WORLDWIDE" (10 March 2022)** (link)