EFPIA/EBE/Vaccines Europe Reflection Paper on a Revision of the EU Variations Regulatory Framework

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.

1. 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.

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 [4,5], 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.

---

[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 http://www.ema.europa.eu/docs/en_GB/document_library/Work programme/2016/06/WC500209512.pdf and http://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/01-HMA_MG_and_PS/2016_02_HMA_Joint_Mult_Annual_Work_Plan.pdf

[4] See activities of the HMA WG on availability of medicines for human use: link here

[5] See IFPMA publication: "The complex journey of a vaccine" Part I and Part II

2. Proposals for revision of the EU variations framework

2.1. 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 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.

2.2. 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.

[6]See:http://www.who.int/biologicals/areas/biological_therapeutics/Annex_3_WHO_TRS_1011_web-7.pdf?ua=1

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.

2.3. 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.

2.4. 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.

[7] For example, a polio antigen is contained in eight vaccines that are covered by 596 authorisations worldwide.

[8] Annex 4, 65th Report, WHO expert Committee on Biological Standardization.

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.

2.5. 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.

2.6. 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.

<u>Conclusions:</u>

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.

2.7. 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)
    - a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer
    - f) Changes to quality control testing arrangements for the active substance- replacement or addition of a site where batch control/testing takes place
    - j) 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.

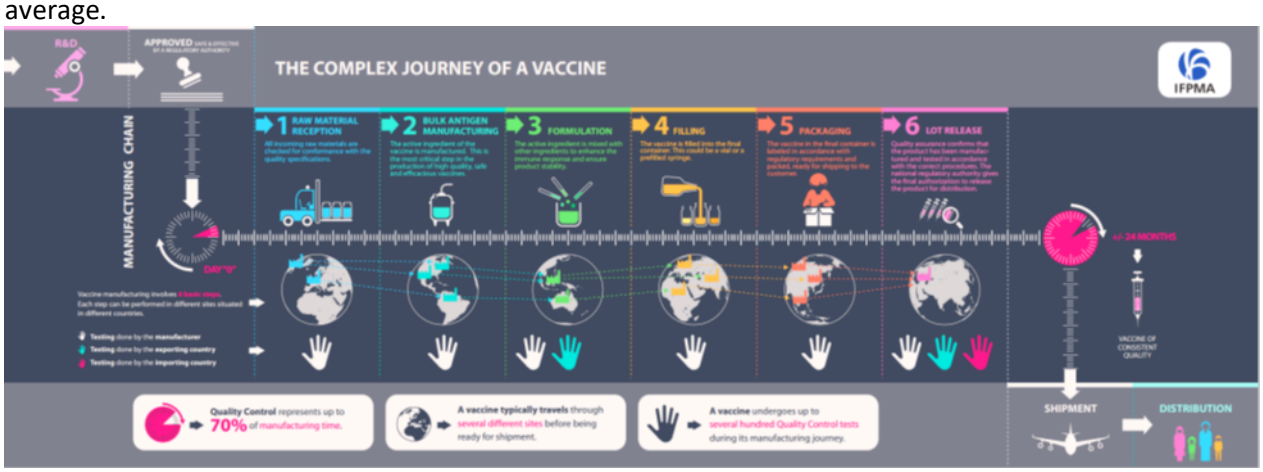


Fig.1: source IFPMA 2016 Paper "The complex journey of a vaccine Part One"

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.

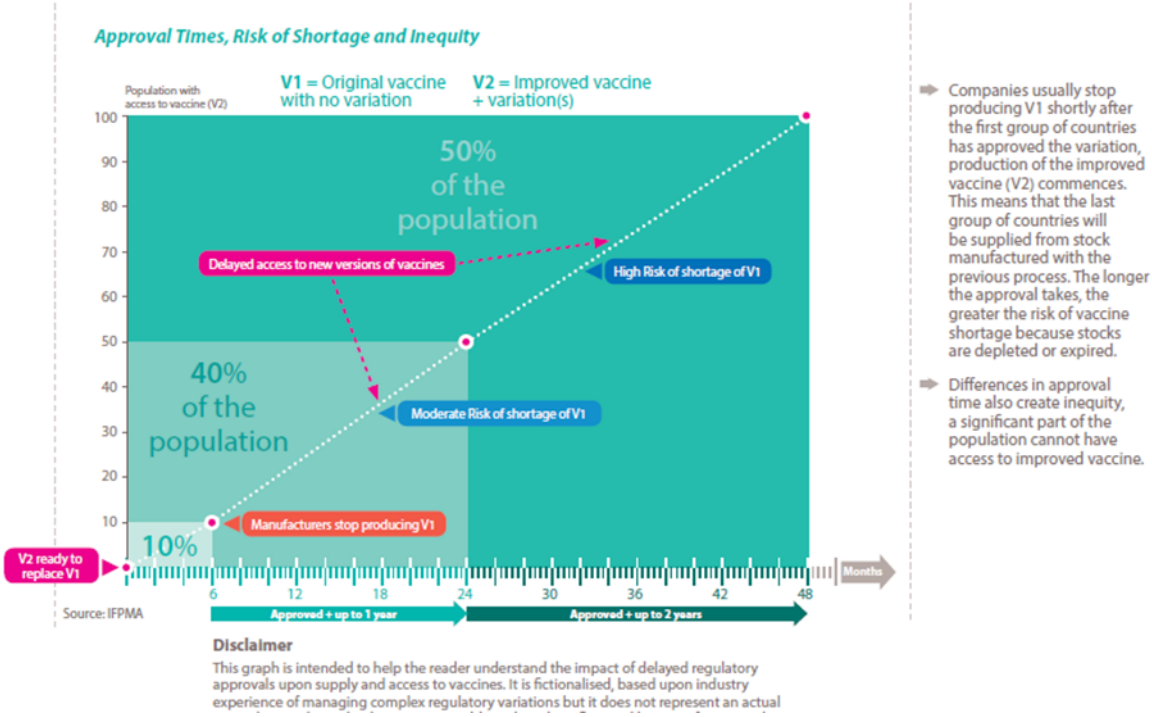


Fig.2: source IFPMA 2016 Paper "The complex journey of a vaccine Part One"

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.

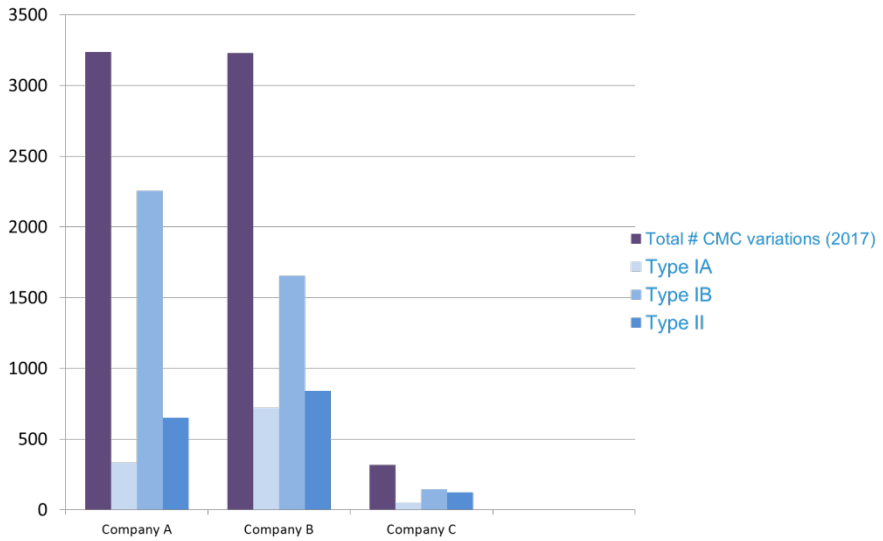


Fig.3: source PDA EU conference on Vaccines in Malaga in April 2018

- 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")*.

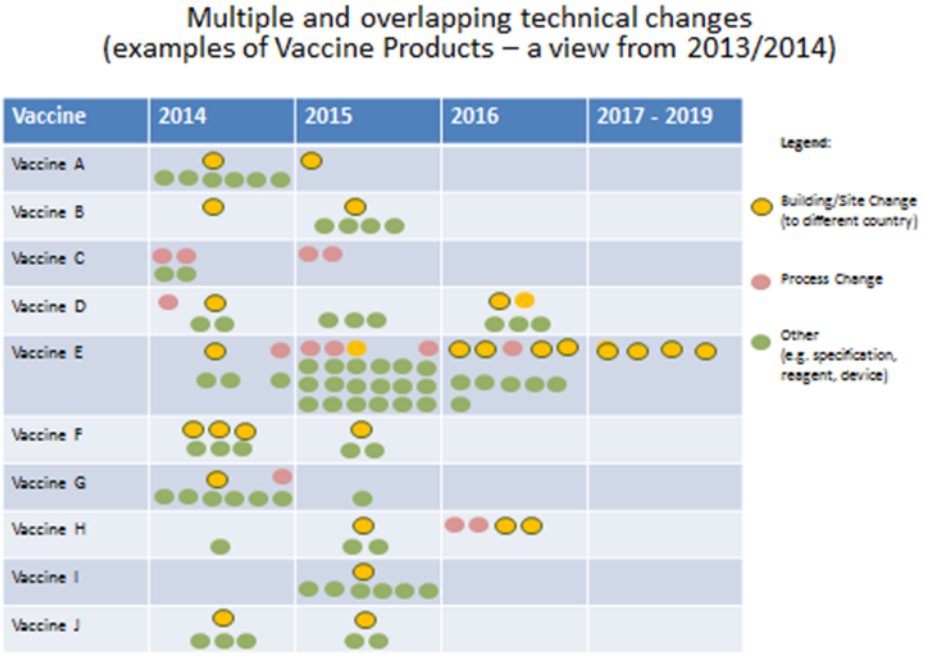
The stringent EU classification has also global impact outside the EU: in this example, the same submission package as for the EU was submitted in Brazil. The approval by the Brazilian Health Authority, ANVISA, was granted after 8 months for 3 products (out of 6), after 18 months for 2 of the remaining 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).



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.