WHY IS NOW THE RIGHT TIME TO MODERNISE THE EU VARIATIONS SYSTEM?

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VOICE OF EUROPEAN SELF-CARE INDUSTRY

Executive Summary

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.

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[1], 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 effort could be saved/resources could be used differently on activities more meaningful for public health[2].
- 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).

[1] Data collected among the members of Medicines for Europe
[2] ROG BUSINESS CASE Business Case No. 1 Optimisation of selected type IA variations, Feb. 2017

- 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.

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INTRODUCTION

INTRODUCTION

The fitness for purpose of the current regulatory framework for the maintenance of medicinal products via the so called "Variations to the Marketing Authorisation".

Ensuring a fit-for-purpose regulatory environment is a key enabler for realising the mission of the Directorate-General for Health and Food Safety (DG SANTE) to protect public health and provide access to high quality medicinal products. The regulatory framework must be efficient, sustainable and continually improve so that patient access to quality medicines is timely and unimpeded. At the same time it needs to secure a sustainable and efficient environment for regulators and industry.

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 the regulatory processes will bring tangible benefits for all participants in the healthcare network of patients, regulatory authorities and the industry. The EU Authorities (the HMA and the EMA) have also recognised a need to strive for efficiency in the regulatory processes, including variations, in its "EU Medicines Agencies Network Strategy to 2020"[3].

> ***"Over recent years various new pieces of legislation had to be implemented by the network. Some of the new legislative provisions were aiming at reducing the regulatory burden on stakeholders and the administrative burden on NCAs, but there are strong views at the level of stakeholders that there is still further room for optimising the regulatory operations. (….). In order to optimise both the administrative and scientific elements, particular emphasis will be put on their operational efficiency and cost-effectiveness This needs to be underpinned by adequate and inter-operable IT services to the network, recognising the major role that IT systems play in supporting the (regulatory) business processes and a better utilisation of available resources within a complex regulatory environment. Efforts have been made over the past years to also reduce the regulatory burden (..), however, there are still demands by the pharmaceutical industry for further work to be undertaken in this field."***

The objectives of this Paper are to:

- Identify the factors in the environment which have significantly influenced the maintenance of medicinal products over last 10 years, since the last revision in 2008.

- Identify and analyse examples where the current European regulatory reporting changes to Marketing Authorisation (MA) fails to facilitate timely access to quality medicines, because the reporting seems to constitute more of a hurdle rather than a support to bringing the necessary changes to ensure ongoing quality, safety and efficacy of medicinal products in the EEA market.

- Analyse situations where the Variations System does not achieve the principles of better regulation, striking the right balance between regulatory objectives and the need to reduce administrative burden for companies and authorities.

- Explore how the EU regulatory system of Variations to the MA can be improved, taking account of the technological and scientific evolution.

[3] EU Medicines Agencies Network Strategy to 2020 https://www.ema.europa.eu/en/documents/other/eu-medicines-agencies-network-strategy-2020-working-together-improve-health_en.pdf

CHANGES IN THE ENVIRONMENT SINCE THE LAST REVISION OF THE VARIATIONS SYSTEM IN 2008

"Doing Less More Efficiently" - Flashback to the objective of the revision in 2006 in the context of Better Regulation.

In 2006, the Commission (EC) announced its intention to create the regulatory framework covering changes to the registered particulars of medicinal products (the 'Variations Regulations') simpler, clearer and more flexible. This initiative was the main contribution of the '**Better Regulation**' EC policy agenda in the field of pharmaceuticals. The new Variations Regulation was adopted in 2008.

In the consequent Consultation Paper issued on 20 October 2006: "BETTER REGULATION OF PHARMACEUTICALS: TOWARDS A SIMPLER, CLEARER AND MORE FLEXIBLE FRAMEWORK ON VARIATIONS", the EC expressed its intention to optimise the variations system:

"The handling of variations requires significant administrative and regulatory resources, both for competent authorities and for the industry. While regulating changes in pharmaceuticals is essential to ensure that EU medicines remain of good quality, safe and efficacious, it is also important that ***such regulation does not hinder but rather stimulates the introduction of changes that are beneficial to patients in particular****, and to society in general. In other words, the* ***framework on variations must strike the right balance between protecting health and supporting innovation. It is equally crucial that the administrative workload*** *entailed by the framework still* ***enables competent authorities to focus on the substantial issues, related to the scientific monitoring of medicines and the protection of public health****."*

After more than 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 the Better Regulation have been achieved and what has changed, and to reflect on possible improvements of the variations' framework.

The factors identified in the environment, since the last revision in 2008, which have significantly influenced the maintenance of medicinal products over last 10 years:

1. Advances in science and technology:

- **a.** Better knowledge and experience gained with a risk-based approach for well-established biological products
- **b.** Continual improvement and a new approach to manufacturing optimisation (ICH Q12, ICH continuous manufacturing, Q14)
- **c.** Regulatory science-patient tailored therapies
- **d.** More complex drug therapies

2. Globalisation of the industry:

- **a.** Mergers and acquisitions
- **b.** Changes in the industry stakeholder/business partner landscape leading to increased supply chain complexity
- **c.** Concentration/optimisation of industry operations (production sites/manufacturing concentration, capacity building, purchasing)

3. Significant progress in digitalisation, including operational activities of the regulators and the pharmaceutical industry:

- **a.** Mandatory use of the fully electronic dossier submission (eCTD), emergence of several EU portals/ databases (i.e. Art 57 database, CESP), on-going process of implementing ISO IDMP/ SPOR, on-going discussion on moving into structured data submission, opportunities of multiple use and further simplification not fully explored/potential to be capitalised on; still a risk of duplication due to multiple databases
- **b.** On-going discussion on the future model of electronic Patient information (e-leaflet)

4. Increased efforts to protect public health by increased pharmacovigilance:

- **a.** Change in PV legislation: creation of PRAC regularly issuing safety recommendations
- **b.** Update of the safety profile of medicines as an outcome of PSUSA, referrals, RMP
- **c.** Changes in the Pharmacovigilance System Master File (replacement of the DDPS)

5. Unexpected political developments i.e. Brexit

6. Implementation of new legislations (i.e. Falsified Medicines Directive; Medical Devices Regulation and Veterinary Medicines Regulation) **and new guidelines** (i.e. Guideline on excipients),

DISPROPORTIONATE RESOURCES ALLOCATED TO THE VARIATIONS PROCESS IN VIEW OF THE OVERALL BENEFIT FOR PATIENTS AND THE ENTIRE REGULATORY SYSTEM

In recent years the proportion of resources spent on maintenance of medicinal products has substantially increased. A point has now been reached where for example, generic medicine companies with large portfolios are spending the same amount of resources on 3-year regulatory maintenance than they invest in R&D per year for new product development.

All these factors mentioned above have made the maintenance of medicinal products very costly and resource consuming. The costs of variations may play a role, particularly in the generic and well-established medicines industry, on the decision to maintain some medicinal products on the market, thereby being a compounding reason that potentially can lead to unavailability of medicinal products on some markets (i.e. MA withdrawals, no MA applications in some markets).

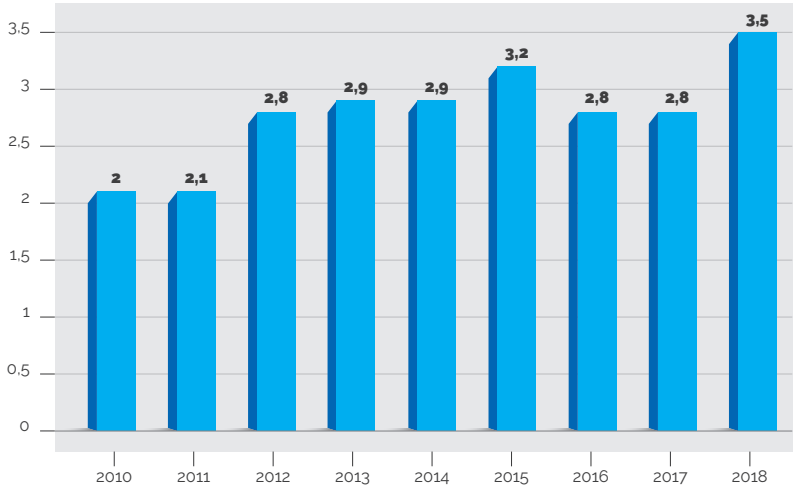
These financial resources could have been invested better – in developing/improving medicinal products, instead of spending on maintenance.

The volume increase in variations has also been driven by a number of specific events. Some are legislative (i.e. Falsified Medicines Directive), some are political (i.e. Brexit), some are connected to the new guidelines/increased requirements. The real issue is that the submission of variations seems to be the default mechanism for implementing any type of changes to the MA which is extremely heavy and resource consuming for the authorities and the industry. There is an urgent need to find a better way of submitting/reporting changes to medicinal products without unnecessary administrative burden.

Variations executed in 2010-2018

Based on data gathered from 2010-2018[4], the number of variations per MA and per year appears to have increased about 75% since 2010 (see the graph below).

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

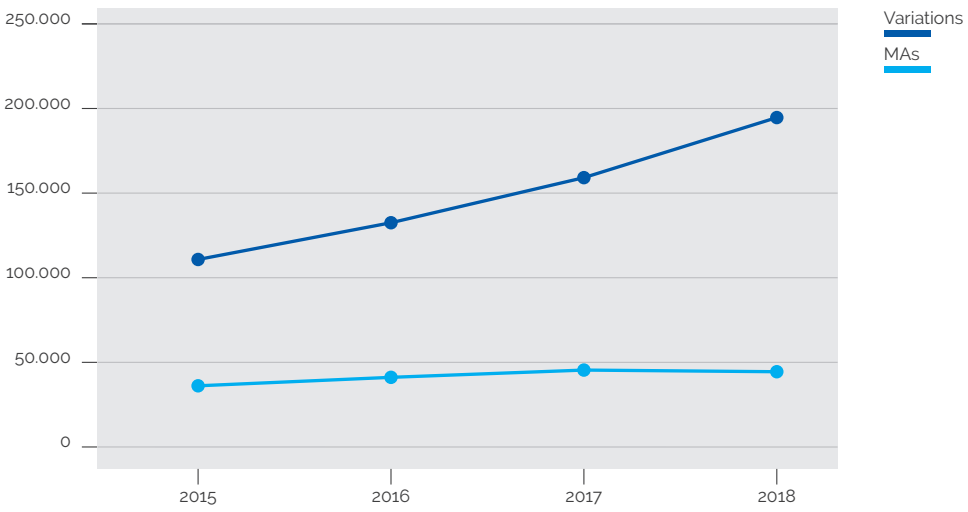


The last big increase in 2018 is associated with the implementation of the Falsified Medicines Directive and Brexit.
It should also be mentioned that, due to limited resources within company regulatory departments and other supportive functions, the filing of some variations has been postponed or kept on hold due to the limited capacity to handle it. As priority is given to variations triggered by external factors to keep regulatory compliance (I.e. implementation of new legislation/revised guidelines/ safety related variations triggered by PRAC/API related changes initiated by API suppliers), the processes of pharmaceutical product improvements suffer from lack of resources to process changes. This is also one of the reasons why the number of variations remains flat in some years (apart from peaks in 2015 and 2018 due to external factors leading to a massive amount of changes to be provided to the authorities).

Ratio between the number of variations per MA and the number of MAs

The graph below shows a clear trend in increasing the ratio between the number of variations per MA and the declining number of MAs within companies that have provided data for the survey (2015-2018)[5].

Trend in numbers of Variations and Marketing Authorisations (MAs) (2015-2018)

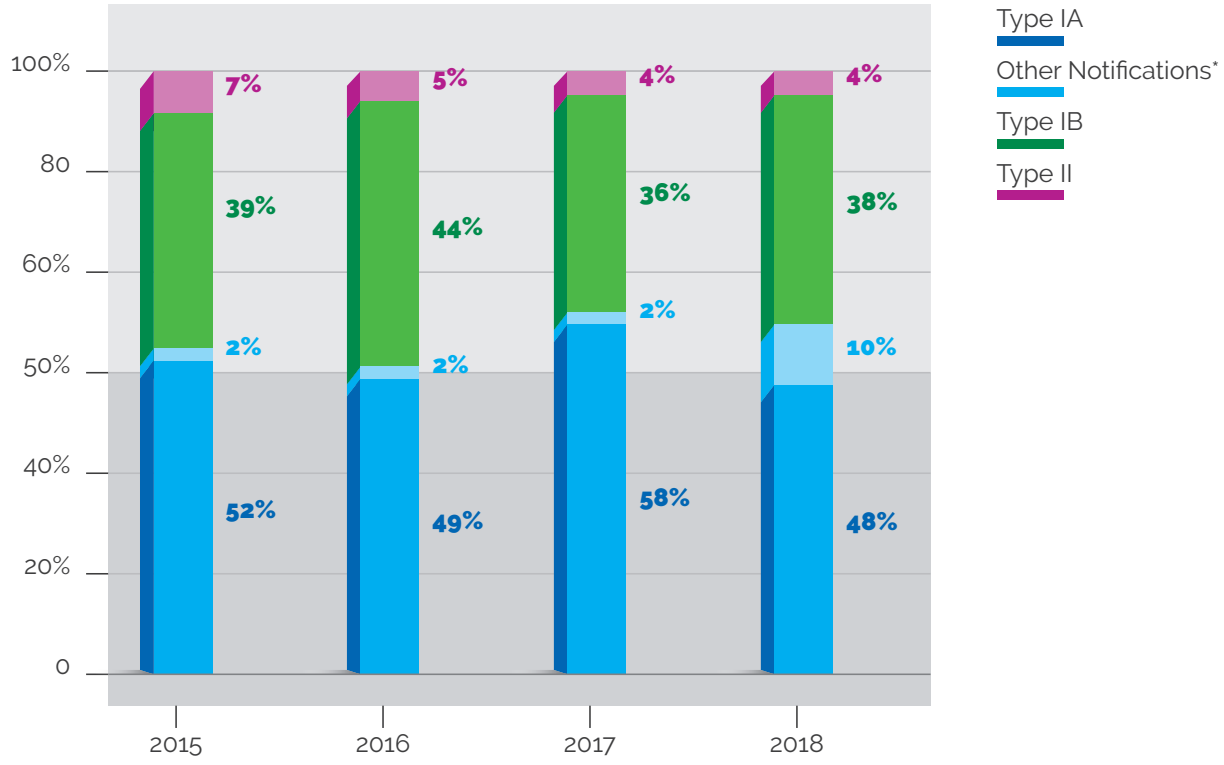


[4] Data collected among the members of Medicines for Europe.
[5] Based on the internal survey conducted by Medicines for Europe in 2019.

Statistics on types of Variations

The statistics below[6] show the significant proportion of minor changes (Type IA Variations and Notifications), reaching over 50% of the total number of variations submitted to the Competent Authorities. It means that a lot of resources are engaged, from both regulators and the industry, to process these minor, mainly administrative submissions without scientific assessment and without real value for patients.

Distribution of submission based on the type of variations (2015 – 2018)



*Other Notifications can include as example Art 61 Notification or MAH transfer.

In 2008, the introduction of minor variations Type 1A ("do and tell") was requested by the industry and has delivered a welcomed simplification. However, as an unintended consequence the overall number of variations submitted by companies has increased. This in turn has increased workload substantially for regulatory agencies. It could be argued that this increase in volumes (especially of Type IA variations) makes it more challenging for both companies and regulators to focus on important changes (other than type IA) that have the most potential impact on product quality/safety/efficacy. The consequential procedural delays due to increased numbers also put a risk on supply chain continuity and delay efficiency improvements.

Type IA notifications consist of minor changes that occur in high volumes for the workload and with no public health impact, creating an administrative burden for both authorities and industry. The changes are relatively easy to process (do and tell) but are considered to require more resources than desirable given the low-risk and low-impact of type IA notifications. Data collection on resource estimates within industry and authorities indicate a significant opportunity to reduce time spent in the process[7].

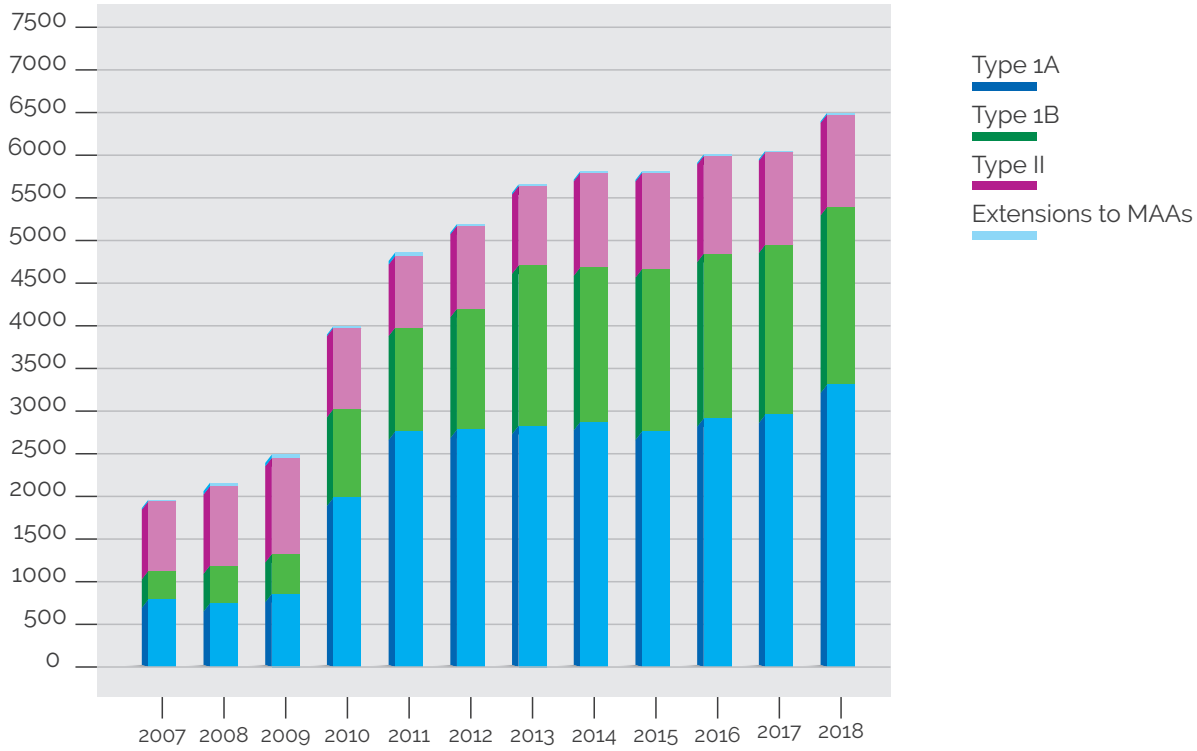
[6] Based on the internal survey conducted by Medicines for Europe in 2019,

[7] Conclusion from the work delivered by the Regulatory Optimisation Group (ROG), the HMA subgroup focused on regulatory/business optimisation, under HMA Multi Annual Working Plan priority Optimisation of the regulatory operations, objective 2, Strive for operational excellence. The background, mandate, composition and working approach of the ROG are described in the "Mandate HMA subgroup on Optimisation of the network: Regulatory Optimisation Group" (as agreed by HMA dated February 20th, 2017).

Data specific for Centrally Authorised Products

The number and type of variations for centrally approved medicinal products submitted annually to the EMA was analysed. Data was obtained from the EMA's own annual reports and the monthly Pharmacovigilance Risk Assessment Committee (PRAC) reports were also reviewed to assess the impact of the introduction of the pharmacovigilance legislation in July 2012.
Figure below, shows the number of submissions for type IA, IB and type II variations on annual basis, together with line extensions.

Variations for Medicinal Products Submitted to the EMA Centralised Authorisation



Since 2007, there has clearly been an increase year-on-year in the number of variations submitted to the EMA, with almost three times as many variations submitted in 2018 compared with 2008 when Commission Regulation (EC) No 1234/2008 was introduced.

Whilst the overall number of variations has increased, the proportion of variation types has also changed. In 2007-2009, the proportion of Type IA and Type II variations was very similar to one another and greater than the proportion of Type IB variations. However, in 2010 there was a shift and the relative proportion of Type II variations decreased, whilst Type IB increased. In their 2011 annual report the EMA attributes this to the implementation of the revised variations legislation in 2010, which changed the default Type II variation to a Type IB and introduced a new classification that resulted in the downgrading of variations from Type II to IB. The introduction of the revised variations legislation may also explain the significant jump in the number of variations overall in 2010, compared to 2009.

From 2010 onwards, the relative proportion of the different variation types has remained fairly consistent with Type IA being the highest followed by Type IB (both continuing to increase year-on-year), and Type II being the lowest. From 2013 onwards an increase in the overall number of Type IB variations can be seen; there is a significant increase in the number of Type IB variations in 2013, compared with 2012 and this increase may be due to the implementation of the new pharmacovigilance legislation in July 2012. The introduction of the Pharmacovigilance Risk Assessment Committee (PRAC) at this time, and the resulting increase in scrutiny of safety signals may have led to this increase in Type IB variations, particularly since PRAC recommendations are usually implemented via the Type IB route. This jump in Type IB variations observed in 2013 appears to have been maintained over the past 5 years.

In conclusion, there has been a considerable increase in the overall number of variations for centrally authorised medicinal products submitted annually to the EMA since the introduction of the Variation Regulation in 2008. Looking forward, if this trend were to continue then the workload for both the Regulators and Industry would be expected to increase year-on-year. This further supports the case made in this position paper that introducing more efficiency and flexibility into the system is necessary to ensure appropriate regulatory oversight and the management of post-approval changes in the future.

Conclusion

There has been a considerable increase in the overall number of variations submitted and processed by the EU Regulatory Authorities network since 2008. It puts a big pressure on efficiency of regulatory operations and adherence to timelines in view of limited resources on both, authorities and industry side. It is urgent to look at new approach to manage post-approval changes without compromising on the appropriate regulatory oversight.

Particularly optimizing the process and reducing the average time spent on processing variations (mainly Type IA) could deliver a real efficiency gain for both regulators and industry. By reducing the average time spent on the type IA notification process as well as lowering the volume by changing the way of reporting, approx. 65% of the current effort could be saved/ resources could be used differently on activities more meaningful for public health[8].

EXPERIENCE GAINED FROM THE PRACTICAL IMPLEMENTATION OF THE VARIATIONS REGULATION 1234/2008

Despite the good intention of the EC in 2006 to make the regulatory framework covering changes to medicinal products (the 'Variations Regulations') simpler, clearer and more flexible, some new elements of the Variations Regulations did not deliver the expected benefit.

KEY OBSERVATIONS:

- The average number of variations per marketing authorisation (MA) and per year has increased over time (75% increase in the period 2010-2018).
- The introduction of the 'grouped variations' approach from the last variation regulation revision led to an increase in the number of variations' submissions (separate variations versus a single Type II).
- While the concept of grouping continues to appear attractive, the practical benefits of grouping remain limited due to higher costs and disharmony in the interpretation of what can/cannot be grouped.
- The possibility offered by the regulation to report variations type IA within 12 months has not fully delivered so far, due to electronic submission/internal company document management systems.
- Recurring scenarios have been identified where changes affecting a single EU MS (within an MRP or DCP) have to be submitted to all involved EU MSs. Thie leads to recurring inefficiencies in the current system.
- Variations versus GMP supervision of the supply chain.
    - New regulatory interpretation on the inclusion of API supply chain additional information into a regulatory dossier led to an increase in the number of variations submitted within a range of about 50% (best case scenario e.g. single source, captive API) to 300% of the current number of variations (worst case scenario, e.g. multiple API sources, outsourced API).
- Complexity/ disharmony of implementation at national level despite the initial spirit of harmonisation/better regulation.

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

SUMMARY OF CASE STUDIES

KEY FINDINGS AND RECOMMENDATION

KEY FINDINGS: CASE STUDIES

Summary of the Case Studies

Case studies listed below (and described in more detail in the Technical Annexes) illustrate these observations and suggest possible solutions for future improvements.

- **CASE STUDY 1-4**
  Maintenance of the Supply Chain
  1. Maintenance of Active Ingredient Manufacturer Information
  2. Maintenance of Certificate of Suitability (CEP)
  3. Maintenance of multiple supply chains/ multiple sources of APIs
  4. Maintenance of Drug Product Manufacturing Information

- **CASE STUDY 5**
  Safety Variations

- **CASE STUDY 6**
  Technical Aspects of Variations Regulations to Improve
  Technical aspect of submission of variations to be handled differently

- **CASE STUDY 7**
  Digitalisation of Regulatory Operations as a Solution

- **CASE STUDY 8**
  Variations Classification Guideline

KEY FINDINGS

The current Variations framework needs to evolve further to better reflect the scientific progress and operational efficiency in line with the spirit of Better Regulation. To facilitate continual improvement of manufacturing processes and global supply chains management, while it is essential to provide full oversight and transparency of the product flow to the competent authorities, the process to maintain the data needs a thorough re-evaluation, with the intention to reduce the burden of regulatory activities at assessing authorities and industry.

- Goals:
  - In the spirit of Better Regulations, optimise variation filings and processing from the agencies and the industry and reduce the administrative burden.
  - Make the variation system quickly responsive to scientific & technological evolution and to patients' needs.
  - Change the way of reporting some minor changes to the supply chain via central database without compromising on full visibility of the supply chain by the Health Authorities.
  - Encourage companies to register multiple, alternative API suppliers to mitigate shortages by revising the management of API related information.
  - Provide patients with most up to date information on their medicinal products.

- Proposal:
  - Modernise the transfer of "information that has changed" which can benefit many aspects of the dossier (supply chain, safety updates, administrative data handling) via digital innovation. E.g. responsible data owner updates the respective databases, which is accessible by each NCA (i.e. leverage the robust ISO IDMP data model via SPOR database).
  - Frequent review of the Annex of the variation classification guidelines (i.e. to implement the article 5 recommendations) by handing over the responsibility from the EC to the regulatory bodies (HMA/EMA) to allow easier updates with growing experience.
  - Develop a regulatory pathway, which maintains API related administrative data by removing the traditional variation filing and optimizing the classical variation procedures.
  - Modernise the way of amending product information leaflet after various revisions (i.e. safety related information) to ensure the last information available to patients.
  - Fine tune the concept for grouping and work-sharing to allow for optimal benefits to the life-cycle management of medicinal products.
  - Introduce a two-way processing for structured content management Agency to Industry and vice versa to optimise the frequently changing documents, such as the Product Information.

SUMMARY: CASE STUDIES 1-4

Quality & Supply Chain Related Variations

In recent years the changes in the legal framework significantly affected managing the Quality and Supply Chain of medicinal products. The main impact was created by:

- The Falsified Medicines Directive (i.e. requirements on APIs).
- Changes to GMP/GDP requirements and extended interpretation of existing guidance.

A trend has been identified, that the API and Finished Dosage Form, supply chain related data is increasingly requested within the regulatory dossier, which has directly resulted in an increase number of variations.

Although it is necessary to have transparency over the supply chain by all stakeholders involved (MAHs, Supply Chain Partners, Competent Authorities) the additional administrative information within the dossier often stems from:

- Changes that have no effect on the quality of the product.
- Inclusion of minor changes which should be managed and controlled through GxP requirements, audits and inspections.

SUMMARY: CASE STUDY 1

Maintenance of Active Pharmaceutical Ingredient (API) Manufacturing Information

Issue statement

Increasing complexity of supply chains and the inclusion of information within the filed dossier, results in high workload to maintain medicinal products via larger, number of variations to be filed.

- Based on Medicines for Europe member companies' feedback[9], it appears that up to 60% of variations related to quality submitted by Marketing Authorisation Holders (MAHs) are APIs-related.
- New interpretation of the regulatory guidelines with regard to the definition of "API manufacturing", led to an increase of API supply chain information to be maintained in the regulatory filing, resulting in an increase in the number of variations submitted within a range of about 50% (best case scenario e.g. single source, captive API) to 300% or even more (in worst case scenario, e.g. multiple API sources, outsourced API).
- API related changes of a purely administrative nature require an excessive amount of processing work for the applicant and the health authority, although in parallel they are controlled by company quality systems, audits and inspections or they are assessed by the EDQM as a part of CEP certification.
- The current way of handling the maintenance of API's related information discourages companies from searching for more alternative suppliers.

Conclusion and recommendations

- A lean approach to providing the authorities with transparency on relevant supply chain functions compared to the current submissions of variations to the health authorities has to be considered.
  - A non-variation based regulatory pathway should be developed to maintain purely administrative data without classical variations filing.
  - Information on the supply chain or changes thereof shall be provided via digital means to the databases accessible by each health authorities (i.e. SPOR database), instead of classical variation procedures. The authorities shall have full access to the information and shall keep full visibility of the supply chain.
  - Minor variations TypeIA/IA_{IN} are the most designated/appropriate for optimisation of the submission process (i.e. submission via the ISO IDMP/SPOR database) due to: the administrative nature, no assessment by the health authorities, direct implementation by the MAH (and notification of the health authorities only within 12 months), no impact on the quality, safety and efficacy (The list of API variations which could be submitted via database are listed in the technical Annexes).
  - All operators in the supply chain are supervised by either the respective authority inspections or by MAH's audit and the responsibilities between industry stakeholders have to be maintained in agreements. By covering these operators in a database, visibility can be ensured but the additional coverage in the respective regulatory filing should be challenged.

[9] https://www.medicinesforeurope.com/wp-content/uploads/2016/03/EGA_Regulatory_Efficiency_Report_2015_low.pdf

SUMMARY: CASE STUDY 2
Maintenance of Certificate of Suitability (CEP)

Issue statement

- A revision of a CEP triggers a filing of a variation as required by Regulation 1234/2008 EU and its Classification Guideline, even if the change is considered as purely administrative (Type IA).
- A single API and its CEP is used by several Finish Product Manufacturers, any change to a CEP results in an enormous burden at assessing authorities and industry due to the number of marketing authorisations affected.
- A single revision of a CEP can easily affect up to a 100 or even 200 users, i.e. requiring at least an equal number of variations to be prepared, submitted and processed. Usually the number of filed variations is multiplied, as several licenses (Marketing Authorisations)/several countries or regions are affected. Every year, the EDQM issues around 1500 modifications of CEPs which are translated into variations to be filed by the MAHs of the Finish Products.
- Based on the case study and statistics collected by the Industry in the context of the work done by the EMA/HMA Regulatory Optimisation Group (ROG), handling variations related to the CEP is the most time and resource consuming category of Type IA variations for industry (see the graph in the Technical Annexes).
- It also engages a significant amount of Competent Authorities' resources. According to a survey performed by the ROG, about 20-25% of IA variations at national competent authorities are linked to CEP updates.

If the CEP holding-company changes administrative details, such as an address or name, the whole range of issued CEPs is impacted, which can result in thousands of marketing authorisations requiring an update and regulatory processing. The most prominent example is the change of an Indian state name presented in the Technical Annex.

Conclusion and recommendations

The Certificate of Suitability (CEP) for APIs issued by the EDQM is a positive example of consolidating the scientific review of quality data for APIs and subsequent reliance on the assessment of the EDQM experts. Applicants using the respective CEP currently need to assess if the change to the CEP affects the quality of the concerned Finish Product or not. Despite a clear benefit of using the CEPs, some improvements could be done in handling the changes to the CEPs and to the Finish Products:

- Optimising the regulatory process to reduce the average time spent on processing such CEP related variations (mainly Type IA) could deliver a real efficiency gain for both regulators and industry.
- There is an opportunity to modernise the transfer of "information that has changed" on the supply chain, via digital innovation. This could result in reduced volume of reporting in the traditional way and provide approx. 65% in saved time/resources, which could be used differently on activities more meaningful for public health[10].
- Changes to a Certificate of Suitability (CEP) as issued by the EDQM, impacting multiple MAHs offer the possibility for a leaner, less administrative approach of maintenance by:
    - Incorporating clear categories for the revision of the CEP changes, based on changes impact the quality of the products (thus triggering variations) and changes that are administrative, with no impact on the quality of the product. (thus triggering a modernised transfer of information).
    - The industry appreciates the on-going discussion on a proposed change in the EDQM policy to stop revisions of the CEP when the change does not affect the content.
    - The introduction to reference the CEP number only in the regulatory dossier, including a reference to the "current edition" as published by the EDQM shall be explored.
        - This would reduce the number of issued CEP revisions by 30% and subsequently will reduce the administrative burden at Competent Authorities.

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

SUMMARY: CASE STUDY 3

Maintenance of multiple supply chains/multiple sources of APIs

Issue statement

The maintenance of multiple sources of APIs is one of the key measures to prevent/mitigate shortages. With an increase of data related to API in the regulatory dossier, the industry effort to maintain multiple API suppliers is under threat due to the high impact on regulatory workload.

Particularly for older, off-patent multi-sourced medicines, the pressure on price reduction and increasing regulatory costs may destabilise this fragile balance, leading to a company decision that the viability of certain licenses, for which multiple sources are filed, needs to be re-evaluated as the MAH is responsible for keeping all the approved sources updated in the regulatory filing, although some sources might not be actively used.

Conclusion and recommendations

The simplification of this process would bring huge benefit and will reduce duplication in the system and waste of resources on both the industry and authorities' sides.
Procedural simplifications are needed to encourage companies to register multiple API suppliers to prevent shortages (list not exhaustive).

- Modernise the transfer of "information that has changed" on the supply chain, via digital innovation by reporting of minor changes via databases (i.e.SPOR).
- Moving towards structured data submission with the support of the Target Operating Model (TOM) as a basis for the future way of handling supply chain information and its changes via digital tools.
- Fast track procedure to add/change API suppliers.
- Avoiding a duplication of APIs chain oversight already controlled by GxP/company's Quality System and contractual arrangement by adding the classical variations filing.

SUMMARY: CASE STUDY 4

Maintenance of Drug Product Manufacturer information

Issue statement

In July 2017 "Guideline on manufacture of the finished dosage form"[11] dramatically increased the number of required variations (due to the need to provide all details of each manufacturer, including contractors and importers, IPC testing and on-going stability testing if different from the manufacturing site(s)).

Often, drug product manufacturers rely on external laboratories for testing of e.g. microbial purity to deal with bottle necks or specific tests that cannot be performed internally. All subcontracted activities are covered by relevant quality/ technical agreements.

With the publication of the aforementioned guideline, all additional sites (even the back-up sites not in use) have to be covered in the regulatory dossier.

Conclusion and recommendations

- The authorities shall have full access to the information and shall keep full visibility of the supply chain. However, a lean approach to transparency on relevant supply chain functions compared to the current submissions of variations to the health authorities has to be considered.
    - Changes of a purely administrative nature generate a disproportionate amount of work for the applicant and the health authority to process. There is a need to incorporate information flow from existing controlled respective quality systems, audits and inspections to facilitate transparency and better lifecycle management of medicinal products.
    - Information on some types of manufacturers in the supply chain or changes thereof shall be provided via digital means to the databases accessible by each health authority (i.e. SPOR database), instead of via classical variation procedures.

[11] EMA/CHMP/QWP/245074/2015.

SUMMARY: CASE STUDY 5
Safety variations

Issue statement

The new pharmacovigilance legislation came into effect in July 2012. More effective monitoring of safety profiles delivers an ultimate benefit to patients safety. As an outcome from different reviews of medicinal products (PRAC recommendations, safety referrals, PSUSAs) the Pharmaceutical Industry has identified an increased frequency of safety filings for the same medicinal products. Over a 12-month timeframe it is highly likely that some medicinal product can undergo several safety variations, which results in complex management of the authorised product information and dissemination into the supply chain. (see examples in the Technical Annexes).

- PRAC, as published on EMA's website, started to generate a continuous stream of recommendations with impact on product information (SmPC, PIL and labelling). These recommendations, depending on the case, are mostly implemented, following type IB variations, often to be submitted following defined timelines. In several cases, the same products are repeatedly affected within the timeframe of 12 months. Although these processes serve the purpose of increased patient safety information, the regulatory burden is significant.
    - In the period between 2012 and 2019, PRAC discussed 966 signals, out of which, 227 (23.5%) are reported to have had an update of product information recommended by PRAC.
    - It might very well be, in case the concerned text fragments are well defined, that there are IT solutions available, which could provide better processes than variation submission to allow quicker implementation and faster patient access to safety information.
- PRAC, since its start, and as published on their website, has initiated a significant number of product safety referrals, mostly leading to Decisions that product information (SmPC, PIL and labelling) need to be updated. These Decisions are to be implemented by type IA variations or by type IB variations.
    - 40 referral procedures started between 01-01-2019 and 30-09-2019 for which the PRAC recommendation led to risk minimisation measures and/or variations. In most cases the outcome of a referral leads to an adaptation of safety information in product labels.
    - Although on an annual basis the number of initiated safety referrals is not high, they often related to "class actions" meaning that the referrals cover several molecules (130 molecules were covered by those 40 referrals).
    - The type IA variations need to be submitted within very short time frames, such as 10 days, and are in fact variations with text fragments dictated by the Decision, which are to be literally copied in the existing product information for notification There is no discussion that these text updates are needed. The question is whether these consequences of Decisions need to be notified. There might be IT solutions available to support such processes.
- Being published by PRAC, having assessed a significant number of PSUSAs, in a very structured way, which was previously less systematically in place, has led to text updates resulting from the assessments.
    - In 2016-2019 (YTD 06-2019), 965 PSUSA assessments were performed leading to 229 text update recommendations from CMDh (NAP only).
- The introduction of Pharmacovigilance System Master File (PSMF) and summary of Pharmacovigilance System as a new approach was positive, overall. However, it is more than likely that for the vast majority of marketing authorisations currently contained in the xEVMPD database has undergone the variation to introduce the sPSMF into the marketing authorisation. It is likely that over 300.000 variations have been submitted to realise this.

Conclusion and recommendations

There are several proposals that could lead to a reduction of the regulatory burden when it comes to implementation of safety related text changes.

- Ensure that, upon publication of a Commission Decision after referral or upon recommendation for a label change coming from PRAC, literal agreed-upon text fragments are available, so that assessment from NCA does not lead to content discussions.

Thus leading to:

  - A setting in which, if literal agreed text fragments are available, by default the Marketing Authorisation Holder should be trusted to implement what he is legally obliged to do. This activity is subject to Health Authority inspection and should thus be adequately controlled.

  - A setting in which, if literal text fragments are agreed upon, the uploading of a text in the XEVMPD database, which is already an obligation, could be considered as a submission, making a variation application via the currently practised route a duplication of work and thus redundant.

- In order to avoid multiple revisions of the same text within a short period of time, whenever there is an outcome of a referral or a PRAC recommendation, the authorities should check if there is an ongoing PSUSA process so that product information update can be combined, if possible.

- Completely change the way in which product information is handled in the currently regulatory system. Move to a model based on structured data and develop processes via which these structured data can be easily updated, specifically when class actions are involved in cases like the Fluoroquinolones mentioned in the Technical Annex.

- Furthermore, whenever new pieces of legislation are developed a more careful impact assessment should be done, preventing that situations like the one related to the introduction of the sPSMF will not happen again. It should however be stressed that the new approach was positive, overall.

SUMMARY: CASE STUDY 6
Technical aspects of variations regulations to improve

Issue statement

Many concepts created in 2008, such as work-sharing procedures, grouping, Article 5 recommendations have great intentions with the potential for huge benefits to be gained, however due to certain constraints these benefits have room for optimisation. Those concepts need to be fine-tuned to deliver full benefit in view of handling variations efficiently.

This section presents miscellaneous cases identifying areas where the technical aspects of variations system can be improved.

1. Massive submission of Variations/Notifications applicable to a large part of a company's portfolio

External factors have triggered the Pharmaceutical Industry to submit a huge number of standalone notifications/variations that, often affect the same marketing authorisations in short period of time or applies to most of the products from company's portfolio.

A relatively minor administrative change, with no impact on product quality or patient safety can result in a large company producing a high volume of variations per year. There is a clear need to rethink the way how those changes, although relevant for the overall public health and patient benefit, can be implemented more efficiently.
These "broad in scope" initiatives are leading to multiple screenings of a company's entire portfolio to assess the impact and multiple updates of dossier sections or labelling which can even contradict a previous revision. These initiatives, appearing in parallel or consecutively, could be better coordinated/combined to improve how variations are filed in view of implementation timelines.

Examples quoted below (further developed in the Technical Annexes):
- Implementation of the of Excipients Guideline and its Annex 1
- Falsified Medicines Directive (QRD update)
- Medical Device Regulation (MDR)

2. Technical aspect of submission of variations which could be handled differently:

- **Modernised transfer of information that has changed – Via SPOR**

Variations Type-IA/IA_{IN} are an ideal segment which can benefit from modernising the transfer of information, between the Pharmaceutical Industry and Health Authorities, offering at the same time a massive potential to reduce administrative burden on resource.
Due to the administrative nature, no assessment by the health authorities and direct implementation by the MAH (and notification of the CAs only within 12 months), those variations could bypass the traditional variation pathway and be entered directly into a central database.

The technical annexes goes into a deeper look at some of the examples stated below:
- Address or name changes without the physical move of a company
- Changes that only affect partial CMS, such as address changes with the physical move of MAH
- MAH transfer- licence transfer (due to divestment/joint-venture)

In total[12], approximately 26 different variation updates (combined type IA/IA_{IN}) were identified as examples that can be transformed, to 'data only' submissions directly to the SPOR database.
This already exists within xEVMPD and the solution was proposed by the EMA (Industry, National Competent Authorities) ISO IDMP Taskforce to enhance iteration 1 of the SPOR implementation. These Organisational variations represent 26 variation guideline numbers, which amounts to approximately 35-40% of the type-IA/IA_{IN} variations in the regulatory system. Other type-IA/IA_{IN} variations that should be considered for submission in the ISO IDMP/SPOR database are the updates of Certificates of Pharmaceutical Products (CEPs) (for more background information, please refer to CASE STUDY 2).

- **Work-sharing/Grouping/Annual Reporting**

Some concepts of the Variations Regulation, such as work-sharing procedures, grouping, Article 5 document are of great benefit, however due to certain constraints are not used to a maximum effect yet. The constraints are demonstrated by practical cases & data in the Technical Annexes. In a nutshell:

- The general concept of do & tell variations is generally much appreciated by the industry, however the idea of "annual reporting" does not fit into data management within companies.
  - As most of the variations qualifying for annual-reporting are of a very administrative nature, industry recommends replacing this workload (also on the authority´s side) by using the benefits of the SPOR concept, i.e. submitting updates to the database directly.

[12] https://www.ema.europa.eu/en/documents/scientific-guideline/annex-european-commission-guideline-excipients-labelling-package-leaflet-medicinal-products-hum an_en.pdf, HMA/ EMA Regulatory Optimisation Group (ROG) BUSINESS CASE Business Case No. 1 Optimisation of selected type IA variations, Feb. 2017

- Grouping and work-sharing procedure concept is very helpful in life-cycle management. However, some requirements constitute unnecessary tasks and thus lead to these procedures not being used as much as anticipated by the regulators or – if execution is unavoidable – to delays.
  - Fine tuning of the grouping and work-sharing is necessary to fully benefit from those two procedures.

• Type IB variation by default

The industry welcomes the introduction of the Type IB variation by default with the new Variation regulation; However, it has been industry experience that:

- In many situations a Type IB does not seem to be the most adequate variation due to the simplicity/straightforwardness of the variation, e.g. when the simple non-fulfilment of a condition for a classified IA variation leads to the upgrade to a IB variation without any scientific reason.

- The process, timelines, and link to Art 5 could be fine-tuned to increase predictability and consistency in interpretation.

- Systematic amendment of the Variations Classification Guideline should be foreseen to reflect the experienced gained.
  - The Variations Classification Guideline could be considered as an EMA/ HMA (CMDh) guideline, instead of a EC guideline in view of more regular/ frequent updates (i.e. yearly update due to Art 5 recommendations; around 50 recommendations have already been issued but the guideline has not been amended).

Conclusion and recommendations

There are several proposals that could lead to an improvement of technical aspects of current variations system to fully benefit from the spirit of the Better Regulation.

- The implementation of SPOR would address the technical issues with eCTD sequences, the annual reporting of IA variations and the issue of eAF of super groupings.
- In the case of introduction of new requirements, impact assessment shall be always performed to show an overall benefit over impact on resources (from the authorities and the industry perspective), including how the requirements shall be practically introduced. Recent examples show the massive variations wave triggered during the implementation (i.e. unique identifier /FMD implementation), although an alternative, more resource efficient solutions than variations/ notifications could have been considered.
- The Annex of the Variations Classification Guidelines should be revised regularly to implement the Art 5 recommendations.
  - The Variations Classification Guideline could be considered as a EMA/ HMA (CMDh) guideline, instead of an EC guideline in view of a more regular/ frequent update (i.e. yearly update due to Art 5 recommendations; around 50 recommendations have already been issued but the guideline has not been amended).
- New way of informing authorities about changes needs should be put in place for a better use of resources:
  - Variations Type-IA/IA_{IN} are the most designated/ appropriate for optimisation of submission process (i.e. submission via the ISO IDMP/SPOR database) due to: administrative nature, no assessment by the health authorities, direct implementation by the MAH (and notification of the health authorities only within 12 months), no impact on the quality, safety and efficacy.
  - Simple changes that are identical for most products and have no need for discussion such as the introduction of QRD version for FMD implementation could be implemented without separate regulatory action.

SUMMARY: CASE STUDY 7

Digitalisation of Regulatory Operations as a Solution

Issue statement

Variations framework and Telematics Systems are "disconnected".

The Commission Regulation (EC) No 1234/2008 ('the Variations Regulation') was adopted in 2008. Therefore, EU legislation concerning regulatory variations (human pharmaceutical products) is not aligned to the newly developed IT tools and Telematics system initiatives, such as eCTD, Art 57, SPOR/ISO IDMP and FMD.
Consequently, the complex and invariably segregated EU Telematics environment fails to make an ideal fit with the submission and processing of regulatory variations. As a result, Industry and Authorities are forced to continue to undertake redundant tasks or adopt workarounds: investing resources and time to manage a huge and annually-growing number of variations: notably administrative, often information-only variations such as changes or corrections of addresses.

Telematics challenges impacting Variations

- The logistics of eCTD discourages submission of annual reports of certain changes. In particular, Type IA_{IN} variations cannot be added to the annual report, due to short implementation timelines. In addition, IB variations affecting the same dossier part, result in an exclusion of this change from the annual report documentation. Therefore, the provision of the annual report in the current regulation as an enabler of efficient life-cycle management of marketing authorisations, has less success in the EU in comparison to the example set by such use in US regulation.

- Implementation of the new e-Application form is recognised as being progressive. However, the one-time usage of data (i.e. lack of reusability) by MAHs is considered to be a missed opportunity to gain efficiency in the regulatory variation process.

- An improvement implemented in 2017, where the Article 57 database receives "data only" submissions, for the changes related to the QPPV and the location of the PSMF, (which prior to implementation, had to be submitted as a classical Type IA variation) showcase the huge value when technology is leveraged. There was a substantial reduction in work that would have otherwise been necessitated by the changes enforced by the UK's invocation of Article 50. The proposed use of the Union Veterinary Database for information-only regulatory changes instead of certain existing Type IA variations is also an important step for future optimised processes in the human medicines sector.

The effective use of information systems can be a powerful enabler for such regulatory efficiencies across the EU Network. However, for these changes to be implemented, the variation regulation also needs to be modified to make it more future-proof by being less prescriptive in defining how the variations process should be executed. Multi-stakeholder benefits can be realised by maximising the opportunities of the SPOR database and the PMS Target Operating Model (TOM) concept, by moving towards electronic notification (through SPOR) of changes to the marketing authorisations and towards structured content management for electronic product information (ePI). There is a major opportunity to connect the dots, link systems and databases and accelerate procedural efficiency, data quality and accuracy; leading to a single trustable source for multiple regulatory uses.

Conclusion and recommendations

It is crucial to capitalise upon existing and future IT systems by:

- Optimising the EU regulatory variations by using the TOM and SPOR data services to manage associated regulatory data in a "one-time" fashion via Telematics projects, such as CESSP, TOM and ePI should be developed, implemented or potentiated with the objective of fitting with the Variations submission. Interoperability and reusability of data can improve dramatically the redundant regulatory activities with a beneficial effect on all stakeholders. A significant cascade of benefits will be on patients firstly (e.g. safety variations can be implemented in a faster way compared to current practice if the variation process is faster and smoother)

- Switching from a document-based processes towards the submission, management and evaluation of structured data via a two-way common EU Regulatory submission gateway.

    - Systems should be specified for adaptive and versatile purpose to ensure an efficient use by the EU Regulatory Network; they should be designed to fit with the full Regulatory environment into which they will be implemented; e.g. the use of SPOR for administrative variations).

- Process should be data driven: submission from Industry and validation from regulators should happen only in structured data.
- Removing redundancy by re-using approved ISO IDMP and application dataset data and avoid risks of re-keying of data in variation submissions.
- Tracking the status of submissions of Variation should be visible for the applicants.
- Building on the success of Common European Submission Portal (CESP) and electronic Application Form (eAF) in harmonising electronic submissions (and thereby making national processes redundant) and moving to future significant improvement via Common European Single Submission Portal (CESSP).
- Investing in Electronic product information (ePI) as an integral part of the Regulatory efficiency concept. In particular a strategic way of designing the ePI IT system would improve the Variation system as well; for example, when MAH informs regulator and changes ePI data, if the ePI system is efficiently designed, these changes can be automatically implemented at once in all affected PI annexes.

SUMMARY: CASE STUDY 8

Variations Classification Guideline

In principle, the purpose of the separation of the Variations Classification Guideline from the Variations Regulation in 2008 was to allow easier updates with growing experience.
Despite several new developments and recommendations (i.e. 46 classifications of variations issued by the CMDh in accordance with Art. 5 of the EC No 1234/2008), the Guideline has not been regularly amended (last update took place in May 2013). The current way of updating the Variations Classification Guideline does not seem to be optimal. For the classification guideline it could be beneficial to hand over the responsibility from the EC to the regulatory bodies being strongly involved in this topic, i.e. make it a combined HMA/EMA guideline.

This chapter presents only one example of the current Variations Classification guideline which needs to be looked at in the context of the scientific progress and experienced gained over the last 10 years. (i.e. herbal medicines and homeopathic medicinal products from herbal origin). However other areas have been also identified for potential reassessment (i.e. well-characterised biologics, vaccines etc).

Herbal Medicinal Products

The life cycle management of herbal medicinal products and in particular their variation classification regime is generally higher than chemically defined medicinal products. Like for synthetised APIs, the average cost of variations/MA has been constantly growing over the years.
In the case of finished products containing chemically defined active substances, minor changes in the manufacturing chain such as the addition of a sieving step for removal of aggregates or changes in the mixing time for blending powders or granules for immediate-release dosage forms, are classified as Variation Type IB for herbal medicinal products whereas they are type IA for chemical compound according to B.II.b.3 a. Classification as type IB is more resource intensive and hinders short term implementation of technical progress. In addition, it is not clear why herbal medicine products are subject to a higher variation level given the fact that there is no impact on the quality of the medicinal product, regardless of whether it is a herbal or chemical medicinal product. The evaluation time is extremely variable from country to country and can be extremely long in some cases.

A change e.g. of cultivation sites or geographic origins only which does not affect the pharmacopoeial requirements should be acceptable without the need to file a prior approval variation ("geographical source" should be removed from variation type II B.I.a.2 d) wording). The quality of the herbal API is proven by conformity with Ph. Eur. Specification, as is the case for chemical APIs. This is of particular relevance because changes in sourcing are often a consequence of conditions during growing or harvesting of plants, which cannot always be influenced by the manufacturer of the herbal medicinal product and might, in the worst case, result in shortages and avoidable out of stock situations. It is particularly problematic when the evaluation time is very long.
The overall goal is to produce state-of-the-art herbal medicinal products and to enable further technical progress under proportionate regulation.
This situation applies to homeopathic medicinal products made from herbal substances/preparations.

Conclusion and way forward

- 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.
- Modernisation of the current Variations System offers multiple advantages of simplification and better use of resources for both industry and authorities, particularly for handling minor, often administrative changes through digital means.
- Optimisation of reporting changes to the supply chain could be an efficient enabler to prevent and mitigate shortages.

INDUSTRY ASK

The pharmaceutical industry coalition calls to modernise the current variations system because it has not evolved to keep pace with the above evolutions in technology and regulatory requirements. 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.

TECHNICAL ANNEX

DETAILED CASE STUDIES

DETAILED CASE STUDIES

Case studies present in detail the issues identified with the current Variations system and highlighted in the first part of the document.

INTRODUCTION

The pharmaceutical industry has faced several changes in legislative framework in recent years affecting Quality and Supply Chain areas. This includes, but is not limited to, the Falsified Medicines Directive (i.e. requirements on APIs), changes to GMP/GDP requirements and extended interpretation of existing guidance.

Due to these factors, a trend is noticed that API and Finished Dosage Form supply chain related data is increasingly requested within the regulatory dossier. Without questioning the necessity to oversee the supply chain by the MAHs and make all supply chain partners visible to the Competent Authorities, the inclusion of all such additional information to the dossier has the potential to significantly increase regulatory maintenance activities through variations, although it could be done more efficiently via other means. It is particularly relevant for changes having no effect on the quality of the product but being more of an administrative nature or those which should be managed and controlled through GxP requirements, audits and inspections.

CASE STUDIES 1-4

Quality & Supply Chain Related Variations

Increasing complexity of supply chains and the reflection thereof in the filed dossier has direct implications on the maintenance of medicinal products, including an increasing number of variations to be filed. Based on Medicines for Europe member companies' feedback[13], it appears that up to 60% of variations related to quality submitted by Marketing Authorisation Holders (MAHs) are related to changes to the APIs.

Due to currently applying guidelines and legal requirements, industry is obliged to provide and to maintain the information related to the manufacturing and supply chain towards the CAs. However, the regulatory activities to keep the administrative details of registered sites up to date via variations is high.

CASE STUDIES 1

Maintenance of Active Pharmaceutical Ingredient (API) Manufacturing Information

Issue Statement:

Historically, "manufacturer" was interpreted by industry and assessors as the site performing the (last) manufacturing steps leading to the active ingredient. With current guidance the filed regulatory information should include (non-exhaustive list):

- Manufacturer of active ingredient
- Supplier of starting material
- Manufacturer of intermediate
- Micronisation/ sterilisation sites
- QC testing sites for intermediate/ active ingredient
- Sites responsible for stability testing

Since 2013, several regulatory guidance documents or application forms have undergone changes with regard to the definition of "API manufacturing" and expressing regulator's expectations for the information to be included in the dossier.

The level of detail as requested by the regulators in section 2.5.3 regarding the manufacturer(s) of the active substance(s) in the marketing application has been changed.

[13] HMA/EMA Regulatory Optimisation Group (ROG) BUSINESS CASE Business Case No. 1 Optimisation of selected type IA variations, Feb. 2017.

Application Form 2002 Notice to Applicants version_2: 2. MARKETING AUTHORISATION APPLICATION	Application Form 2013 Notice to Applicants version current 2. MARKETING AUTHORISATION APPLICATION PARTICULAR
MAA application form section 2.5.3 Manufacturer(s) of the active substance(s) - "Note: only the final manufacturer to be mentioned"	MAA application form section 2.5.3 Manufacturer(s) of the active substance(s) "Note: All manufacturing sites involved the manufacturing process of each source of active substance, including quality control/ in-process testing sites, should be listed. Broker or supplier details alone are not acceptable. For biotech products include all sites of storage of master and working cell bank and preparation of working cell banks when relevant. For each site provide the relevant information."

As a result, the number of sites to be maintained in the regulatory file e.g. the drug substance section has significantly increased and consequently, it has also led to an increase in the number of variations submitted within a range of about 50% (best case scenario e.g. single source, captive API) to 300% or even more (worst case scenario, e.g. multiple API sources, outsourced API).

Example 1: API INN A Filmcoated tablets API manufacture is outsourced	Previous conditions	Based on current guidelines and interpretations by regulators
	API Source 1 for INN A	API Source 1 for INN A
	Manufacturer of the INN A	Manufacturer of the INN A
		NEW Intermediate A
		NEW Intermediate B
		NEW Stability Testing Site
	1 site	4 sites (i.e. +3 NEW sites)
	API Source 2 for INN A	API Source 2 for INN A
	Manufacturer of the INN A	Manufacturer of the INN A
		NEW IPC testing site
		NEW Release testing site
	1 site	4 sites (i.e. +3 NEW sites)
TOTAL for example 1	**2 sites**	**8 sites (i.e. +6 NEW sites)**

Example 2: API INN D API manufacture is internal	Previous conditions	Based on current guidelines and interpretations by regulators
	API Source 1 for INN D	API Source 1 for INN D
	INN D manufacturer	INN D manufacturer
	Intermediate A	Intermediate A
	Intermediate B	Intermediate B
		NEW control testing site for intermediate A
		NEW control testing site for intermediate B
TOTAL for example 2	**3 sites**	**5 sites (i.e. +2 NEW sites)**

Example 3: API INN B/INN C Filmcoated tablets API manufacture is outsourced	Previous conditions	Based on current guidelines and interpretations by regulators
	Manufacturer of the INN B	Manufacturer of the INN B
	Manufacturer of the INN A	NEW Intermediate X
		NEW Intermediate Y
		NEW Stability Testing Site
		NEW Stability Testing Site
	1 site	4 sites (i.e. +3 NEW sites)
	API Source 2 for INN B	API Source 2 for INN B
	Manufacturer of the INN B	Manufacturer of the INN B
		NEW Intermediate X
		NEW Intermediate Z
		NEW Intermediate L
		NEW Quality Control
	1 site	4 sites (i.e. +3 NEW sites)
	API Source 1 for INN C	API Source 1 for INN C
	Manufacturer of the INN C	Manufacturer of the INN C
		NEW Intermediate N
		NEW Intermediate M
		NEW Stability Testing Site
	1 site	4 sites (i.e. +3 NEW sites)
	API Source 2 for INN C	API Source 2 for INN C
	Manufacturer of the INN C	Manufacturer of the INN C
		Additional Manufacturing Site
		NEW Intermediate O
		NEW Intermediate P
		NEW Quality Control
	1 site	4 sites (i.e. +3 NEW sites)
TOTAL for example 3	**4 sites**	**16 sites (i.e. +12 NEW sites)**

It must be noted that all sites were, and still are, managed and controlled through GxP requirements, audits and inspections. In line with Article 46 of Directive 2001/83/EC, the MIA holder responsible for dispensing the API into the drug product manufacturing process and/or responsible for batch release, must provide a signed "QP declaration". The declaration is issued on the basis of successful audits by "suitably trained and experienced person(s), who may be a third party contractor" and the audit has to include "each manufacturing site to be registered that is involved in the manufacture of the active substance should be stated, beginning from the first use of the designated starting material".

Conclusion and recommendations

The objective of the industry is to provide insights on the supply chain actors without an unnecessary demand on workload, manpower and expenses, as the information requested by the regulators can be made available via other means. Some changes in the supply chain are currently handled via variation procedures to keep the submitted information into the regulatory dossier updated although already extensively covered by existing GxP requirements. The industry proposes that non-quality related changes (administrative) shall be handled via IT systems/ databases (already existing which need to further evolve or being under development) or other pathways.

CASE STUDY 2
Maintenance of Certificate of Suitability (CEP)

Issue statement

The Certificate of Suitability (CEP) for APIs issued by the EDQM is a positive example of consolidating the scientific review of quality data for APIs and subsequent reliance on the assessment of the EDQM experts. Applicants using a respective CEP currently need to assess if the change to CEP affects the quality of the concerned Finished Product or not. However, any revision of a CEP triggers a filing of a variation as required by Regulation 1234/2008 EU and its Classification Guideline, even if the change is considered as purely administrative (Type IA). As each API and its CEP is used by several Finished Product Manufacturers, any change to a CEP results in an enormous burden at assessing authorities and industry due to the number of licenses affected.

This is exemplified by data below as provided by two API producers (CEP holders). Each API producer provided the number of affected CEP users for their top 5 APIs covered by a CEP of a given substance.

	CEP HOLDER A	CEP HOLDER B
	Number of affected CEP users[14]	
API Top 1	110	185
API Top 2	102	146
API Top 3	65	83
API Top 4	48	82
API Top 5	39	76

As a consequence, any revision of a CEP can easily affect up to a 100 or even 200 Market Authorisation Holders, i.e. requiring at least an equal number of variations to be prepared, submitted and processed. Usually a number of filed variations is multiplied as several licenses (Marketing Authorisations)/ several countries or regions are affected.

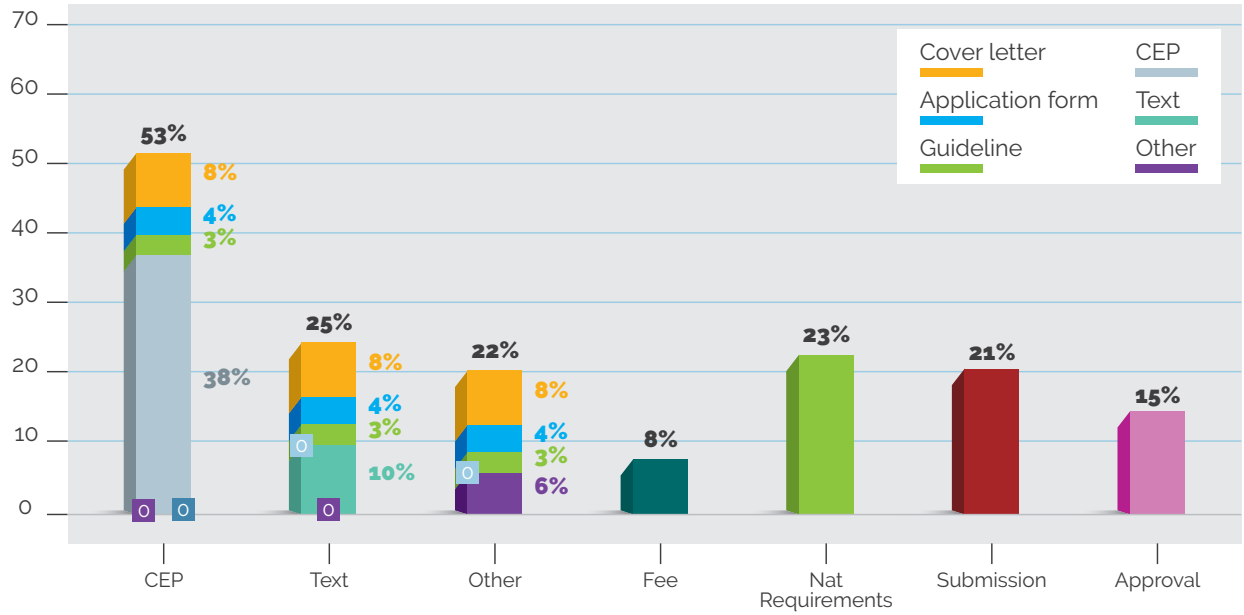
EXAMPLES OF IMPACT

- The most prominent example for the above change stemed from the Indian government creating a change in the name of the state in 2013. Andhra Pradesh was changed to Telangana, which directly impacted the address change of CEP holders/ manufacturing sites located in that specific region. All impacted CEP holders had to revise their Certificates. All MAHs/users of the impacted CEP subsequently, had to file the administrative change for each MA where those CEPs were used.
- The table below, illustrates the scale of resources engaged, which resulted in multiple submissions by multiple MAHs globally:

	2017	2018
Issued by EDQM	1428 CEP revisions	1449 CEP revisions

Based on the case study and statistics collected by the Industry in the context of the work done by the EMA/HMA Regulatory Optimisation Group (ROG), handling variations related to the CEP is the most time and resource consuming category of Type IA variations for industry (see the graph below). It also engages a significant amount of Competent Authorities' resources.

Total assembly time IA variation/MA



[14] Number of CEP user" is counted as a number of declaration of access to the CEP which the CEP holder issued.

Conclusion and recommendations

In general, optimising the process and reducing the average time spent on processing these CEP related variations (mainly Type IA) could deliver a real efficiency gain for both regulators and industry.

The industry appreciates the on-going discussion on proposed changes in the EDQM policy to stop revisions of the CEP when the change does not affect the content. This would reduce the number of issued CEP revisions by 30% and subsequently will reduce the administrative burden at CA. According to a survey performed by the Regulatory Optimisation Group (ROG), about 20-25% of IA variations at national competent authorities are linked to CEP updates.

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 effort could be saved/resources could be used differently on activities more meaningful for public health[15].

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

CASE STUDY 3

Maintenance of multiple supply chains/ multiple sources of APIs

Issue statement

The maintenance of multiple sources of the APIs is one of key measures to prevent/mitigate shortages.
With an increase of data related to the API in the regulatory dossier, the industry effort to maintain multiple API suppliers due to the high impact on regulatory workload is under threat due to high impact on regulatory workload.
Particularly for older, off-patent multi-sourced medicines, the pressure on price reduction and increasing regulatory costs may destabilise this fragile balance, leading to a company decision that the viability of certain licenses for which multiple sources are filed needs to be re-evaluated as the MAH is responsible for keeping all the approved sources updated in the regulatory filing, although some sources might not be actively used.

Conclusion and recommendations

The simplification of this process would bring huge benefit and will reduce a lot of duplication in the system and waste of resources for both the industry and authorities.
Procedural simplifications will also stimulate companies to register multiple API suppliers to prevent shortages.
Possible simplifications (list not exhaustive):

- Reporting of minor changes via databases (i.e.SPOR).
- Moving towards structured data submission with the support of the Target Operating Model (TOM) as a basis for the future way of handling supply chain information and its changes via digital tools.
- Fast track procedure to add/change API suppliers.
- Avoiding a duplication of API chain's oversight already controlled by GxP/ company's Quality System and contractual arrangement by adding the classical variations filing.

CASE STUDY 4
Maintenance of Drug Product Manufacturer information

Issue statement

Similar to the changes that affected the information for the active substance manufacturer (as described above), in July 2017 the "Guideline on manufacture of the finished dosage form"[16] was adopted by CHMP and came into effect 6 months after publication. The guidance on section 3.2.P.3.1 Manufacturer(s) added clarity on regulators' expectations, thereby dramatically increasing the regulatory consequences:

"The name, address and responsibility of each manufacturer, including contractors and importers should be provided. This applies also to all quality control sites, including IPC testing and on-going stability testing if different from the manufacturing site(s)."

Often, drug product manufacturers rely on external laboratories for testing of e.g. microbial purity to deal with bottle necks or specific tests that cannot be performed internally. All subcontracted activities are covered by relevant quality/ technical agreements.

With publication of the aforementioned guideline, all additional sites have to be covered in the regulatory dossier, even if they only provide back-up. With the increase of administrative information in the dossier, the regulatory burden and variations to be filed for maintenance of the sites again increases as demonstrated in the example below:

Example 1: Drug product FCT 50 + 250 mg	**Previous conditions**	**Based on current guidelines and interpretations by regulators**
	DP Source for FCT 50mg	DP Source for FCT 50mg
	A) DPM for FCT 50 mg	A) DPM for FCT 50 mg
	B) Intermediate supplier of blend	B) Intermediate supplier of blend
		C) Intermediate QC testing site
		D) IPC testing site for DPM A
	DP Source for FCT 250mg	DP Source for FCT 250mg
	C) DPM for FCT 250 mg	E) DPM B for FCT 250 mg
	B) Intermediate supplier of blend	B) Intermediate supplier of blend
	D) Secondary Packaging, release site D	E) Secondary Packaging, release site C
		F) Release testing site for specific parameter
		G) Release testing site for specific parameter
		H) Stability testing site for DPM A/ B
TOTAL for example	**4 sites**	**9 sites (i.e. +5 NEW sites)**

Again, industry is fully committed to transparency on the stakeholder involved in the drug product flow, importers and on involved testing sites but the approach to maintaining the information via a classical submission of variations has to be reconsidered.
With the new requirement that the import of pharmaceutical goods into the EEA is also defined as **manufacturing**, the respective sites must have a "Manufacturing and/or Import Authorisation" in place. As a result of the change in legislation, for medicinal products or bulk imported from 3rd countries at least an additional "site of physical import" needs to be registered and consequently included in section 3.2.P.3.1 Manufacturer(s).

The control of the site is already ensured by GxP as for all other sites involved in the flow of goods, so the maintenance of the importer in the regulatory dossier is questionable. Transparency on the flow of goods shall nevertheless be ensured for CAs but certain information should be handled in a less time-consuming manner, not by filing of variations.

[16]EMA/CHMP/QWP/245074/2015.

OVERALL SOLUTIONS AND RECOMMENDATION FOR QUALITY AND SUPPLY CHAIN RELATED VARIATIONS

The first priority for regulatory authorities and pharmaceutical companies is to ensure access to medicines for patients without putting quality, safety or efficacy at risk. This is top priority and the main driver for all stakeholders, but a joint position of authorities and industry should determine what level of information is truly necessary in the regulatory filing and how it could be efficiently maintained.

Industry fully commits to the need for transparency on the product flow and involved stakeholders but the means to maintain the data need a thorough re-evaluation in order to reduce the burden of regulatory activities for assessing authorities and industry. All examples demonstrate that an increased maintenance level for information of active substance or finished product manufacturer is required. With the increase of sites included in the dossier, the burden to maintain administrative details increases, thereby consuming resources at industry and agency level without gain in quality of medicines.

Therefore:

- 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 (by incorporating ICH Q12 into the existing EU Variations framework).

- While it is essential to provide full oversight and transparency of the product flow and involved stakeholders to the competent authorities, how the data is maintained need a thorough re-evaluation in order to reduce the burden of regulatory activities for authorities and industry.

- A lean approach to providing the authorities with transparency on relevant supply chain functions compared to the current submissions of variations to the CAs have to be considered.

  - Information on the supply chain or changes thereof shall be provided via digital means to the databases accessible by each CA (i.e. SPOR database), instead of classical variation procedures. The authorities shall have full access to the information and shall keep full visibility of the supply chain.

  - All operators in the supply chain are supervised by either respective authority inspections or by MAH's audit and the responsibilities between industry stakeholders have to be maintained in agreements. By covering these operators in a database visibility can be ensured but the additional coverage in the respective regulatory filing should be challenged.

- The current way of handling the maintenance of API related information discourages companies from registering several alternative API suppliers (as alternative suppliers could be a way to mitigate shortages, optimisation would be very beneficial).

  - Non-variation based regulatory pathway should be developed to maintain purely administrative data without classical variations filing.

  - It should be evaluated what changes are truly adding to patient safety and require a scientific assessment by competent authorities and which data could also be adequately maintained e.g. in databases or other IT systems.

  - Minor variations Type-IA/IA_{IN} are the most designated/appropriate for optimisation of submission process (i.e. submission via the ISO IDMP/SPOR database) due to: administrative nature, no assessment by the CAs, direct implementation by the MAH (and notification of the CAs only within 12 months), no impact on the quality, safety and efficacy.

  - Certain functions and/ or operating steps could be handled purely in IT databases as GxP compliance is managed through audits, inspections and quality agreements (without undermining transparency of the product flows.

  - Reference to the EudraGMDP database for sites covered and/or a maintenance of the respective data in a database.

- Changes to a Certificate of Suitability (CEPs) as issued by the EDQM, impacting multiple MAHs offer the possibility of a leaner, less administrative approach to maintenance.

  - Revision of the CEP impacting the quality of the products (thus triggering variations) shall be differentiated from changes without impact and shall be handled differently from a process perspective.

  - For administrative changes to CEP/ TSE certificates, a simplified regulatory pathway should be implemented making use of either available or planned IT databases.

  - It should allow the inclusion of a reference to the CEP number only including a reference to the "current edition" as published by the EDQM.

CASE STUDY 5
Safety variations

Issue statement

The new pharmacovigilance legislation came into effect in July 2012. Effective monitoring of safety profile delivers an ultimate benefit to patients, however it also triggers more regulatory actions to implement the outcome of pharmacovigilance, including an increase of safety variations (outcome of PRAC recommendations, safety referrals, PSUSAs). In several cases, the same products are repeatedly affected within the timeframe of 12 months.

- PRAC, as published on EMA's website, started to generate a continuous stream of recommendations with impact on product information (SmPC, PIL and labelling). These recommendations, depending on the case, are mostly implemented, following type IB variations, often to be submitted following defined timelines, which cannot really be influenced by marketing authorisation holders.
  In several cases, the same products are repeatedly affected within the timeframe of 12 months.
  Although these processes serve the purpose of increased patient safety information, the regulatory burden is significant. It might very well be, in the case where the concerned text fragments are well defined, that there are IT solutions available, which could provide better processes than variation submission to allow quicker implementation and faster patient access to safety information.

- PRAC, since its start, and as published on their website, has initiated a significant number of product safety referrals, mostly leading to Decisions that product information (SmPC, PIL and labelling) need to be updated. This is illustrated on the presentation of the 5 years of operation presented by the PRAC chair at the occasion of the 11th stakeholder forum on the pharmacovigilance legislation in September 2017 (available here). These Decisions are to be implemented by products listed on the Annex 1 to the referral by type IA variations and other products by type IB variations.
  The type IA variations need to be submitted within a very short time frame, such as 10 days, and are in fact variations with text fragments dictated by the Decision, which are to be literally copied in the existing product information for notification.
  There is no discussion that these text updates are needed. The question is, whether these consequences of Decisions need to be notified. There might be IT solutions available to support these processes.

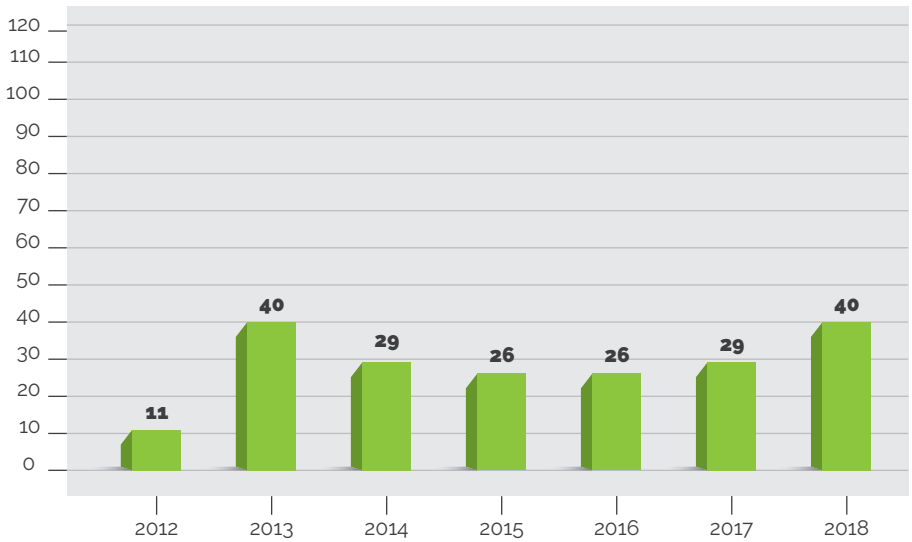
- As published by PRAC, having assessed a significant number of PSUSAs, in a very structured way, which was previously less systematically in place, has led to text updates resulting from the assessments.

- The introduction of the summary Pharmacovigilance System Master File led to a once only, almost unprecedented exercise in which all Marketing Authorisations in the European Union had to undergo a change via a variation submission to include the needed references in the marketing authorisation. Fortunately, the updates could be done via an update of the article 57 database and waiving of the respective variations. This sets a precedence which we would like to use for similar cases where the update can be made once using the telematics system and making unnecessary the submission of variations.

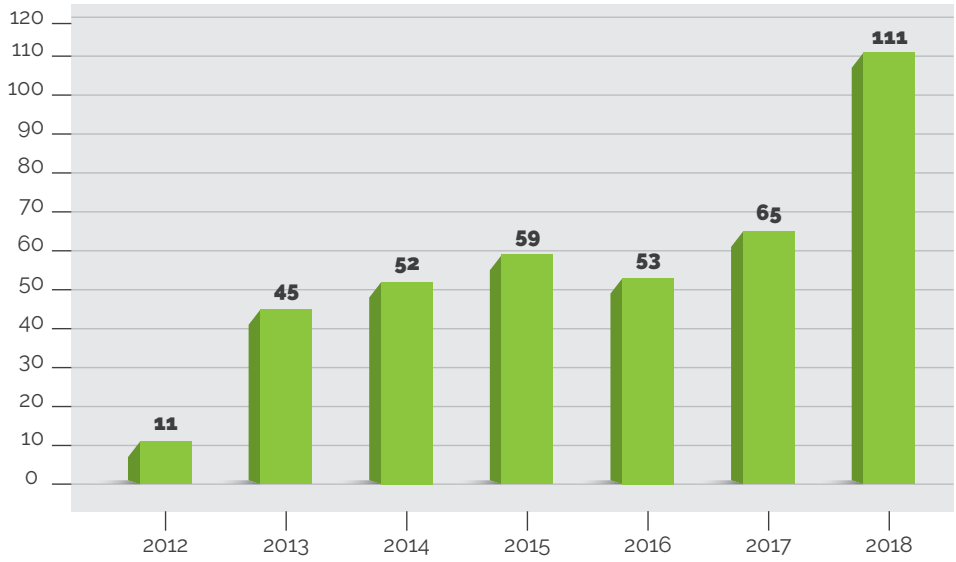
We have identified three major sources that contribute to the large number of safety variations:

1. PRAC recommendations

In the period between 2012 and 2019, PRAC discussed 966 signals, out of which, 227 (23.5%) are reported to have had an update of product information recommended by PRAC.
In their own monthly reports PRAC published the number of cases leading to recommendations to update texts:



Affecting the following number of APIs



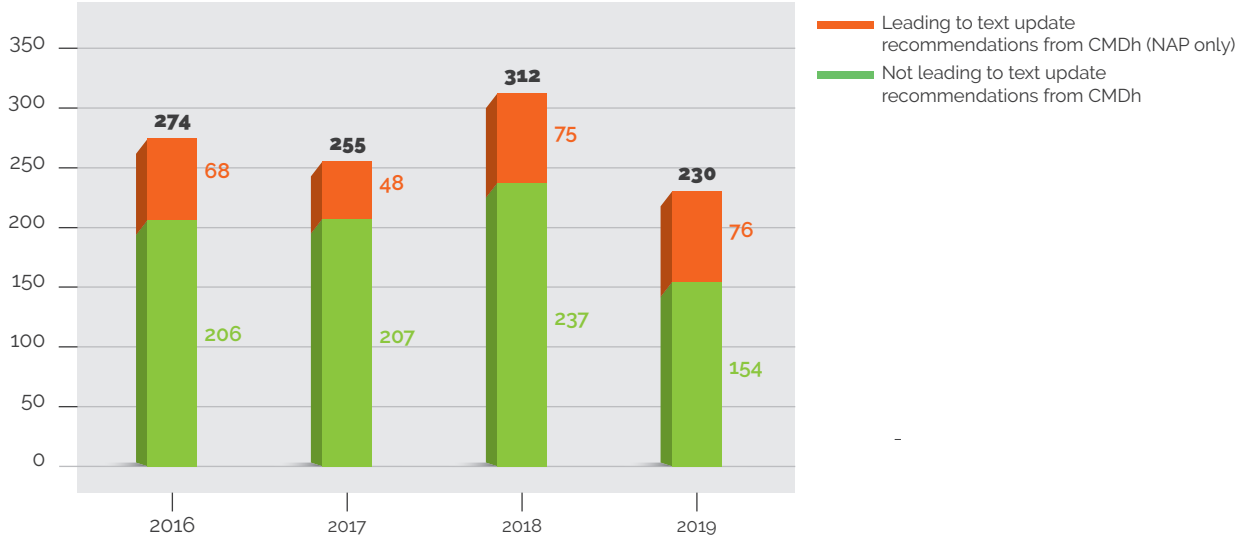
Amongst the molecules/classes of molecules occurring in the list, there are several molecules with multiple cases or cases where next to PRAC recommendations, there are also PSUSA outcomes to be implemented, or article 20, 31, 107i referral outcomes.

2. PSUSA outcomes

Specific attention is asked for the number of PSUSA assessments leading to a recommendation to submit a safety label change, in the table below.
In this table only the PSUSA outcomes are included where NAP exists, since these are changes normally affecting more than one MAH and one MA, such as when the product is only centrally approved.

Year	# of PSUSA assessments	Leading to text update recommendations from CMDh (NAP only)
2016	274	DP Source for FCT 50mg
2017	255	A) DPM for FCT 50 mg
2018	312	B) Intermediate supplier of blend
2019 (YTD 06-2019)	115	C) Intermediate QC testing site

Source EMA Website, Medicines_output_periodic_safety_update_report_single_assessments



It would be very beneficial if an agreed wording could also be introduced with any ongoing labelling variation instead of filing another separate Type IA_{IN} labelling variation. This would significantly reduce the work load and consequential cost.

3. Referrals

Although on an annual basis the number of initiated safety referrals is not high, they often relate to "class actions" meaning that the referrals cover several molecules. In most cases the outcome of a referral leads to an adaptation of safety information in product labels.

The table presents statistics on the number of molecules going through safety referrals since 2012 until 30 September 2019, for which the PRAC recommendation led to risk minimisation measures and/or variations.

	Number of referrals started	Number of molecules involved
Total number	40	123

Source: procedures started between 01-01-2019 and 30-09-2019 for which the PRAC recommendation led to risk minimisation measures and/or variations, according to EMA's database.

Examples of multiple revisions of the SmPC/PIL within a short period of time to the same molecule

Example 1

A typical example of such a case is **Ciprofloxacin (Fluoroquinolone)**, which was taken/is being taken through ***the variation application process three times in past twelve months*** alone:

IAIN	CIZ	Safety – Fluoroquinolones for systemic and inhaled use — see EMA/PRAC/595691/2018
IB	CI3Z	Safety - ciprofloxacin (systemic use) – see PSUSA – PSUSA/00000775/201801
IB	CI1B	Safety – quinolone and fluoroquinolone* – see Article 31 – EMEA/H/A-31/1452

Example 2

Another example is **Ritonavir**, which also went through the application process ***three times in twelve months***:

IAIN	CIZ	Safety - Ritonavir — PRAC Recommendation 02/2018 — EMA/PRAC/59224/2018
IAIN	CIZ	Safety – Antiretrovirals* — PRAC recommendation 08_2018 – EMA/PRAC/414645/2018
IAIN	CIZ	Safety – Antiretrovirals* — see EMA/PRAC/689235/2018

Example 3

A third example on perindopril/amlodipine ***updated 6 times in 3 years*** is included below:

MOLECULE	Number of updates in the 2016-2017-2018	Details
Perindopril/amlodipine	4 X PSUSA 1 req. from comp. auth. 1 x PRAC	PSUSA/00002354/201510 Request by MHRA (interaction between amlodipine and NSAID) PSUSA/00000536/201604, PSUSA/00000174/201703 PSUSA/00000749/201802 EMA/PRAC/826440/2018

- CMDh position (EMA/CMDh/137570/2017) adopted by consensus following PRAC recommendations of the PSUSA procedure (PSUSA/00000536/201604).

European Medicines Agency published the Scientific conclusions from single assessments of periodic safety update report for amlodipine (PSUSA/00000174/201703).

- On 11.12.2017 the MAH received request from MHRA regarding changes to the SmPC and PIL for perindopril/amlodipine tablets. The interaction between amlodipine and NSAID should be removed from section 4.5 Interaction with other medicinal products and other forms of interaction since it is not stated/included in the texts of other products containing amlodipine.
- Change in the generic SmPC/PIL following the same change of the reference product.
- New safety information with regards to mTOR inhibitors was noticed in originator's texts for amlodipine (Istin, Pfizer).
- EMA/PRAC/752056/2018 published requirements from the PSUSA (PSUSA/00000749/201802) procedure. PRAC recommendations on signals (EMA/PRAC/452657/2016).

In summary, a high percentage of active pharmaceutical ingredients (API) affect multiple marketing authorisation holders, especially when a molecule is off-patent and available in generic medicinal products.
It can be noted that referrals and PSURs have in particularly a significant impact on the variation burden for both marketing authorisation holders and regulators.

4. Introduction of sPSMF

The introduction of sPSMF as a new approach was positive, overall. However, as indicated under the problem statement, it is more than likely that the vast majority of marketing authorisations, as currently contained in the xEVMPD database, has undergone the variation to introduce the sPSMF into the marketing authorisation.
It is likely that over 300.000 variations have been submitted to realise this.

Solutions and Recommendation

There are several proposals that could lead to a reduction of the regulatory burden when it comes to implementation of safety related text changes.

- Ensure that, upon publication of a Commission Decision after referral or upon recommendation for a label change coming from PRAC, literal agreed-upon text fragments are available, so that assessment from NCA does not lead to content discussions.

Thus leading to:

1. A setting in which, if literal agreed text fragments are available, by default the Marketing Authorisation Holder should be trusted to implement what he is legally obliged to do. This activity is subject to Health Authority inspection and should thus be adequately controlled.

2. A setting in which, if literal text fragments are agreed upon, the uploading of a text in the XEVMPD database, which is already an obligation, could be considered as a submission, making a variation application via the currently practised route a duplication of work and thus redundant.

- In order to avoid multiple revisions of the same text within a short period of time, whenever there is an outcome of a referral or a PRAC recommendation, the authorities should check if there is an ongoing PSUSA process so that product information update can be combined, if possible.

- Completely change the way in which product information is handled in the currently regulatory system. Move to a model based on structured data and develop processes via which these structured data can be easily updated, specifically when class actions are involved in cases like the mentioned Fluoroquinolones.

- Furthermore, whenever new pieces of legislation are developed a more careful impact assessment should be made, preventing situations such as the one related to the introduction of the sPSMF from happening again. It should however be stressed that the new approach was positive, overall.

CASE STUDY 6

Technical aspects of variations regulations to improve

Issue statement

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 a maximum effect. Those concepts need to be fine-tuned to deliver full benefit in view of handling variations efficiently.

This section presents miscellaneous cases identifying the areas where the variations system can be improved.

Massive submission of Variations/Notifications applicable to a large part of a company's portfolio

Quite often marketing authorisation holders have been obliged to submit a huge number of standalone notifications/ variations that, although triggered from different external factors, affected the same product and most of the products of a company's portfolio many times.
These situations could be triggered by a relatively minor update of some Quality Guidelines or some (minor/administrative) consequences of the revised legislation when the way of implementing new requirements was not well thought through. Although the change looks very simple (i.e. administrative changes that have no impact on the safety, efficacy or quality of the product) it can lead to many variations for all MAHs for all products. These initiatives, broad in scope, are leading to multiple screenings of a company's entire portfolio to assess the impact and multiple updates of dossier sections or labelling which can even contradict a previous revision. Those initiatives appearing in parallel/or consecutively should be better coordinated/combined in the sense of filing changes and adapting implementation timelines.

- **New or updated Quality Guidelines/Regulations:**
  New or revised Guidances, although relevant for overall public health and patient benefit, are triggered by different factors and generate variations to the same product, at the same time and are often transversal to the complete product portfolio of a company. These changes are in general well understood and supported by industry in view of public health needs, however, the implementation, timelines and the effort for the consequential implementation into all existing marketing authorisations, are translated into a massive resource engagement by the regulators and companies to process these changes in a very inefficient way.

Below are some examples demonstrating the above mentioned issue:

- **Example of Excipients Guideline and its Annex 1**
  An updated Guideline on Excipients was published in October 2017 with the implementation deadline of October 2020. The industry understands the relevance of this guideline and the need to update the product information with the recommendations concerned; however, we would like to highlight constraints encountered during the implementation.

  - Conflicting messages from authorities and inefficiency in practical implementation:
    - The Q&A, as published on EMA's website, clearly states that the amount and proportion of the WHO daily recommended intake of dietary sodium contained will be provided in Section 2 of the PL and Section 2 of the SmPC. However, the requests from the authorities have shown to be different; namely, it has been requested many times to be included under section 4.4. of SmPC (independent of the applied threshold). There is a clear disharmony between published Q&A and the Authorities position that lead to several revisions of the product information prior to final approval. Due to the unclarity of the Guideline and the late issuance of Q&As that did not totally answer all questions, many discussions and uncertainties occurred in the course of implementation.
  - Implementation leading to possible confusion among patients
    - As excipients are being assessed by the EMA in a staggered approach, several changes for the same package leaflet might be needed for the same product due to more than one excipient.
    - It would have been more efficient if the all relevant recommendations had been published at once, allowing the all relevant changes to be made at once.
  - Impact on resources and associated workload
    - The whole company portfolios had to be screened before respective regulatory actions can be taken. The average percentage of MAs requiring regulatory action is very high (as an example- based on evaluation made by one of Medicines for Europe member companies), this process will affect around 60% of its portfolio).

- **Falsified Medicines Directive (QRD update)**
  Introduction of the Unique Identifier for each pack as a part of the implementation of the Falsified Medicines Directive (FMD)[17] triggered a huge number of notifications in order to update the labelling. . When possible, labelling changes related to the FMD were included with other variations (only if the change was already affecting labelling). However, this was not possible for some products for which a separate regulatory action was needed, (even though no assessment was necessary as only a space on the box for a Unique Identifier was introduced). For one large company (a member of Medicines for Europe), for approximately 62% of products (European procedure only, nationally authorised products not being considered), the implementation was done by a stand-alone notification (as combining with other variations was not possible). It generated a huge amount of submissions and resources engaged to process those notifications.

  This process also created a real challenge for manufacturers to synchronize regulatory process with the manufacturing sites' implementation of serialisation. For this reason, many standalone variations had to be submitted as it was not possible to combine/ wait for other changes. The main issue was that many manhours were required to determine the best submission strategy and timing as well as the coordination of submissions whereas this requirement

[17] Guideline as published on EMA's website

could have been introduced via another way than a QRD update. A more suitable way could have been a simple confirmation to regulatory bodies that the labelling will be in compliance by the deadline.

- **Medical Device Regulation (MDR)**
  The New MDR has a huge impact on Medical Devices, however one article, i.e. article 117 has a hidden impact for Industry potentially not familiar with medical devices' regulations, namely for industry dealing with Drug Device Combination products.

  The MDR implementation date is May 2020, and despite the short deadline it was only in February 2019 that EMA published a very limited list of Q&A and a draft Quality Guideline in May 2019. Although many issues concern the industry, including the lack of appropriately designated Notified Bodies, clear understanding of responsibilities, clear guidance on the implementation and specifically regarding variations, the published Q&A did not bring clarity with respect to understanding what are considered as "substantial changes". The implementation seems to be very unclear for companies and should be considered in the Variations regulation and/or guideline.

Technical aspects of the submission of variations which could be handled differently:

- **Administrative variations that could be handled through SPOR**
  Variations Type-IA/IA_{IN} are the most designated/appropriate for optimisation of the submission process (i.e. submission via the ISO IDMP/SPOR database) due to: the administrative nature, no assessment by the CAs, direct implementation by the MAH (and notification of the CAs only within 12 months), no impact on the quality, safety and efficacy.

Some practical cases of variations which could be submitted via database:

- **Address or name changes without the physical move of a company**: situations that are not under the responsibility of any of the manufacturers/suppliers and that have no effect on the safety, efficacy or quality of the product lead to high administrative burden on both sides (regulators and companies)

- **Changes that only affect partial CMS, such as address changes with physical move of MAH**:
  It is clear that a Type IA_{IN} variation has to be submitted in the CMS of the MAH whose address is changed and RMS,
  However, the requirement to submit this same variation in all CMSs should not be necessary.

- **MAH transfer - licence transfer** (due to divestment/joint-venture).

- In total[18], it was identified that there are approximately 26 types of type-IA/IA_{IN} variation that could be 'data only', as the data is already available in xEVMPD or in the Iteration 1 of the ISO IDMP/SPOR proposal. These Organisational variations represent 26 variation guideline numbers, which amount to approximately 35-40% of the type-IA/IA_{IN} variations in the regulatory system.

[18]HMA/EMA Regulatory Optimisation Group (ROG) BUSINESS CASE Business Case No. 1 Optimisation of selected type IA variations, Feb. 2017.

Some of these identified variation types can be found in the table below:

Variations Type D	Guideline Number	Operation	Field
IAIN	A1	Change in	name and address MAH
IA	A4	Change in	name and address ASMF holder, manufacturer excipient, starting material, reagent, intermediate
IAIN	A5A	Change in	name and address of the DP-manufacturer/importer responsible for batch release
IA	A5B	Change in	name and address of the DP-manufacturer/importer
IA	A7	Delection of	DS-manufacturer, manufacturer intermediate, DP-manufacturer, Primary packaging site, Secondary packaging site, batch release site, batch control/testing site, batvh release site, including batch control/testing, supplier of a starting meterial, supplier of a reagent, supplier of a excipient, manufacturer intermediate
IA	A8	Change in	Date of the audit to verify GMP compliance
IAIN	BIA1A	Replacement of/Addition of	DS-manufacturer / manufacturer starting material manufacturer reagent / manufacturer intermediate
IA	BIA1F	Replacement of/Addition of	DS-manufacturer / manufacturer starting material manufacturer reagent / manufacturer intermediate
IA	BIA1I	Addition of	DS-manufacturer / manufacturer starting material manufacturer reagent / manufacturer intermediate
IAIN	BIIB1A	Replacement of/Addition of	Secondary packaging site
IAIN	BIIB1B	Replacement of/Addition of	Primary packaging site
IA	BIIB2A	Replacement of/Addition of	batch control/testing site
IAIN	BIIB2B1	Replacement of/Addition of	batch release site, not including batch control/testing
IAIN	BIIB2B2	Replacement of/Addition of	batch release site, including batch control/testing
IAIN	BIIB2C1	Replacement of/Addition of	batch release site, not including batch control/testing
IAIN	BIIB2C2	Replacement of/Addition of	batch release site, including batch control/testing
IA	BIIE7A	Deletion of	supplier of packaging components or devices
v	BIIE7B	Replacement of/Addition of	supplier of packaging components or devices

Other type-IA/IA_{IN} variations that should be considered for submission in the ISO IDMP/SPOR database are the updates of Certificates of Pharmaceutical Products (CEPs) (for more background information, please refer to CASE STUDY 2).

Variations Type D	Guideline Number	Operation	Field
IAIN	BIII1A1	Submission of	new CEP for active substance, starting material reagent, intermediate, excipient
IA	BIII1A2	Update of	CEP for active substance, starting material reagent, intermediate, excipient
IAIN	BIII1A3	Submission of/Replacement of	new CEP for active substance, starting material reagent, intermediate, excipient
IA	BIII1A4	Deletion	CEP for active substance, starting material reagent, intermediate, excipient
IAIN	BIII1B1	Submission of	new TSE CEP for active substance, starting material reagent, intermediate, excipient
IA	BIII1B2	Submission of/Replacement of	new TSE CEP for active substance, starting material reagent, intermediate, excipient
IA	BIII1B3	Update of	TSE CEP for active substance, starting material reagent, intermediate, excipient
IA	BIII1B4	Deletion of	TSE CEP for active substance, starting material reagent, intermediate, excipient

- **Work-sharing/Grouping/Annual Reporting**

Additionally, some concepts of the Variations Regulation, such as work-sharing procedures, grouping, Article 5 document are of great benefit, however due to certain constraints are not yet used to a maximum effect.
The constraints are demonstrated below by practical cases & data, followed by possible solutions and recommendations.
The general concept of do & tell variations is generally much appreciated also in EEA, however the idea of "annual reporting" that is well established in US seems not to work for EEA as the setting is different. In EEA the need to follow up on the individual "expiry date" of individual stockpiled variations together with technical hurdles as elaborated below are not counterbalanced by any incentives to follow this pathway, thus it is usually easier for companies to delay type IA variations only to some extent, usually a date when other variation types requiring immediate submission occur anyway. As most of the variations qualifying for annual-reporting are of very administrative nature industry recommends replacing this workload (also on the authority´s side!) by using the benefits of the SPOR concept, i.e. submitting updates to the database directly.

Industry appreciates the grouping and work-sharing procedure concept; in fact, grouping and work-sharing approaches are very helpful in life-cycle management operations for medicinal products. However, some requirements constitute unnecessary tasks and thus lead to these procedures not being used as much as anticipated from regulators or – if execution is unavoidable – to delays. More flexibility would bring significant benefit to Public Health by further reducing time for review/approval of the change and its implementation by the company.

Such hurdles include:

- For desired **groupings** that are not listed in Annex III or published in the separate CMDh document with acceptable groupings, an agreement from the authority must be sought in advance, leading to potential delay. Annex III should be updated with more examples of possible groupings.

- Some **groupings** may be allowed by some authorities but not by others. Inconsistencies in classifying groupings makes the management of these variations throughout EU very cumbersome for the same change with no added value for the authority, as it is the exact same change.

- In the case of **groupings** where different classifications of variations are included (Type IA/IB and II mixed), the approval of minor variations can be delayed. This is a problem even for IA variations as the official approval letter might be needed as reference for countries outside EEA.

- "**Super-grouping**": The applicant first has to contact one of the authorities to be the lead (RMS) of the procedure, this process can take some time, and in case of Type IA_{IN} variations, this is an issue as for changes requiring immediate notification this planning time is not always available.

- "**Super-grouping**": additional simplification of the process for reporting Type IA variations could be considered for "super-grouping" procedures to allow submission of "super-grouping" application encompassing multiple types of procedures and multiple countries. This type of submission is without obvious reason currently restricted to CP, or to MRP/DCP (or to purely national MAs within one single MS). Alignment between work-sharing and "super-grouping" procedures in that respect would bring a significant improvement to the current system.

- In case of big **work-sharing** procedures harmonisation is not always easy to achieve, there is a risk of ending up with disharmonised solutions or further delay

- For **super-grouping/work-sharing/annual reporting** there are also very technical issues that make the handling difficult, especially for changes affecting many licenses:

  - For all affected procedures in super-grouping/work-sharing procedures independent eCTD sequences must be available at the same time thus have to be prepared in parallel

  - Some eCTD systems allow only one open sequence at a time so planned IA variations have to be kept outside the system and cannot be prepared in advance when there is time (problem for "annual reporting").

  - Grouping of multiple, e.g. 50 procedures is extremely difficult with respect to the electronic application form (eAF) that can result in easily 70-80 pages and consumes a lot of time as it is connecting to the internet, there is no easy reuse of previous eAFs especially as often the combination of products changes depending on the variation scope. The current concept of CESP will unfortunately not bring any improvement to this situation.

  - Where CAPs and NAPs are included in groupings/work-sharing the allocation of the "delivery file" needed for submission is cumbersome.

- **Type IB variation by default**

The industry welcomes the introduction of the Type IB variation by default with the new Variation regulation; however, it has been our experience that in many situations a Type IB does not seem to be the most adequate variation due to the simplicity/straightforwardness of the variation, e.g. when the simple non-fulfilment of a condition for a classified IA variation leads to the upgrade to a IB variation without any scientific reason.
The theoretical timeline for a CMDh recommendation on the classification of an unforeseen variation according to Article 5 is already 45 days. However, many variations are deemed as not applicable for Article 5 recommendation and therefore the direct consequence is that industry must (afterwards) contact the RMS and that the timeline to have a response is unpredictable.
In such cases when the industry requests the RMS' opinion and agreement on a classification, our findings are that the feedback can differ between authorities and/or procedures and additionally the position taken by an RMS is not published. Thus, the applicant is forced to ask for the same opinion per procedure/RMS, leading to repetitive work without benefit for either side, regulators and industry.
Depending on the classification request the outcome might be published on CMDh meeting minutes, Questions and Answer papers, Article 5 recommendations or not at all, making it very difficult to check previous decisions and to refer to them. Such decisions should be published frequently and in a consolidated manner.

The Guidelines on the details of the various categories of variations and the CMDh recommendations acc. to Art. 5 of the EC No 1234/2008 have been separated from the regulation itself on purpose to allow easier updates with growing experience. Nevertheless, we cannot see regular updates of mentioned documents:

- 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/ last update May 2013

- CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC)No 1234/2008 / last update Dec 2018 / only 46 classifications in years 2010-2018 (5 in 2016, 1 in 2017, 1 in 2018) For the classification guideline it could be beneficial to hand over the responsibility from the EC to the regulatory bodies being strongly involved in this topic, i.e. make it a combined HMA/EMA guideline.
  Industry would strongly support a more routinely update of the classification guideline for e.g. refinement of Type IB conditions and the broader use of the Article 5 database as information source for any already discussed classifications issues that might be of interest for other companies.

OVERALL SOLUTIONS AND RECOMMENDATIONS

- New guidelines should always be published with detailed guidance on implementation (clear, detailed and complete Q&As) and examples should be presented to demonstrate how the implementation will look in practice for the various situations. New guidelines and Q&As should be published well before the implementation date of New Regulations, in order to allow proper preparation by the Industry and also Regulators. Industry should be involved in all stages of discussion and decision making to broaden regulatory intelligence and experience. Regulators should state a dedicated contact for certain topics so that all remaining questions can be answered in a harmonised manner.

- Pre-classification recommendation by Regulatory bodies should be updated/published regularly in just one place.

- A change in the Commission Regulation (EC)No 1234/2008 ('the Variations Regulation') would be needed, either changing the wording under Article 7 b) or update of Annex III to address the concern with variation groupings.

- A change to the Chapter 6, CMDh Best Practice Guide for the processing of Grouped application in MRP would be needed to specify a speedier procedure in case of Type IA_{IN} variations.

- The implementation of SPOR would address the technical issues with eCTD sequences, the annual reporting of IA variations and the issue of eAF of super groupings.

- Simple changes that are identical for most products and have no need for discussion such as introduction of QRD version for FMD implementation could be implemented without separate regulatory action. A deadline would be given for implementation only and either a simple confirmation (list of products where relevant) that the changes have been implemented would suffice or any further submission could be used to update the documentation (more flexibility on timelines for MAHs to avoid stand-alone notifications/variations); where applicable, administrative variations should be handled via SPOR only.

- New way of informing authorities about changes should be put in place to reduce a waste of resources

  - Variations Type-IA/IA_{IN} are the most designated/ appropriate for optimisation of submission process (i.e. submission via the ISO IDMP/SPOR database due to: administrative nature, no assessment by the CAs, direct implementation by the MAH (and notification of the CAs only within 12 months), no impact on the quality, safety and efficacy.

- NCA should keep striving for even greater harmonisation of requirements and predictability and refrain from raising individual opinions, mutual trust regarding assessment should be fostered.

- Greater commitment of NCAs to rely on each other´s assessment, greater willingness for harmonisation without exemptions on national level. The industry would like to recommend that Art. 5 recommendation procedure be simplified, and that the requests from MAHs and subsequent clarification be made public frequently including a deadline for NCAs to respond to requests.

  - The Annex of the Variations Classification Guidelines should be revised regularly to implement the Art 5 recommendations.

- The Variations Classification Guideline could be considered an EMA/ HMA (CMDh) guideline, instead of a EC guideline in view of more regular/ frequent update (i.e. yearly update due to Art 5 recommendations; around 50 recommendations have already been issued but the guideline has not been amended).

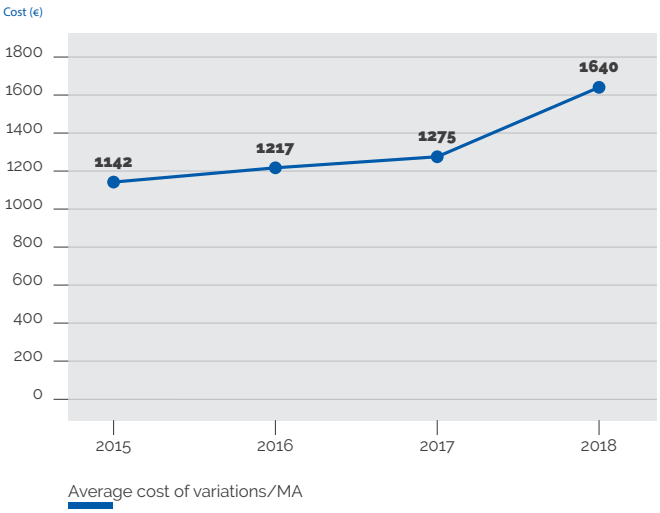
CASE STUDY 8

Variations Classification Guideline – case of herbal medicinal products

Herbal Medicinal Products

- The life cycle management of herbal medicinal products and in particular their variation classification regime is generally higher and more complex than chemically defined medicinal products. It is not clear why herbal medicine products are subject to a higher variation level given the fact that there is no impact on the quality of the medicinal product, regardless of whether it is a herbal or chemical medicinal product, e.g. if pharmacopeial specifications are not affected.

  However, it has been observed that similarly to chemically defined products, the cost allocated to variation has been constantly growing over the years.



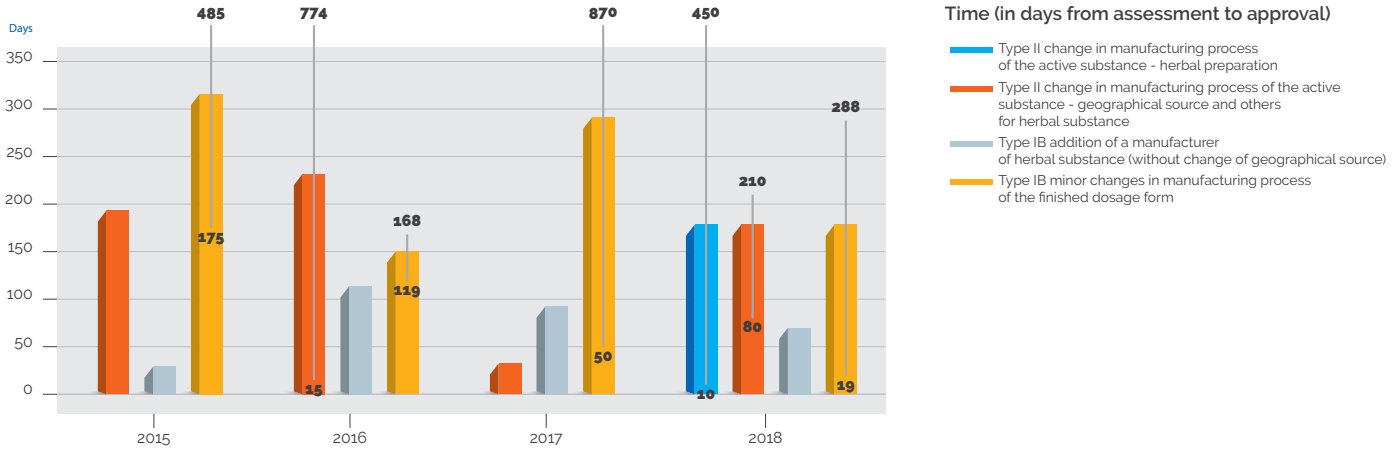
- In the case of finished products containing chemically defined active substances, minor changes in the manufacturing chain such as the addition of a sieving step for removal of aggregates or changes in the mixing time for blending powders or granules for immediate-release dosage forms, are classified as Variation Type IB for herbal medicinal products whereas they are type IA for chemical compound according to B.II.b.3 a. Classification as type IB is more resource intensive and hinders short term implementation of technical progress. In addition, it is not clear why herbal medicine products are subject to a higher variation level given the fact that there is no impact on the quality of the medicinal product, regardless of whether it is a herbal or chemical medicinal product. The evaluation time is extremely variable from country to country and can be extremely long in some cases.

- A change e.g. of cultivation sites or geographic origins only which does not affect the pharmacopoeial requirements should be acceptable without the need to file a prior approval variation ("geographical source" should be removed from variation type II B.I.a.2 d) wording). The quality of the herbal API is proven by conformity with Ph. Eur. Specification, as is the case for chemical APIs. This is of particular relevance because changes in sourcing are often a consequence of conditions during growing or harvesting of plants, which cannot always be influenced by the manufacturer of the herbal medicinal product and might, in the worst case, result in shortages and avoidable out of stock situations. It is particularly problematic when the evaluation time is very long (as it is sometimes the case – see graph below).

- The overall goal is to produce state-of-the-art herbal medicinal products and to enable further technical progress under proportionate regulation.

- In addition, in some countries, grouped variations are sometimes as expensive as new THMP-applications. This is because THMP applications have reduced application fees, but the variation fees are the same for all product (generics, WEU, full applications).

- The classification of variations by NCAs is not harmonized. Any classification from Type IA to II, or splitting to several IA and IB by NCAs have occurred. In one case, a grouped package was accepted by one country with a grouping of 4 variations, whereas other countries splitted the package to up to 11 variations.



ABOUT MEDICINES FOR EUROPE

Medicines for Europe represents the generic, biosimilar and value added medicines industries across Europe. Its vision is to provide sustainable access to high quality medicines, based on 5 important pillars: patients, quality, value, sustainability and partnership. Its members directly employ 190,000 people at over 400 manufacturing and 126 R&D sites in Europe, and invest up to 17% of their turnover in R&D investment. Medicines for Europe member companies across Europe are both increasing access to medicines and driving improved health outcomes. They play a key role in creating sustainable European healthcare systems by continuing to provide high quality, effective generic medicines, whilst also innovating to create new biosimilar medicines and bringing to market value added medicines, which deliver better health outcomes, greater efficiency and/or improved safety in the hospital setting for patients. For more information please follow us at www.medicinesforeurope.com and on Twitter @medicinesforEU.

ABOUT AESGP

The Association of the European Self-Care Industry (AESGP) is a non-profit organisation which represents the manufacturers of non-prescription medicines, food supplements and self-care medical devices in Europe, an area also referred to as consumer healthcare products.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