



## Optimising Post-Approval Change Management for Timely Access to Medicines Worldwide

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### Executive Summary

Post-approval changes (PACs) to the registered information of authorised medicinal products, hereafter referred to as 'variations', are introduced routinely worldwide to: enhance the robustness and efficiency of the manufacturing process; improve quality control techniques; respond to changes in regulatory requirements; and upgrade to state-of-the-art facilities. This continued effort is critical to continuously improve existing medicines and is, in many ways, as important as bringing new medicines to the market.

Once marketed, medicinal products are used more widely than the population in clinical development and this helps to refine knowledge of the product safety profile. For the benefit of patients and Health Care Professionals (HCPs), it is critical that such information is reflected in the product label in a timely manner, through variations to the prescribing information.

As regulatory systems develop and evolve worldwide, the requirements to submit and review variations in multiple markets are becoming even more complex. International collaboration and cooperation towards regulatory convergence has been recognised as the way to address the challenges of National Regulatory Agencies (NRAs) to address such increases in workload (see WHO working documents on Good Regulatory Practice - QAS/16.686). Industry believes that global convergence will provide a more efficient environment for the management of post-approval changes to Marketing Authorisations (MAs) worldwide, and will contribute to ensuring patients' continuous access to state-of-the-art medicines, and up-to-date product safety information. At the same time, industry acknowledges that more measures like advanced planning of changes at start of the life-cycle, more strategic combination of changes as well as transparent communication of supply challenges need to be taken from their side to contribute to complexity reduction. Ultimately, all of these activities will contribute to enhancing global public health.

This paper aims to describe the challenges with the current landscape for managing variations, and presents opportunities and recommendations for global convergence and improvement, in line with the World Health Organisation (WHO) guidelines. The paper addresses both quality variations (also referred to as Chemistry Manufacturing and Control, CMC) and safety label updates, and the recommendations aim to bring consistency and predictability to the global management of variations, whilst contributing to patients' timely access to quality medicines and the latest safety information.

For quality post-approval changes and variations, the recommendations align with the concepts being considered in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q12 guideline (Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management), which is intended to provide a framework to facilitate the management of post-approval changes to the Chemistry Manufacturing and Control (CMC) dossier in a more predictable and efficient manner across the product lifecycle.

The key elements moving forward are:

- Clear procedural guidance with appropriate and predictable timelines (and implementation of a risk-based approach). This should be introduced in a step-wise approach with developing agencies first adopting simple, clear classifications with reliance on Stringent Regulatory Agencies (SRA).
- The classification system should have moderate and major changes requiring assessment and approval before implementation, and minor changes requiring only notification or no reporting (dependent on certain conditions).
- Administrative requirements should be converged and unnecessary submission of data eliminated
- Industry and agency resources should be focussed on the handling of major changes, with a dedicated and expedited process for safety label information, longer term moving towards global acceptance of electronic product information for speedier access to up-to-date safety information
- Stakeholders should make use of novel tools in the form of post approval change management plan (a mechanism to enable industry to plan and communicate changes better).
- There should be an optimised use of resources within regions by introducing mutual reliance and, ultimately, mutual recognition of assessments and outcomes.
- “Market implementation” (e.g. Quality Assurance release of a product batch) should be universally defined and there should be a collective agreement on common market implementation time-windows that reflects the impact of the change and urgency to implement.

We therefore recommend the following set of actions:

Short to mid-term	Longer term
Converge requirements through the adoption of international standards (WHO) through a risk-based approach to the classification of variations, data requirements, and timelines.	Implement in a stepwise manner collaboration among regional NRAs that enables work-sharing, mutual reliance of assessments and, in the longer term, mutual recognition of approvals
Minimize the number of country-specific requirements (examples are provided in the paper)	
Consider how best to focus resources to ensure that important public health aspects i.e. supervision of supply chain, counterfeits, pharmacovigilance, are in place. These measures may be more impactful in ensuring quality of medicines to its population than re-assessing a change already evaluated by other agencies.	
Encourage exchange of knowledge between the review and inspection departments	Implement best practices and principles from ICH Q12. Increasingly rely on the companies' Pharmaceutical Quality Systems (PQS) to effectively manage minor changes without the need to file variations
Dedicate resources for the review and approval of safety labelling variations in an accelerated manner	Implement broad acceptance of e-labelling and progressive deletion of paper leaflets in the pack, in line with information technology capability in countries worldwide
Allow flexible implementation periods for technical and labelling variations	
Industry to improve planning of changes through the product life-cycle and seek to adopt new mechanisms that are expected in the future such as Post Approval Change Management Protocol (PACMP).	

Industry believes that where properly planned and executed, variation and change management activities will ensure patients' access to safe, well-tolerated, high quality and compliant products and those patients are informed about the safe and effective use of medicines and vaccines worldwide.

Global convergence of regulatory requirements will contribute to meeting that objective, through increased collaboration amongst NRAs, both within a region and globally. ICH is a significant contributor to this process for global harmonization. Mutual reliance on assessments and mutual recognition of approvals, as well as cross-talk between functions within NRAs (e.g. inspectors and assessors) needs to be encouraged to optimise the use of regulatory resources and help avoiding drug shortages. Efficiency could be further enhanced by adopting international standards (ICH, WHO variation classification guidelines), developing partnerships, harmonisation, using technical advances to more rapidly disseminate up to date product information.

Together, these measures will contribute to the ultimate goal to facilitate timely access to medicines worldwide.

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## 1. Introduction

- \* Variations to the registered information of authorised medicinal products are introduced routinely worldwide to ensure patients' continuous access to high quality medicines, and up-to-date product label information. This continued effort is critical to improve existing medicines and is, in many ways, as important as bringing new medicines to the market.
- \* Industry submits changes to ensure processes operate more efficiently, to update to state of the art technology, expand manufacturing facilities to ensure supply, or simply to replace raw materials or components that can no longer be used. Variations may also be needed if a product development and registration process is accelerated in order to meet an unmet medical need requiring changes to be made to an initial manufacturing process.
- \* Once marketed, medicinal products are used in a much wider population, bringing additional knowledge to the safety profile of a product. It is important that such information is reflected in the product label in a timely manner, for the benefits of healthcare professionals and patients.
- \* As regulatory systems are continually developing and evolving worldwide, the requirements to submit and review such changes in multiple markets are becoming ever more complex. Regulatory oversight is critical to ensure that high quality, well tolerated and effective medicines are licensed for use, and this must be achieved without reducing access to pharmaceutical products. Indeed, regulators and the pharmaceutical industry have a collective responsibility to assure an uninterrupted supply of compliant, safe and efficacious medicines to patients globally.
- \* This complexity has already been recognised, leading to the development of measures to try to address this observation. In part, initiatives such as the upcoming ICH-Q12<sup>1</sup> guideline (which is anticipated to provide a framework which will facilitate the management of post-approval CMC changes in a more predictable and efficient manner across the product lifecycle) and current and upcoming WHO guidelines seek to tackle the problem.
- \* Nonetheless, other measures may also be needed and thus the purpose of this document is to outline the pharmaceutical industry position for a more efficient, science- and risk-based handling of post-approval changes to quality (Chemistry, Manufacturing and Controls - CMC) and safety labelling information<sup>2</sup> with the ultimate goal to facilitate timely access to medicines worldwide.

## 2. Current Regulatory Landscape for Post-Approval Changes

### 2.1 Quality - Chemistry, Manufacturing and Control (CMC) changes

- \* The following section presents a series of observations and comments concerning the current regulatory landscape. The following points are highlighted:
  - Heterogeneous classification systems
  - Specific local requirements
  - Unpredictable and variable approval timelines

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<sup>1</sup> ICH Q12 Technical and Regulatory considerations for pharmaceutical products lifecycle Management - <http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>

<sup>2</sup> This paper focuses on safety information (or changes to an efficacy profile which could impact safety) rather than indication changes or expansion of the pharmacodynamics section. Indication changes or added pharmacodynamics data help to expand or qualify the use of a product and can be subject to longer assessments especially in the context of different populations. In contrast addition of safety information must be communicated as soon as possible to the patient.

- Divergent decisions by regulatory bodies
- Variable implementation periods

### 2.1.1 Observations of the Current Regulatory Landscape for Quality Changes

#### Heterogeneous classification systems

- \* Variations are heterogeneously classified all over the world. As a result the classification of the same CMC change can differ significantly e.g. from major change to minor or notification depending on local requirements and the level of registered information. In addition, some of these classifications do not take into consideration the impact of a change on the quality, safety and efficacy (QSE) profile of the product, nor the Marketing Authorisation Holder (MAH) knowledge of the product.

#### Specific local requirements

- \* Specific and often divergent local requirements hinder the efficient management and implementation of post-approval change activities by manufacturers globally. This can impact access or at least availability of medicines that have improvements in quality as a result of the change. They include:
  - Data package: some countries solicit specific requirements (e.g. administrative information, samples, etc.) which do not only differ from other countries, but add to the complexity of the submission and approval process. They include Good Manufacturing Practice (GMP) related documentation such as batch records, GMP certificates, and other documentation. This can also extend to requests for raw data (such as individual chromatograms) and divergent stability requirements which lead to staggered rather than simultaneous submissions across countries. The ideal is to submit and approve a change with the same dataset and at the earliest possible time.
  - Format: different regions and countries around the world use different submission formats. Even in cases where common formats are available, they are customized by NRAs, preventing the same submission across all countries.

#### Unpredictable and variable approval timelines

- \* Approval timelines vary widely from NRA-to-NRA and a global approval may not be obtained in a reasonable time frame. For example, approval to introduce a new or additional manufacturing site to ensure continuous supply of a product, can take up to 3 to 5 years due to the global staggering of different approvals and implementation times. This compares to one major agency such as the European Medicines Agency (EMA) in the European Union (EU) which typically takes around 6 months to approve a major site change (with the GMP inspection normally occurring in advance of the regulatory action). This observation is also connected to the variable classification of variations as highlighted in the first section.
- \* Even if approval timelines are stated by the regulatory agency these may not be adhered to making predictability more challenging.
- \* NRAs' constraints such as limited human and technical resources can generate significant backlogs. Consequently, it can take from months to years before an assessment is initiated regardless of the impact on QSE. During this period, the variation is pending review and

approval, and thus the updated product cannot be marketed and remains unavailable to HCPs and patients.

- \* For many regulatory agencies, evidence of authorisation in the source country (country of manufacture or reference authority) is required at submission or approval of the variation by the NRA. This can be helpful when reliance on reference agency is needed as an agency is developing but can also delay the variation especially when an agency then conducts its own review.

### **Divergent decisions by regulatory bodies**

- \* We also observe divergent decisions by regulatory authorities based on the same data set, e.g. quality control specification or manufacturing process change.

### **Variable implementation periods**

- \* For the same change the implementation period can vary amongst countries from immediate to 18 months post-approval without taking into account the nature of the modification and its impact on supply in countries worldwide.

### **2.1.2 Impact of the Current Regulatory Landscape (Quality)**

- \* The circumstances above lead to several approved variants of the same product, with companies having to manage multiple inventories. This can dramatically affect how a product is released – in many instances companies have to maintain multiple levels of specification criteria to release a product globally. This adds unnecessary complexity and increases the risk of compliance and conformance errors.
- \* In addition to complex supply planning, changes pending approval can often result in companies engaging with Health Authorities to request exceptional approvals (or other action) requiring further resource for all stakeholders.
- \* Immediate implementation can have the unintended consequence of delaying or staggering submissions across markets which have shared packs in order to achieve a common approval date and hence implementation date.
- \* As a result, it is extremely difficult for pharmaceutical companies to plan for the submission and implementation of variation applications globally. Balancing the supply of current and new stocks to ensure that compliant products are released to the market requires a highly sophisticated manufacturing and supply planning and adequate levels of stocks. Even if carefully managed, complex supply chains increase the risk of stock-out situations.
- \* These factors lead to a reduced ability for companies to respond to countries' demands for medicinal products, which can be sudden, in a timely and predictable manner. They are major challenges for guaranteeing continuous supply of high-quality medicines to patients.

## **2.2 Safety labelling**

Product labels include information on the safe and effective use of a medicine, for the benefit of HCPs and patients. It is therefore of the utmost importance that this information is kept updated, and rapidly accessible, throughout the lifecycle of a medicine, as new safety data emerge.

### **Approval process for safety label changes can be lengthy and unpredictable**

- \* The approval process for safety labelling changes can be lengthy (up to 3 years).
- \* Countries often rely on Stringent Regulatory Authorities (SRAs) and other regional reference NRAs for submission and approval of labelling variations. Whilst we encourage and support such mutual reliance, if the reference country takes significant time to approve, this leads to a corresponding delay for the NRA to approve the same safety variation.
- \* In addition to being a lengthy process, approval timelines are unpredictable and vary from NRA-to-NRA.

### **Variable implementation periods**

- \* Individual NRAs have different and unaligned implementation periods, i.e., 3 – 6 months after approval, which are also affected by variable approval timelines.

### **2.2.2 Impact of the Current Regulatory Landscape (Safety Changes)**

- \* Approval delays slow down HCPs and patients' access to up-to-date product information, including the latest approved Benefit-Risk profile of the product. Delayed approvals can also have direct consequences on pharmacovigilance procedures, as safety signals and reporting periods are based on the approved product information.
- \* Unpredictable regulatory and implementation timelines further add to the complexity of the planning of updated labels on the market. This can potentially increase risks for patients whereby HCPs, and patients themselves, do not have access to otherwise available information.
- \* With much product information now being available over the internet – which patients across countries can access – the different approval timelines can create confusion.

## **3. Recommendations for a highly efficient global landscape for post-approval changes**

In the previous sections the following observations of the current system were highlighted:

- \* Heterogeneous classification systems
- \* Specific local requirements
- \* Unpredictable and variable approval timelines
- \* Divergent decisions by regulatory bodies
- \* Variable implementation periods

In this section, industry proposes a set of recommendations to address these observations which build on ICH and WHO considerations, for a more efficient variation and post-approval change management landscape.

## Define and Follow Clear Procedural Guidance with Appropriate and Predictable Timelines

### *Implement a unified risk-based variation classification system*

- \* Predictability and transparency for variation submission and approval should become guiding principles for all NRAs, with continuous dialogue with the applicant. This would enable all relevant stakeholders to plan implementation according to clearer and more predictable approval processes, which would speed up patients' access to medicines manufactured by state-of-the-art technology and processes.
- \* However, in recognition of the varying levels of resources available to NRAs, implementation of a risk-based variation classification system could be achieved in a step-wise manner.
  - At a minimum NRAs should establish a basic classification of minor, moderate or major that is in line with WHO principles and is science and risk-based.
  - For NRAs with limited resource, reliance on the approval of a SRA should be sufficient with minimal review of major variations and limited or no review of minor/moderate variations.
- \* Then in a second step expand the approach to follow a common variation classification system which is science and risk-based and which establishes the same data requirements across all NRAs (see next section).
- \* We recommend that the following features are considered:
  1. Minor quality variations and other modifications (e.g. administrative changes) should not require regulatory approval prior to implementation. They could either be notified in a periodic report or maintained in-house by the applicant within its quality system and reviewed during inspections.
  2. Moderate and major quality variations should be reviewed within a set and predictable timeline (no more than 3 and 6 months respectively), before their implementation

It should be noted that a key reference for industry regarding global changes is the WHO 'Vaccines Guidelines on Procedures and Data Requirements for Changes to Approved Vaccines'. We suggest its principles are expanded to all products. The rationale for using the WHO Vaccines Guideline as a basis is that this document clearly describes different changes and the variation categories and timelines. The currently published draft guideline for changes for biotechnological products is another key document and we encourage WHO to drive implementation in order to provide a basis for worldwide classification.

- \* As a further maturation of a science- and risk-based categorisation system, NRAs could allow the possibility for the applicant to justify a downgrading (i.e., lower reporting category) of the variation. This would bring benefits for the applicant and regulator as would lead to shorter regulatory review timelines allowing product with new and lower risk changes to be introduced more quickly. One important possibility in this context is the use of a post-approval change management protocol.
- \* Countries should consider ways to reduce backlogs. Recently ANVISA (*Agência Nacional de Vigilância Sanitária*) introduced a one-off system to assess and approve variations for certain products in an intensive period (one week). More recently the Saudi Food and Drug Administration has announced its reliance on SRAs to accelerate the timetable of variations and regulatory approvals. Another option to consider is to enable variations that have not been approved after a certain period of time has elapsed, beyond the agreed maximum time, to be subject to automatic approval to permit implementation. For example, if the required time is six months for review and approval, and if a further three months has elapsed and there is still no decision, then automatic approval would be assumed.

## Converge Administrative Requirements for the Submission of Variations

*And re-evaluate the necessity of all data and additional documentation to be submitted*

- \* We believe it would be helpful if NRAs agree on common administrative information needed in variation submissions. This will increase the homogeneity among variation dossiers, speed up the preparation and submission process, and ultimately facilitate work sharing (see below).
- \* We recommend that consideration is given to eliminating data requirements that provide limited or no added value to variations applications (including the substantial workload demanded by legalisation of various certificates) or which can be verified during inspections. For example, testing samples when production sites are certified for GMP compliance. Regarding the latter, many countries require, as well as GMP certificates, a Certificate of Pharmaceutical Product (CPP) which includes a statement on GMP.
- \* Where data is required (e.g. full validation reports / supportive data reports) there should be a standardized format and content common to all issued by WHO or ICH and then adopted by agencies worldwide. As such data sets potentially contain elements that are subject to change, standardization will help to minimise the complexity if there are subsequent changes.
- \* Novel approaches to reduce the data needed to support applications should also be considered. For example matrix approaches to rationally reduce the lots required to support a manufacturing change for validation and stability e.g. for vaccine combination products (WHO Technical Report Series No. 993, 2015, Annex 4, Vaccine variation guideline) can reduce the number of vaccines lots that are analysed. This in turn can lead to faster submission and approval timelines and less destruction of lots (which reduces vaccine supply)<sup>3</sup>.

## Create opportunities to work together and further convergence

- \* Industry strongly supports the principle of reliance especially for maturing NRAs. We suggest the following stepwise progression for post-approval change assessment:
  - Maturing NRAs should first rely on assessment by SRAs to shorten the regulatory process. This could enable immediate implementation or confirmatory administrative notification to make a formal change to licence particulars.
  - Then as NRAs gain more experience through utilisation of the notification and reliance system and knowledge gained from WHO and SRAs, they could develop a more active role in variation assessment in alignment with international standards (WHO categorisation).
  - NRAs should then consider grouping with other NRAs in a geographic region and/or where aligned by similar regulatory principles and procedures. Collaboration and work-sharing among agencies should be fostered, relying on practice and assessment from more experienced NRAs, and adopting common ways of working based on international standards.
- \* We would like to acknowledge that work-sharing can be done between regions and between countries of different regions (e.g. countries from different regions already have memoranda of understanding). Thus, the benefit does not need to be limited to geographically co-located markets.
- \* As a further maturation of a reliance system, NRAs could work together towards developing centres of regulatory expertise, whereby a NRA with appropriate expert resources acts as lead-

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<sup>3</sup> As fewer batches are needed for the analysis and faster approval timelines mean that validation lots can be used to for supply.

reviewer in that discipline and leads the assessment for the whole group. Robust processes for appointing NRAs as lead-reviewers would be needed. NRAs in the cluster should then adopt stepwise measures that would lead to mutual reliance of assessment and ultimately mutual recognition of the outcome.

#### **Seek Future Opportunities and Solutions to Enhance Life Cycle Management**

- \* NRAs should be encouraged to adopt novel tools that enable multiple variations to be assessed and approved at the same time, e.g. grouping of a same variation to multiple products, or of multiple variations to a same product, and/or approved quickly according to pre-agreed protocols. If these are coupled with a work-sharing-type approach, where an agency takes the lead to review, this can further maximize resource utilization for the cluster of countries in the workshare. These measures will facilitate the overall submission, assessment and approval process.
- \* New regulatory mechanisms are emerging that may help to reduce the number of formal variations or reduce the review effort required. They include the ICH Q12 concept of a Post Approval Change Management Protocols (PACMP) which is a description of specific changes that a company would like to implement during the lifecycle of the product and how these would be prepared and verified (EMA/CHMP/CVMP/QWP/586330/2010). This allows early evaluation of the change strategy to enable planning of future change(s) by the applicant during the life cycle of a product. PACMPs would require approval by the regulatory authority, and the conditions and acceptance criteria outlined in the protocol must be met in order to implement the change(s).
- \* In the future, product knowledge should be used to increasingly tailor change needs and change management (e.g. design space (ICH Q8) / concept of established conditions (ICH Q12)). In this regard we recommend increasing reliance on a company's internal Pharmaceutical Quality Systems, i.e., change management, knowledge management, etc. to manage many changes with oversight as part of inspections rather than regulatory review. This is in line with ICH Q10; similar principles are also being developed in ICH Q12.
- \* Improvements that new information technologies could bring to the life cycle-management should also be considered to further enhance efficiency in review. For example, posting information in a cloud for NRAs access, using QR-Codes<sup>4</sup> to reduce burden on labelling changes, and using communities to share assessments on variations.

#### **Define and Agree Common Market Implementation (QA release) Time-Windows**

- \* In rare cases for variations addressing serious QSE concerns, we believe immediate implementation should be required in order to bring the change into effect without delay. This would work effectively only if common approval times apply across countries.
- \* In the majority of cases, to ensure availability of medicinal products, we recommend that 'current' and 'new' products should co-exist on the market during a transition period. Flexible timelines are needed to ensure smooth transition and supply continuity of the new drug version, whilst approval processes may still be on-going in other regions of the world.

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<sup>4</sup> A type of matrix bar code

## Safety Labelling Updates Should be Simplified, Faster and More Efficient

- \* We recommend that NRAs should dedicate resources to facilitate the handling of safety labelling variations, due to their importance to patients. Thus, the existing procedures for assessing safety labelling variations should be simplified, faster and more efficient. This would speed up submission, review, approval and public access to the benefit-risk profile of the product and provide the latest safety information on how to use a medicine safely and effectively.
- \* Where a NRA may require more time to review, to e.g. assess the change in the context of the local medical setting, this should be justified and notified to the applicant accordingly.
- \* In the absence of dedicated resources, mutual recognition of the reference labels should be fully adopted. If not, labels then evolve with variable content from major markets (e.g. the USPI); this creates complex dependency relationships and potential inconsistencies, which is confusing for HCPs and patients.
- \* Work towards global or regionally unified labelling templates and content/formatting requirements to simplify transfer of content between labels.
- \* Standardise categorisation of labelling changes across countries, with specific allowance for fast track important safety changes that need to be quickly approved to assure patient safety
- \* Promote trusted authoritative NRA websites where approved labels are stored, maintained and can be accessed with certainty.
- \* Consider progressive introduction of e-labelling through learnings from pilot phases.

## Tabulated Summary of Proposed Changes and Linkage with Resolving the Current Observed Issues

**Table 1: Outline of current situation and proposals for improvement**

Current Situation		Proposals for Improvement
Heterogeneous classification systems	<b>QUALITY</b>	Implement a unified risk-based variation classification system
		Introduce mechanisms to allow simultaneous submissions (i.e. grouping)
		Create opportunities for regulatory agencies to work together and develop further convergence
Specific local requirements		Converge administrative requirements for the submission of variations, and eliminate unnecessary submission of data
Unpredictable and variable approval timelines		Define and follow clear procedural guidance with appropriate and aligned timelines
		Seek future opportunities and solutions to enhance life cycle management
Divergent decisions by regulatory bodies		Mechanisms described above will optimise convergent decisions
Variable implementation periods		Agree on common market implementation (QA release) time-periods for introducing the product with the new change.
Safety labelling review and implementation process can be lengthy, and unpredictable	<b>SAFETY LABEL</b>	Safety labelling should follow a dedicated and expedited process, independent from quality and technical variations
		Longer term, electronic labels should be considered (after suitable pilot assessments), as a mechanism to enable direct access to the most recent product information.

## 4. Conclusion

A more efficient landscape for the handling of post-approval changes to MAs worldwide will contribute to enhancing global public health by ensuring patients' continuous access to state of the art medicines, and up-to-date product safety information. The potential benefits of alignment and harmonization include: reduced shortage/stockouts, faster access to product made with process improvements, and encouragement of new technologies.

International collaboration and cooperation towards regulatory convergence has been recognised as the way forward to address the NRAs' challenges with handling an increasing number of post-marketing authorisations' applications (see WHO working documents on Good Regulatory Review Practice - QAS/16.686 (draft of October 2016) and ICH Q12 will also seek to address these challenges).

In the first instance, the basis for many NRAs worldwide is the use of a reference agency approval to support the variation (cf. "CPP" procedure). Industry supports this approach as it can assist with alignment of regulatory decisions and shortens timelines. However, as NRAs develop, consideration should be given as to whether re-evaluation is required and, where necessary, measures are taken to minimise the additional review period and to avoid unnecessary delay. Ultimately, the aim for the use of a reference approval should be to align and minimise the time for wider review and approval of the post-approval change.

In this regard, NRAs should investigate how to adapt to the growing number of change requests from manufacturers, according to their available resources, and ensure that every regulatory action adds value to patients. Industry believes that NRAs should not only focus on convergence and harmonisation but also on methods to increase local (and perhaps regional) efficiency.

On this basis all agencies should first seek to optimise resources that impact important public health aspects i.e. supervision of supply chain, counterfeits, pharmacovigilance and employ a simple notification system that relies on reference agency approval. Only once these critical elements are established, should expanded resources be used for post-approval changes and this should be done in alignment with other agencies taking opportunities for mutual recognition and convergence. This may be more impactful in ensuring the quality of medicines to its population, than re-assessing a change already evaluated by other agencies.

We believe that globally the process for post-approval changes needs to be simplified, with consistent and clear classifications and timelines, greater mutual reliance between regulators and the use of novel regulatory and scientific tools. At the same time, industry acknowledges that more measures like advanced planning of changes at start of the life-cycle, more strategic combination of changes as well as transparent communication of supply challenges need to be taken from their side to contribute to complexity reduction. The proposals in this paper thus aim to optimise resources, ensure focus important public health aspects (i.e. supervision of supply chain, counterfeits, pharmacovigilance) which, together with an efficient change management system involving all stakeholders, will ultimately contribute to enhancing global public health.

## 5. Annex

## Definitions

- \* Changes (referred to as 'Variation' in this document): amendment to the terms of a marketing authorization with regard to its technical information or labelling. Technical variations relate to the quality of the drug substance and product (CMC), while labelling changes are variations based on evidence which have an impact on the product label.
- \* Submission: the dossier and all the associated requirements (administrative documents and others) which are officially sent to the NRA for approval.
- \* Time-window: period in which the previous version of the medicine can be imported and sold in a given country before the new approved version has to be solely imported and commercialised in the same country.
- \* Market implementation: Time when the first batch of medicine, which includes the new and approved modifications, is released into the market.
- \* Work-sharing: A process by which NRAs of a number of jurisdictions share activities. Work-sharing entails exchange of information consistent with the provisions of existing agreements and compliant with each agency's or institution's legislative framework for sharing such information with other NRAs. Other opportunities for work-sharing include: jointly assessing applications for marketing authorizations or therapeutic product manufacturing sites, joint work in the post-marketing surveillance of therapeutic product safety, joint development of technical guidelines or regulatory 17 standards, and collaboration on information technology. [Taken from WHO Good regulatory practices: guidelines for national regulatory authorities for medical products (QAS/16.686) (draft October 2016)]
- \* Grouping: The possibility for a marketing authorisation holder to submit more than one variation for a medicine in a single application<sup>5</sup>. Additionally it can be submitted in a single application one variation that affects multiple market authorisations.
- \* Stringent Regulatory Authority (SRA): the medicines regulatory authority in a country which is: (a) a member of the International Council on of Technical Requirements for Pharmaceuticals for Human Use (ICH), i.e. The European Commission of the European Union represented by the European Medicines Agency (EMA), The US Food and Drug Administration (FDA) (United States of America) and The Ministry of Health, Labour and Welfare of Japan (MHLW) also represented by the Pharmaceuticals and Medical Devices Agency (PMDA) (Japan); or (b) an ICH Standing Member, i.e. SwissMedic and Health Canada; or (c) a Regulatory member, i.e. The Agência Nacional de Vigilância Sanitária (ANVISA, Brazil) and The Ministry of Food and Drug Safety (MFDS, South Korea), both members since November 2016; or (d) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time); and — only in relation to good manufacturing practices (GMP) inspections: a medicine regulatory authority that is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as specified at <http://www.picscheme.org><sup>6</sup>

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<sup>5</sup> Definition taken from the European Medicines Agency Grouping of variations Q&As

<sup>6</sup> Definition taken from: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report. WHO Technical Report Series 961.

## Acronyms

- \* ANVISA : *Agência Nacional de Vigilância Sanitária*
- \* CMC: Chemistry, Manufacturing and Controls
- \* CPP: Certificate of Pharmaceutical Product
- \* EMA: European Medicines Agency
- \* EU: European Union
- \* ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
- \* GMP: Good Manufacturing Practice
- \* HCPs: Healthcare Professional(s)
- \* ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
- \* LCM: Life Cycle Management
- \* NRA: National Regulatory Authority
- \* MA: Marketing Authorisation(s)
- \* MAH: Marketing Authorisation Holder
- \* PAC: Post-approval changes
- \* PACMP: Post Approval Change Management Protocols
- \* QA: Quality Assurance
- \* QSE: Quality, Safety and Efficacy
- \* SRA: Stringent Regulatory Authority (as defined by WHO)
- \* USPI: United States Product Information
- \* WHO: World Health Organization

## References

WHO Good regulatory practices: guidelines for national regulatory authorities for medical products (QAS/16.686) (draft October 2016)

WHO Technical Report Series No. 993, 2015, Annex 4 Guidelines on procedures and data requirements for changes to approved vaccines

Questions and answers on post approval change management protocols  
EMA/CHMP/CVMP/QWP/586330/2010

ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management  
– Currently in Step 1 of ICH process

ICH Q8 Pharmaceutical Development

ICH Q10 Pharmaceutical Quality System (PQS)