IPRP
International Pharmaceutical Regulators Programme

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A Survey of Participating Regulatory Authorities and Organisations of the International Pharmaceutical Regulators Programme (IPRP) on Administrative Procedures and Terminologies for Quality-related Changes to Pharmaceuticals

This document reflects the views of subject matter experts participating in the IPRP Quality Working Group and should not be construed to represent the official views of any given regulatory authority participating in the IPRP.

ABSTRACT

Once a certification for an active pharmaceutical ingredient (API) or a marketing authorisation for a drug product has been issued, the administrative procedures and terminologies for Quality-related changes to APIs and drug products vary across regulatory authorities and organisations. During discussions and collaborations amongst regulatory authorities and organisations (e.g., those taking place within the International Pharmaceutical Regulators Programme (IPRP)), it has been noticed that ambiguity is increased when speaking about changes to an Active Substance Master File (ASMF) / Drug Master File (DMF) or a drug product dossier due to the different procedures and terminologies that are used in pharmaceutical product lifecycle management.

This report on the results of a survey of members and observers of the IPRP Quality Working Group (QWG) on their terminologies and procedural aspects has been prepared to assist in clarifying these differences and increasing an understanding of the procedures used for changes to APIs and drug products (e.g., categories/levels) for both regulators and the pharmaceutical industry. In addition, this work could potentially support international collaborative efforts on information sharing and regulatory convergence.

IPRP
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INTRODUCTION

The *International Pharmaceutical Regulators Programme (IPRP)*[1] was created to establish a forum for its regulatory members and observers to exchange information on issues of mutual interest and enable regulatory cooperation. The *IPRP Quality Working Group (QWG)* identifies opportunities for regulatory convergence and information sharing by exchanging and discussing information from members' organisation regarding issues of common interest related to Quality information. The QWG also develops tools and templates and identifies best practices for the assessment of Active Substance Master Files (ASMFs)/Drug Master Files (DMFs) and drug product applications.

Representatives from the following IPRP regulatory authorities and organisations have contributed to the preparation of this paper: National Administration of drug, food and medical Devices (ANMAT, Argentina), Agência Nacional de Vigilância Sanitária (ANVISA, Brazil), Control of Pharmaceuticals and Enforcement Division, State of Israel Ministry of Health (CPED, Israel), European Commission / European Medicines Agency (EC/EMA, Europe), Health Canada (HC, Canada), the Health Sciences Authority (HSA, Singapore), Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA, Colombia), the Ministry of Food and Drug Safety (MFDS, South Korea), the Ministry of Health, Labour and Welfare / Pharmaceuticals and Medical Devices Agency (MHLW/PMDA, Japan), the South African Health Products Regulatory Authority (SAHPRA, South Africa), the Swiss Agency for Therapeutic Products (Swissmedic, Switzerland), the Taiwan Food and Drug Administration (TFDA, Chinese Taipei), the Therapeutic Goods Administration (TGA, Australia), the United States Food and Drug Administration (USFDA), as well as observer organisations from the European Directorate for the Quality of Medicines and HealthCare (EDQM) and the World Health Organization (WHO).

During discussions within the IPRP QWG, it has been noticed that the administrative procedures and terminologies vary across regulatory authorities and organisations for Quality-related changes to active pharmaceutical ingredients (APIs) and drug products, once a certification or a marketing authorisation has been issued. In order to have a common understanding of these differences, members and observers have completed a survey on their respective administrative procedures and terminologies. The outcome of this survey is summarised below. This paper also complements the *Lexicon of Quality Terms*[2] previously developed by the QWG.

It should be noted that this paper reflects information that was current at the time of its publication on the IPRP website. The paper may be updated periodically to reflect further developments or to include information for new regulatory authorities and organisations that have joined IPRP since its original development and publication.

NOMENCLATURE

All members have a system in place for managing changes to APIs or drug products, but the terminology may be different. The most commonly used terms to describe Quality-related changes are "variation" (utilised by CPED, EC/EMA, HSA, SAHPRA, Swissmedic, TGA, and WHO (for drug products)) and "post-

[1] http://www.iprp.global/home
[2] http://www.iprp.global/page/lexicon-quality-terms

approval change" (utilised by ANMAT, ANVISA, TFDA, MFDS and US FDA). For most members, the system for variations/post-approval changes does not distinguish between innovator and generic products.

The terms utilised by IPRP members and observers are summarised in Table 1 (together with references to where respective further information and guidance may be found).

Table 1: Summary of terms referring to a "change" to an API or a drug product

Regulatory Authority or Organisation	Term	Reference/Further Information
ANMAT (Argentina)	Post-approval Change	Decree 150/92 and its modifications (modifications and / or rectifications of the characteristic identifying data related to a certificate of drug product). According regulation 6077/97, each allowed "post-approval change" has a specific guideline with its requirements for each kind of variation
ANVISA (Brazil)	Post-approval Change	RDC 73/2016 (post-approval for drug products – in Portuguese) RDC 361/2020 (post-approval changes of APIs in Drug Products – in English) RDC 359/2020 (post-approval changes of APIs – in English)
CPED (Israel)	Variation	Pharmaceutical Order 1981, IL, (Corr. 8, 1999) & Pharmaceutical Order 1981, IL, (Corr. 24, 2016) & Pharmaceutical Regulation 1986, IL (Corr. 2000)
EC/EMA (Europe)	Variation	Commission Regulation (EC) No 1234/2008 Chapter 5 - Guidelines on the details of the various categories of variations
EDQM	Revision	Guideline on requirements for revision/renewal of Certificates of Suitability (PA/PH/CEP (04) 2) of the Certification of Suitability procedure
HC (Canada)	Post-Notice of Compliance (NOC) Change	Section C.08.003 of the Food and Drug Regulations Post-Notice of Compliance (NOC) Changes - Framework document and Post-Notice of Compliance (NOC) Changes - Quality document
HSA (Singapore)	Variation	Health Products Act (Chapter 122D) Health Products (Therapeutic Products) Regulations 2016 Guidance on Therapeutic Product Registration in Singapore (Chapter H Minor Variation (MIV) Application Submission)
INVIMA (Colombia)	Modification	Decree 677/1995 Article 18 (in Spanish) (https://www.alcaldiabogota.gov.co/sisjurMantenimiento/normas/Norma1.jsp?i=9751) Decree 843/2016 Article 6 (in Spanish) (https://www.alcaldiabogota.gov.co/sisjurMantenimiento/normas/Norma1.jsp?i=66149#10)
MFDS (South Korea)	Post-approval Change	Regulation on Safety of Pharmaceuticals (Ordinance of the Prime Minister) Article 8 (Application for Change of Approved Matters, etc.) Regulation for Pharmaceutical Approval, Notifications and Reviews (Ministry of Food and Drug Safety Notification) Article 3-2 (Processing revision in pharmaceutical approval & notification), [Annex 15]
MHLW/PMDA (Japan)	Partial change	Partial change application: Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, Article 14 (13) PAB Notification No. 483, dated April 10, 1980 Minor change notification: Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, Article 14 (14)

Regulatory Authority or Organisation	Term	Reference/Further Information
		Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, Article 47 PACMP confirmation application: Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, Article 14-7-2 PSEHB/PED Notification No. 0616-14, dated June 16, 2021
SAHPRA (South Africa)	Variation	EMA Variation guideline (https://www.sahpra.org.za/wp-content/uploads/2020/10/Interim-Variations-Addendum-for-Human-and-Veterinary-Medicines_-Final.docx.pdf) BAU (sahpra.org.za)
Swissmedic (Switzerland)	Variation	Ordinance on the requirements for the authorisation of medicinal products, Annex 7 (List of variations in accordance with Articles 21-24 TPO) Guidance document Variations and extensions HMV4
TFDA (Chinese Taipei)	Post-approval Change	Regulations for Registration of Medicinal Products, Article 45 to Article 70 Appendix 12 (only for drug substances)
TGA (Australia)	Variation	The Therapeutic Goods Act 1989 (refers to variations). The Therapeutic Goods Regulations 1990 (refers to evaluation timeframes and also includes the Notification codes). Minor variations to prescription medicines: Process guidance Minor variations to prescription medicines - Appendix 1: Variation change types – chemical entities
US FDA (United States)	Post-approval Change	21 CFR 314.70 and 21 CFR 314.97 (Code of Federal Regulation) Guidance for Industry - Changes to an Approved NDA and ANDA
WHO	Amendment (for ASMFs) Variation (for drug products)	Guidance on amendments to an active pharmaceutical ingredient master file (APIMF) submitted in support of a prequalified finished pharmaceutical ingredient (FPP) or prequalified API (2016) (https://extranet.who.int/pqweb/sites/default/files/documents/30_AmendmentGuidance_Oct2019_newtempl_0.pdf) Guidelines on variations to a prequalified product (2013) (https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex3TRS-981.pdf?ua=1)

SYSTEMS FOR APIs AND DRUG PRODUCTS

Most members have one system that covers both APIs and drug products. However, some members have different systems that cover APIs and drug products (ANVISA, MHLW/PMDA, TFDA and WHO).

Furthermore, with the exception of ANVISA, EDQM, and WHO, all other members only assess changes to the ASMF/DMF in relation to a submission of a change to the application for the drug product. For these latter members, the ASMF/DMF and drug product are linked and changes to the ASMF/DMF cannot be assessed separately from the drug product.

CATEGORIES AND LEVELS OF CHANGES

All IPRP QWG members have different levels or categories for the changes, varying from only two levels/categories (e.g., minor, major) to 5 or more levels/categories (e.g., Immediate Notification, Annual Notification, Minor Revision, Major Revision, Grouped Revision). These categories are summarised in Table 2.

Except for ANMAT, INVIMA, TFDA and TGA, all members have a type of variation/change which is considered a "do and tell" or notification approach, which means that the marketing authorisation holder can implement the change in its quality system and inform the authorities about this change afterwards (e.g. within one year).

EC/EMA, MHLW/PMDA and TFDA have changes that do not fall within the variation legislation in their jurisdiction. For instance, for EC/EMA a change in marketing authorisation holder does not fall within the scope of the variation regulation.

Although a large variety of changes do fall under legislation for changes, the changes which do not fall under the legislation may differ per regulatory authority. Each regulatory authority has written guidance on the management of changes.

Table 2: Summary of levels/categories of quality changes

Regulatory Authority or Organisation	Levels/Categories of Changes
ANMAT (Argentina)	• New dosage form • New route of administration • New strength • New marketing presentation • Modification of pharmaceutical formulation/ composition • Modification of strength • Modification of excipients • Modification of packaging • Modification of the shelf life / expiration date • Modification of storage conditions • Modification of manufacturer facilities • New alternative country of origin • New brand name • New therapeutic indication • And Others
ANVISA (Brazil)	For APIs: • I - Annual Notification; • II - Immediate Notification; • III - Minor Change; • IV - Major Change. For Drug Products (DP): • I - Immediate Implementation with Annual Notification; • II - Immediate Implementation with Individual Notification Protocol; • IIIa - Implementation depends on Anvisa's approval - Priority Type. • IIIb - Implementation depends on Anvisa's approval - Ordinary Type.
CPED (Israel)	• IA- variation with minor or without any impact on the quality, safety and efficacy of the product. • IA immediate notification (IN) - variation with minor or without any impact on the quality, safety and efficacy of the product, but which affect the routine control of the product, or changes the license details. • IB (foreseen / unforeseen) - variation with minor or without any impact on the quality, safety and efficacy of the product, but which does not comply with IA conditions. • II - major variation that might affect quality, safety and efficacy.
EC/EMA (Europe)	• Type IA_{IN} (Immediate Notification, do and tell within 2 weeks) • Type IA (Annual reporting, do and tell within 1 year)

Regulatory Authority or Organisation	Levels/Categories of Changes
	• Type IB (tell and do after 30 days) • Type II (wait for prior approval)
EDQM	APIs only: • Immediate Notification • Annual Notification • Minor Revision • Major Revision • Grouped Revision • Monograph revision • Sister File • Renewal (after 5 years)
HC (Canada)	• Level I - Supplement • Level II - Notifiable Change* • Level III - Annual Notification • Level IV - Record of Changes (* note: Level II - Notifiable Changes are not applicable for Quality changes for pharmaceutical (chemical entity) drugs)

HSA (Singapore)	• Major Variation Application (MAV) (clinical only):
	  ○ MAV-1,
	  ○ MAV-2
	• Minor Variation Application (MIV) (clinical, quality and administrative):
	  ○ MIV-1,
	  ○ MIV-2,
	  ○ MIV-2 (Do & Tell)

INVIMA (Colombia)	• Automatic Modification with posterior evaluation • Traditional Modification
MFDS (South Korea)	• Annual report (AR) • Immediate report (IR) • Major change (Cmaj) • Minor change (Cmin)
MHLW/PMDA (Japan)	For APIs/MFs: • Application for changes in MF registration (Review for a change to the registered items commence only after all the partial change applications for the necessary relevant drugs have been submitted) • Minor change notification (Notification within 30 days after implementation or shipping) For Drug Products: • Partial change application (Application for prior approval) • Minor change notification (Notification within 30 days after implementation or shipping) • PACMP confirmation application
SAHPRA (South Africa)	• Type IA Immediate notification (do and tell within 1 month, timelines 37 working days) • Type 1A (minor variation) (do and tell within 1 year, timelines 37 working days) • Type 1B (minor variation) (do and tell within 1 month, timelines 37 working days) • Type II (major variation) (wait for prior approval, timelines 120 working days)
Swissmedic (Switzerland)	• Type IA_{IN} Immediate notification (do and tell within 1 month) • Type IA Notification (do and tell within 1 year) • Type IB Notification (tell and do after 60 days) • Type II (wait for prior approval)
TFDA (Chinese Taipei)	• Major Change • Minor Change
TGA (Australia)	• Major variation

Regulatory Authority or Organisation	Levels/Categories of Changes
	• Minor variation: Category 3 requests (including minor changes under s. 23 and requests under 9D3) and Self-assessable requests (SARs) • Notification
US FDA (United States)	• Prior Approval Supplement (PAS) – Major change • Changes Being Effected in 30 Days Supplement (CBE-30) – Moderate change • Changes Being Effected Supplement (CBE) – Minor change • Annual Report (AR)
WHO	• Major Variation • Minor Variation • Immediate Notification • Annual Notification

TARGET PERFORMANCE STANDARDS/TIMELINES FOR CHANGES

Most regulatory authorities and organisations have target performance standards (timelines) for the assessment of the various categories of changes. These standards (timelines) are summarised in Table 3. In addition, Table 3 includes where the regulatory authorities and organisations have a stop the clock mechanism following the assessment of a dossier for a change.

Table 3: Target performance standards (timelines) for the categories of changes

Regulatory Authority or Organisation	Levels/Categories of Changes	Target Performance Standards (Timelines) for the Categories		
		Round 1	Clock stop	Round 2
ANMAT (Argentina)	Modifications to Decree 150/92 (according Provision 6077/97) e.g.: • Provision 4824/97: New/modification of the dosage form and/or strength, • Provision ANMAT 556/09 Guidelines for scale changes and post-approval changes for drugs which must demonstrate bioequivalence, • Provision ANMAT 853/89 Excipient change and/or packaging, • Provision ANMAT 854/89 change of manufacturer facilities, • Provision ANMAT 3366/12. change of manufacturer facilities, • Provision ANMAT 855/89 New marketing presentation, • Provision ANMAT 857/89: new brand name, • And others	Each regulation establishes the timeline. Generally, it is 60 working days. In accordance with the "administrative procedures law" 19.549/72	60 days, with an extension of 30 days more. Law: 19549 "Administrative Procedures Law"	The review does not always end in Round 2 (the review continues until there are no further questions).

Regulatory Authority or Organisation	Levels/Categories of Changes	Target Performance Standards (Timelines) for the Categories		
		Round 1	Clock stop	Round 2

ANVISA (Brazil)	For drug products:
	• Immediate implementation
	  ○ Individual notification / protocol
	  ○ Annual notification / protocol
	• Revision (has to wait for prior approval)
	  ○ Priority type
	  ○ Ordinary type
		• For Revisions (major):
		  ○ Priority type - 60 days; Ordinary type - 180 days.
			• If there are any queries, the timeline mentioned in round 1 stops as soon as the query is sent to the company (120 days for the company to reply).	• For Revisions:
				  ○ Priority type - 60 days#;
				  ○ Ordinary type - 180 days#.
				• # the total timeline, considering all rounds of submission.

EC/EMA (Europe)	1. Type IA Immediate Notification; do and tell authorities within 2 weeks 2. Type IA Annual reporting; do and tell authorities within 1 year 3. Type IB; tell authorities and do after 30 days if no comments received 4. Type II; tell and wait for prior approval	1. Type IA IN: 30 days 2. Type IA: 30 days 3. Type IB: 30 days 4. Type II: 60 days All in calendar days	1. Type IA IN: No 2. Type IA: No 3. Type IB: 30 days 4. Type II: up to 120 days All in calendar days	1. Type IA IN: No 2. Type IA: No 3. Type IB: 30 days 4. Type II: 30 All in calendar days
EDQM	• Immediate Notification: do and tell • Annual Notification: do and tell within 1 year • Minor Revision • Major Revision • Grouped Revision	• Immediate Notification - 30 days • Annual Notification - 30 days • Minor Revision - 30 days • Major Revision - 60 days • Grouped Revision - 30 days	• Immediate Notification: No • Annual Notification: No • Minor Revision: 30 days • Major Revision: 30 days • Grouped Revision: No	• Immediate Notification: N/A • Annual Notification: N/A • Minor Revision: 30 days • Major Revision: 30 days • Grouped Revision: N/A
HC (Canada)	• Level I - Supplement • Level II - Notifiable Change • Level III - Annual Notification • Level IV - Record of Changes	• Level I - 180 calendar days • Level II - 90 calendar days • Level III - none • Level IV - none	• Level I - yes • Level II - yes • Level III – N/A • Level IV – N/A	

HSA (Singapore)	• MIV-1
	• MIV-2
	  ○ Notification- shall be submitted at least 40 working days before implementation of the variation
	  ○ Notification, Shall be submitted biannual- with effect from 1 Jan 2019
		• MIV-1:
		  ○ Evaluation Abridged - 120 WDs
		  ○ Evaluation Verification - 90 WDs
		• MIV-2:
		  ○ Notification - 40 WDs
			• 20 working days
			• 20 working days	

INVIMA (Colombia)	• Automatic Modification • Traditional Modification	• Automatic - 15 working days	• N/A • 60 working days	• N/A • 60 working days

Regulatory Authority or Organisation	Levels/Categories of Changes	Target Performance Standards (Timelines) for the Categories		
		Round 1	Clock stop	Round 2
		• Traditional - 60 working days		
MFDS (South Korea)	• Annual report (AR) • Immediate report (IR) • Major change (Cmaj) • Minor change (Cmin)	• Annual report (AR) : from notification date to later that year (about 1~12 months) • Immediate report (IR): 20 days • Major change and (Cmaj) Minor change(Cmin) : Timelines are established by the Regulation on Safety of Pharmaceuticals	• Annual report (AR) : N/A • Immediate report (IR) : N/A • Major change (Cmaj) and Minor change (Cmin) : 60 days	• Annual report (AR) : N/A • Immediate report (IR) : N/A • Major change (Cmaj) and Minor change (Cmin) : 10 days
MHLW/PMDA (Japan)	For Master Files (MFs): • Application for changes in MF registration (Review for a change to the registered items commence only after all the partial change applications for the necessary relevant drugs have been submitted.) • Minor change notification (Notification within 30 days after implementation or shipping) For drug products: • Partial change application (Application for prior approval) • Minor change notification (Notification within 30 days after implementation or shipping) • PACMP confirmation application (The pilot program (PACMP consultation) ended and this application started on August 1, 2021.)	For Drug products: • Partial change application (Application for prior approval) ○ There are several standard timelines in partial change applications (in the case of generic drugs, there are three types of standard timelines: 3, 6 and 12 months).	If there are any questions, the inquiry is sent to the MAH and the time clock is stopped while the MAH prepares the answers (in the case of generic drugs, the first clock stop is one month or less depending on the standard timelines).	The review does not always end in Round 2 (the review continues until there are no further questions).
SAHPRA (South Africa)	1. Type IA Immediate Notification; do and tell authorities within 2 weeks 2. Type IA Annual reporting; do and tell authorities within 1 year	• Type IA: 37 working days • Type IB: 37 working days • Type II: 120 working days	• None	

Regulatory Authority or Organisation	Levels/Categories of Changes	Target Performance Standards (Timelines) for the Categories		
		Round 1	Clock stop	Round 2
	3. Type IB; tell authorities and do after 30 days if no comments received 4. Type II; tell and wait for prior approval			
Swissmedic (Switzerland)	• Type IA Immediate Notification (do and tell within 1 month) • Type IA Notification (do and tell within 1 year) • Type IB Notification (tell and do after 60 days) • Type II Variation (tell, await approval and do)	• Type IA: 30 days • Type IB: 60 days • Type II: 120 days	• N/A	• Type IA: 30 days • Type IB: 60 days • Type II: 70 days
TFDA (Chinese Taipei)	• Major Change • Minor Change	• Major Change: 180 days • Minor Change: 180 days		
TGA (Australia)	• Major Variations requiring either BE, clinical or nonclinical data (e.g. new strengths) - Category 1. • Minor Variations requiring either BE, clinical or nonclinical data (e.g. increases to impurity limits with non-clinical data) - Category 1 • Minor variations requiring evaluation of quality data only – Category 3 • Self-assessable requests (SARs - Verification of details provided by the sponsor) • Notifications (Legal assurance provided that specific conditions are met. No assessment performed)	• Category 1 Variations: 170 days - target, 255 working days - statutory timeframe (ST) • Category 3: 45 working days (ST) • Self-Assessable Requests (SARs): 45 working days (ST) • Notification: No statutory timeframe	• Category 1 Variations - 30/60 calendar days • Category 3 Variations - 20 working days	
US FDA (United States)	• Prior Approval Supplement (PAS) • Changes Being Effected in 30 Days Supplement (CBE-30) • Changes Being Effected Supplement (CBE) • Annual Report (AR)	• Timelines are established by the Generic Drug User Fee Act (GDUFA) and Prescription Drug User Fee Act (PDUFA)		
WHO	For drug products: • Major Variation • Minor Variation • Immediate Notification (IN) • Annual Notification (AN)	• Major – 90 days • Minor – 60 days • IN – 45 days • AN - N/A		

CHANGES REQUIRING PRIOR APPROVAL AND APPROVAL LETTERS

Table 4 includes a summary of categories of changes that require prior approval and those that do not require prior approval from the regulatory authorities and organisations before the changes can be implemented. Also, Table 4 includes a summary of circumstances when an approval letter is sent by the regulatory authority or organisation to the ASMF/DMF Holder or applicant.

ANMAT, INVIMA and TFDA require prior approval for all levels/categories of changes before implementation; whereas prior approval is not required by the other regulatory authorities and organisations for all levels of changes (e.g., some changes can be made through notification procedures). For the regulatory authorities where prior approval is not required for all categories, only major changes usually require prior approval before implementation.

Approval or notification letters are sent for all categories of changes for ANMAT, ANVISA, EDQM, INVIMA, TFDA, HSA and SAHPRA. For the other members, approval letters are not sent for all categories of changes. For EC/EMA, a notification is always sent for the end of procedure, which in some cases needs to be followed by a national implementation (e.g. update of product information documentation).

Although guidance regarding the implementation of changes is available from the regulatory authorities, marketing authorisation holders often have an interest in having approval letters issued to be able to include the change in the quality system.

Table 4: Summary of categories of changes that require and do not require prior approval and where approval letters are issued

Regulatory Authority or Organisation	Prior approval or no prior approval?	Approval letters issued for
ANMAT (Argentina)	Most variations require prior approval. However, there is a limited number of low risk post approval changes that have a timeline to be assessed and after this time they have an automatic approval (these are outlined in each provision)	All changes
ANVISA (Brazil)	For API: • III - Minor change: prior approval • IV - Major change: prior approval For Drug Product: • IIIa - Priority type: prior approval • IIIb - Ordinary type: prior approval	The assessed categories
EC/EMA (Europe)	• Type IA Immediate Notification: no prior approval • Type IA Annual reporting: no prior approval • Type IB: prior approval • Type II: prior approval	• Acknowledgement of an acceptable notification sent • Acknowledgement of an acceptable notification sent • Notification on a Type IB variation sent • Outcome of procedure sent
EDQM	• Immediate Notification: no prior approval • Annual notification: no prior approval • Minor revision: prior approval • Major revision: prior approval • Grouped Revision: no prior approval	• Immediate Notification: acknowledgement of a valid notification or revised CEP issued • Annual notification: acknowledgement of a valid notification or revised CEP issued • Minor revision: letter of approval or revised CEP issued

Regulatory Authority or Organisation	Prior approval or no prior approval?	Approval letters issued for
		• Major revision: revised CEP issued • Grouped Revision: acknowledgement of a valid notification or revised CEP issued
HC (Canada)	• Level I – Supplement: prior approval • Level II - Notifiable Change: prior approval • Level III - Annual Notification: no prior approval • Level IV - Record of Changes: no prior approval	Level I - Supplement Level II - Notifiable Change
HSA (Singapore)	• MIV-1: prior approval • MIV-2: prior approval • MIV-2 (Do & Tell) : no prior approval	MIV-1: Approval letter MIV-2: Notification letter
INVIMA (Colombia)	All changes require prior approval	All changes
MFDS (South Korea)	• Annual report (AR): no prior approval • Immediate report (IR): no prior approval • Major change (Cmaj): prior approval • Minor change (Cmin): prior approval	Major change Minor change
MHLW/PMDA (Japan)	• Minor change notification: no prior approval • Partial Change application: prior approval	For minor change: a receipt of notification issued For partial change: an approval letter sent
Swissmedic (Switzerland)	• Type IA Immediate Notification: no prior approval • Type IA Notification: no prior approval • Type IB Notification: no prior approval • Type II Variation: prior approval	Type II variation
SAHPRA	• Type IA Immediate Notification: no prior approval • Type IA Annual reporting: no prior approval • Type IB Minor Variation: prior approval • Type II Major Variation: prior approval	Type 1B Type II
TFDA (Chinese Taipei)	All changes require prior approval	All changes
TGA (Australia)	All reportable changes require prior approval	All reportable changes
US FDA (United States)	• Prior Approval Supplement (PAS): prior approval • Changes Being Effected in 30 Days Supplement (CBE-30): no prior approval • Changes Being Effected Supplement (CBE): no prior approval	Letters issued for these changes
WHO	Major Variation	All changes

FEES

In most cases, companies need to pay fees for changes to the ASMF/DMF or to the drug product dossier. When members have a fee system in place, the fee amount per type of change differs from no fee for minor changes to the highest amount for major changes.

Within Europe, the situation is mixed as fees for procedures are not determined on a European level, but in national legislation. Therefore, companies have to pay for fees in some countries in Europe and others not. If no fee is required per change, the company has to pay an annual fee per marketing authorisation.

RENEWALS

ANMAT, ANVISA, EC/EMA, EDQM, INVIMA, MFDS, MHLW/PMDA TFDA and WHO have systems in place for the renewal of registrations or marketing authorisations (e.g., to confirm the benefit profile), although it may be called differently. For example, within the WHO it is called a requalification process. The renewal usually takes place after 5 years and is only needed once. In certain cases an additional renewal after 5 years or every 5 years can be necessary. Within the members, the level of assessment differs for a renewal; it can vary from an administrative process to a full assessment.

On the other hand, MHLW/PMDA have the re-examination system to reconfirm the efficacy and safety of new drugs ("new drugs" mean the drugs obviously different from already-approved drugs in terms of active ingredients, routes of administration, indications, dosages/administrations, etc.). When new drugs are applied for marketing, detailed data are required and subjected to strict reviews, but since there are naturally limitations to the number of subjects enrolled in clinical trials conducted before approval, applicants are required to continue surveys and studies on the use of their drugs even after approval, and their safety and efficacy are re-examined after 4 to 10 years as a rule.

HSA's regulatory framework adopts a life-time registration approach, which enables a risk-based life-cycle management where the product will stay on the register as long as there is no post-market data suggesting any changes to the product's quality, efficacy or safety. If there are changes, the registrants are required by law to furnish data to the authority for re-evaluation.

Table 5: Summary of renewal systems within the various members

Regulatory Authority or Organisation	Renewal in place and how it is called	After how many years	How many renewals	Assessed?	What is assessed?
ANMAT (Argentina)	Yes, Renewal	5 years	Every 5 years	Yes	Administrative assess
ANVISA (Brazil)	Yes	10 years	Multiple times	Mostly administrative	Proof of marketing of the drug product
CPED (Israel)	Yes	5 years	Every 10 years	First renewal is assessed, second renewal and on are mostly administrative	File A (updated certificates) and Module 3
EC/EMA (Europe)	Yes, Renewal	5 years	Full MA: 1 or more Generic: 1	Full MA: yes Generic: administrative	Full MA: benefit-risk Generic: none
EDQM	Yes, Renewal	5 years	1	Yes	Compliance to latest regulatory requirements
HC (Canada)	No	N/A	N/A	N/A	N/A
HSA (Singapore)	No	N/A	N/A	N/A	N/A
INVIMA (Colombia)	Yes, Renewal	5 years	Every 5 years	Yes	Full assessment
MFDS (South Korea)	Yes, Renewal	5 years	Every 5 years	Yes	Compliance to latest

Regulatory Authority or Organisation	Renewal in place and how it is called	After how many years	How many renewals	Assessed?	What is assessed?
					regulatory requirements
MHLW/PMDA (Japan)	Please refer to the above explanation for the re-examination.				
SAHPRA (South Africa)	No	N/A	N/A	N/A	N/A
Swissmedic (Switzerland)	Yes, Renewal	5 years	1	administrative	administrative
TFDA (Chinese Taipei)	Yes	5 years	Every 5 years	administrative	administrative
TGA (Australia)	No	N/A	N/A	N/A	N/A
US FDA (United States)	No	N/A	N/A	N/A	N/A
WHO	Yes (for drug products)	5 years	Every 5 years	Assessed for specific issues	Several components are reviewed to confirm the drug product meets current standards.

N/A = not applicable

CONCLUSION

Once a certification or a marketing authorisation has been issued, all IPRP QWG members and observers have systems to manage changes, and overall there are some similarities in these systems. However, the handling of changes differs on details (e.g., terminologies, what categorisation is used, timelines and whether these are in calendar or working days). One of the more prominent differences is found in the number of different levels or categories for the changes/variations (varying mostly from 2 to 5 levels) and whether or not prior approval is necessary.

Convergence of systems for managing post-approval changes/variations is challenging as the differences may not only be found in the terminology, but also in the details of the different procedures (e.g., how to categorise a change and when documentation needs to be submitted). Furthermore, for some members modifications in the post-approval changes may require changes to legislation. The differences observed via this survey in the handling of post-approval changes/variations could be further discussed in order to identify areas to foster information sharing and regulatory convergence which are in line with the mandate of the IPRP QWG.

Having input from many regulatory authorities and organisations, the information compiled in this paper creates a unique opportunity to increase the knowledge and comprehension of some of the complexities in regulating pharmaceuticals globally. A greater understanding by regulators and the pharmaceutical industry on the frameworks used internationally for managing Quality-related changes as described in this paper can enhance awareness for navigating these various systems, facilitate constructive dialogue and potentially enable convergence of standards and procedures in this area. This awareness and dialogue may lead to the identification of potential opportunities for further regulatory cooperation, convergence and information sharing. This, in turn, can promote clarity, transparency and predictability on several key elements for effective pharmaceutical product life cycle management.

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