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Position paper on efficient CMC/GMP for Access To Innovative Medicine

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APAC taskforce for ATIM (access to innovative medicine) has been working to streamline issues around CMC/Quality and GMP for the fast supply of innovative medicine to Asian people. The taskforce issued a position paper in April 2019 to encourage introduction of science based approach to the post approval change regulatory review and was endorsed in the APAC conference. We acknowledge progress of sponsor – regulatory agency understanding on the approach. To further enhance the trend, the taskforce would propose revision of the position paper by incorporating recent knowledge and agreements. Whilst, with the pandemic of COVID-19 impacted the supply of the medicines and vaccines to the patients. We would stretch the recommendations to this point.

GOAL and ACHIVEMENT

APAC 2021 proposes the following recommendations for the efficient post approval change activities while keeping regulatory science justification:

1) Introduce science and risk base approach to secure product stability during/after post approval change.
2) Implement mutual understanding and commitment approach by increasing regulatory reliance [1] and convergence among Health Authorities and streamline of communication from the industry. This could be applied for the change management using the tools such as Post-Approval Change Management Protocol (PACMP) and Biopharmaceutics Classification System (BCS).
3) Increase opportunities for dialogue and collaboration between industry and regulators to discuss integrated science and risk based approaches to have regulatory flexibility for the Product Lifecycle Management and to support the stability of the product.

BACKGROUND

The pharmaceutical industry is responsible to develop and supply high quality medicines that help people's health. For the purpose, the industry is working closely with Health Authority (HA) of each country to register and manufacture innovative medicines in a sustainable manner.

For the efficient pharmaceutical development and succeeding regulatory assessment, the pharmaceutical industry and regulators have been working together to streamline and harmonize the process for registering safe and efficacious new medicines globally approved and making patient's to access earlier for treatment. One of the achievements of the collaborative works is the guidelines released by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) which began its work in 1990s.

ICH has been focused to harmonize regulatory requirements, which help facilitate global development and patients' access to medicines, and now expands its scope to the lifecycle of medicines. In addition to such global movement, regional harmonization activities including the Association of Southeast Asian Nations (ASEAN) pharmaceutical guidelines have actively engaged in clarifying the requirements and we acknowledge its post approval change guide is one of the trophy of the activities.

Asian Partnership Conference of Pharmaceutical Association (APAC) has been aspiring the mission for "**To expedite the launch of innovative medicines for the peoples in Asia**" since 2011. "Quality and GMP" has been taken up as one of the scopes to achieve the mission, since the 5th APAC meeting and the Access To Innovative Medicine Task Force (ATIM TF) has been formed to discuss the topics.

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[1] *Reliance: is the act whereby a regulatory authority in one jurisdiction may take into account and give significant weight to evaluations performed by another National Regulatory Agencies (NRA) or other trusted institution for reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others. (WHO 2019)*

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The 2020 outbreak of the COVID-19 pandemic have drawn significant attention to bring the development of the availability of the medicine and vaccines related to COVID-19. This effort have brought increasing regulatory network to have more regulatory reliance and seeking an opportunity for the convergence of the related guidelines. The impact is not limited to bring the COVID-19 related medicine and vaccines, but also lead to delay the development and the launch of the other innovative medicine desired by the patients with the reduced personnel and reduced work to expedite the new drug due to the national emergency.

ATIM TF, together with other members from JPMA, is currently considering following approaches for the faster approval medicines including post approval changes and for the secured supply.

- A common use and understanding of GMP and their inspectorial scheme, such as Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP, and have confident skills to move to Memorandum Of Understandings (MOU)/Mutual Recognition Agreement (MRA) to use the same inspection information for the efficient assessment and qualification of the submitted GMP site. Particularly, at the time of inability to travel "normally" and may impede some regulatory process such as on-site inspection or face-to-face interview. **(About GMP Qualification)**
- Elimination or reduction of additional data requirement beyond the requirement given in the globally harmonized guidelines, such as ICH and PIC/S, and consider to resolve the issue by having more weight on the regulatory reliance. (**About GMP Qualification, About Pharmaceutical Quality System)**
- Having transparency of the review process and maintaining the transparency throughout the lifecycle of the established drug. Also, enhanced use of digital solutions for communications and acceptance of electronic documents **(About CMC dossier registration)**
- Shortening the review process at regulatory agency to accept change submissions by referring to the already existing available data through the risk based evaluation. Accepting commitment of conducting stability study and report of any out-of-specification results will be critical for both to the HA and market authorization holders (MAH) to secure the safety and efficacy of the drug in a more efficient way. In the premises of conducting BE study is the last resort for securing availability of the changed product, apply flexible justification to waive resource intensive human study by considering properties of substances and essence of manufacturing change. **(About Change Control)**
- For the approved products, consider the stability studies to support a post-approval CMC change is to confirm the previously approved shelf-life and storage conditions, instead of submission of data as part of a regulatory change submission. For this intent, seek ways to fulfill convergence with the global guideline's as number of batches, matrixing and bracketing, site specific stability, on-going stability at the time of change or to accept the commitment of the stability study for the efficient assessment of the change **(About Stability Studies)**

The issues and challenges for the considering approaches for the faster approval medicines including post approval changes and for the secured supply is given in the Appendix.

Appendix

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Issues and challenges

About GMP Qualification:

Good Manufacturing Practice (GMP) has been the subject of several harmonization efforts. The ICH Q7[i] *"GMP for API"* was implemented very early in the ICH process and now the guideline is a part of requirement as PIC/S Part II for Active Pharmaceutical Ingredient (API). ICH GMP principles are similar to the GMP issued by a number of regions (e.g. Europe, US) and by the WHO.

The GMP requirement and implementation brings confidence for the safety and efficacy of the medicines. PIC/S implemented the harmonized GMP guideline for the efficient use by the inspectorate. The GMP practice is performed on site, however, each country has different approaches to register the GMP qualification of the site. The qualification had been performed by either document base or on-site inspection, however in recent years the memorandum of agreement (MOA) scheme enables the mutual utilization of inspection report prepared by authorities/agencies across countries/regions. To expedite the process, for the time where "normal" operations are adversely impacted, a key consideration to tackling is to have in place regulatory reliance mechanisms, such as sharing of one's on-site inspection or document audit records and other regulatory information on the assessment of the manufacturing site, to inform another HA's regulatory decision-making, waiving of the need for "wet" signatures, acceptance of electronic documents (e.g. eCPP) The key to expedite mutual agreement for keeping the levels of inspection same remains the same and JPMA will continue to support PMDA sponsored Asian Inspection Training Center since 2016 by providing training manufacturing sites to conduct the mock inspection for the trainees and also sending the experts as trainers.

About Pharmaceutical Quality System:

Lifecycle management and robust GMP operation are attained through good pharmaceutical quality system (PQS). The PQS manages the understandings and knowledge gain of the product through development, technological transfer, and commercialization. The enablers to operate the PQS are knowledge and quality risk management and in the end, this will bring the innovation and continuous improvement for the product. The ICH Q10[ii] *"Pharmaceutical Quality System"* finalized in 2010 prescribes how the quality of medicines is secured throughout its lifecycle by science and risk management.

Lifecycle management is being discussed separately as ICH Q12[iii] guideline, whereas PQS encourages the users to improve quality and secure the supply.

One of the challenges for the industry is that each economy or region has its own requirement for the changes and those submissions. From the industrial perspective, it is idealistic if a generated data could be applicable to all the regulators and all regulators have the similar requirements of change management system or guideline medicines.

In this difficult time, JPMA would like to re-highlight the use of fundamental effective tools to endorse the PQS by implementation of a suitable approach to quality risk management (QRM) principles as set out in ICH Q9. The principles have had wide spread adoption by the industry. Regulators are observing stagnation and limited innovation in the approaches being applied. Benefit could be brought for example, by placing increased emphasis on learning from other industries, which could be applicable to pharmaceuticals.

About CMC dossier registration:

Applicant or market authorization holder (MAH) submits the Chemistry, Manufacturing and Controls (CMC) dossier according to ICH M4Q[iv] Common Technical Document (CTD) format. Among the member state in APAC, the participant from ASEAN countries follows ASEAN-CTD (A-CTD) format, which is analogue to ICH CTD guideline.

Despite the content in the CTDs (ICH CTD or A-CTD) are agreed to harmonize from the regulatory perspectives, the different requirement from each countries challenges the industry applicants to generate more data and takes longer time to prepare the dossier. To expedite the enhancement and efficiency of the review process, one of the solutions would be utilization of enhanced digital solutions, such as acceptance of more electronic documents and seek other options to resolve the impact by the on-going pandemic on the availability of medicines and vaccines.

About Change Control:

Each country or region has issued guidelines for any post-approval change, although MAHs should admit (point out)

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those guidelines are sometimes arbitrary understood resulting member states or reviewers adopt their own measures for the change control.

In ASEAN, the variation guideline addresses point-to-consider to identify the major and minor changes and what may the requirement for the submission of the change, however, the full endorsement of ASEAN Variation guidelines is yet to be implemented and still local requirements are prioritized.

Additional information for stability study or data is most common request by the agencies during the calibration/review of post-approval change submissions.

In the premises of conducting BE study is the last resort for securing availability of the changed product, apply flexible justification to waive resource intensive human study by considering properties of substances and essence of manufacturing change. Also, the change control management tool, such as Post-Approval Change Management Protocol (PACMP) could be a useful tool to bring effective and efficient way to obtain the predicable tools to implement the change.

About Stability Studies (*):

RECOMMENDATIONS/PROPOSALS FOR STABILITY STUDY

- Encourage **science- and risk-based approaches** to stability studies while adopting ICH/WHO recommendation especially for post approval changes:

    a. Avoid rigid requirements for defined numbers of batches in stability studies and allow matrix and bracketing approaches has been prescribed in ICH Q1D[v] stability guideline.
    b. Accept the use of scientifically-based predictive models to statistically justify proposals for adequate shelf-life (ICH Q1E), including API retest period. This will reduce the need to submit shelf-life extensions and re-labelling and facilitate access to medicinal products.
    c. Adopt flexible approaches to the interpretation of stability requirements need to support the assurance of product quality, instead of employing a conventional set of tests for API and dosage forms.
    d. Consider aligning the stability requirements to support post-approval changes within the region (ASEAN guideline) or with those defined in other regulatory frameworks (e.g. EU guidelines[v]).
    e. Eliminate or reduce the requirements for site specific stability if none of the stability related quality attributes have changed in batches produced at the new site. Stability data generated on product manufactured at alternate sites should be considered representative of the drug product, provided that the manufacturing process has been validated for all sites and none of the stability related quality attributes have changed.
    f. Accept the use of appropriate stability data (e.g. accelerated, thermal cycling) or predictive modelling (e.g. Accelerated Stability Assessment Program (ASAP)) to support temperature deviations from the approved label conditions during transport. The company quality system should have procedures to handle such deviations.

- Allow quality reviewers the **flexibility** to accept risk-based approaches and alternative stability proposals when scientifically justified, e.g. long term stability for Zone IVb countries at other conditions than 30°C/75%RH with a scientific justification of the proposed shelf-life and labelling. Note that according to WHO, alternative storage conditions can be used if justified.

- Increase opportunities for **dialogue and collaboration** between industry and regulators across the region and throughout the lifecycle of the product to discuss integrated science and risk based approaches to stability.

    a. Industry would propose updates or revisions to guidelines/regulations during the drafting stage, prior to public consultation) Reasonable time for comments should be provided.

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b. Encourage dialogue on innovative approaches (PACMP[vi], BCS[vii]) to rationalize post approval commitments and streamline regulatory process for changes in shelf life and storage condition.

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[i] ICH Q7 "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients", Adopted November 2001, PMSB/ELD Notification No. 1200
[ii] ICH Q10 "Pharmaceutical Quality System", Adopted 19 February 2010, PFSB/ELD Notification No. 0219-1 & PFSB/NCD Notification No. 0219-1
[iii] ICH Q12 "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management", Step 3
[iv] ICH M4 "The Common Technical Document", M4Q(R1), Adopted on July 1st 2003, PFSB/ELD Notification 0701004
[v] ICH Q1D "Bracketing and Matrixing Designs for Stability Testing of New Drug Substance and Products", adopted 31 July 2002 PFSB/ELD Notification No. 0731004
[vi] "Questions and answers on post approval change management protocols", 20 March 2012, EMA/CHMP/CVMP/QWP/586330/2010
[vii] "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System", Dec 2017, US. Department of Health and Human Service, FDA, CDER