European Federation of Pharmaceutical Industries and Associations

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Vaccine Lot Release in ASEAN

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✱ Position Paper

Executive Summary

This position paper describes a high-level landscape analysis and understanding of the identified issues and proposed advocacy activities to meet the challenges and barriers faced by the industry due to requirements for vaccine lot release and/ testing triggered by the WHO proposed Regulatory System Strengthening (RSS) framework.

The objective of this briefing paper is to highlight some of the consequences and challenges of implementing this requirement in the ASEAN region

- The implementation of such requirements might have several unintended consequences, such as delay in release of Vaccines, ultimately access of Vaccines to patients.
- Infrastructure challenges for industry and NRA to adopt this requirement.
- The concern on adopting the RSS framework intended as a guidance for NRAs to regulate local vaccine manufacturers and not imported Vaccines.

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1. Introduction

- Lot release is a system specifically established for the regulatory release of specified biological products[3]. The focus is to ensure the quality, safety and efficacy of biological products through regulatory release systems. Lot release testing is performed on every batch of specific biological products by manufacturers prior to releasing to the market for sale.
- For vaccines, there are different approaches used by NRAs for conducting confirmatory lot release including paper review of summary protocols, summary protocols with independent testing, recognition and acceptance of lot release certificates from the responsible National Regulatory Authorities (NRAs) or National Control Laboratory (NCL).
- As part of improving regulatory oversight of all medical products in individual NRAs, the WHO has proposed a framework to drive towards Regulatory Systems Strengthening (RSS)[1], potentially to be implemented end 2019.
- This framework will be used to evaluate NRAs and also will be used to publicly designate them as WHO-Listed Authorities (WLA).
- This framework is also intended to guide international and national procurement decisions on medicinal products and vaccines and increase the pool of regulators contributing to the WHO Prequalification program.
- Supported by the World Health Assembly (WHA) Resolution 67.20 on RSS for medical products, the Global Benchmarking Tool (GBT)[2] is being rolled out which will help measure national regulatory systems against defined indicators. These indicators enable WHO and regulatory authorities to:
    - Identify strengths and areas for improvement
    - Facilitate the formulation of an institutional development plan (IDP) to build upon strengths and address the identified gaps;
    - Prioritise IDP interventions;
    - Monitor progress and achievements
- To be accredited with an acceptable level of maturity by WHO, many NRAs will try to fulfil all the indicators listed in the GBT.
- One of the proposed GBT for Evaluation of National Regulatory System of Medical Products is for NRA Lot Release (LR)[3].
- Within the "NRA Lot Release (LR): Indicators and fact sheets", one of the indicators LR04 "Procedures established and implemented to perform NRA lot release" serves as a guidance for NRAs to release products manufactured locally in their countries. This could have led several NRAs within ASEAN to either introduce or considering introducing requirements for additional quality control testing upon importation of medicinal products, specifically vaccine products imported into their countries, before releasing into the market.
- However, WHO does not recommend the implementation of systematic testing by NCL but recommends reliance as promoted by the WHO-National Control Laboratory Network for Biologicals

- The objective of this position paper is to provide an overview of ASEAN countries that have implemented or are considering implementation of testing upon import for vaccines and the impact on industry and ultimately access of Vaccines to patients.

2. Background & Current Situation in ASEAN

The requirement for analytical testing of drug product, particularly vaccines, is not a new requirement globally, however it is for the ASEAN region. As many NRAs are slowly driving towards the proposed Regulatory Systems Strengthening (RSS) initiated by the WHO, they are considering introducing requirements, for additional quality control testing before commercial batch release into the market.

From the industry perspective, initiatives to strengthen the regulatory systems which will benefit public health are welcomed especially when these results into an improvement in the quality of medicines and vaccine, potentially with better and faster access for patients.

A few examples of NRAs who are currently trying to implement or have implemented lot release testing systems are listed as follows:

Philippines

- Vaccines are required to secure a Lot Release Certificate prior to release of the products to the market. Current practice involves paper evaluation of the summary lot protocol, Certificate of Analysis and Lot Release Certificate from NRA/NCL of the producing country.
- The Philippines Food and Drug Administration-Common Services Laboratory (FDA-CSL) has communicated to companies on 29-Aug-2019 that it was currently in the process of applying as a World Health Organisation (WHO) recognized NRA/NCL (National Control Laboratory).
- As part of the application, it was recommended by WHO that the Philippines FDA should establish good communication channels from various manufacturers, so that FDA-CSL can gather information to allow transfer and qualification/validation of methods and procedures, and eventually conduct tests on vaccines and biological products.
- Long-term goal for FDA-CSL is to develop test methods and policies for vaccines and biological products testing.

Singapore

- Singapore Health Sciences Authority (HSA) is currently reviewing their vaccine lot release strategy as an on-going effort to enhance public health protection and to provide adequate assurance on the quality of vaccines administered to the Singapore population.
- HSA had requested feedback from the industry on the feasibility of implementing a vaccine lot release strategy in Singapore.
- HSA is aware that there are several approaches to lot release of vaccines including leveraging the lot release certificates issued by other NRAs/NCL; or by the review of manufacturers' summary protocols which may be further supplemented by independent testing.

- For the initial consultation with the industry stakeholders, HSA sought feedback from different companies on the feasibility to furnish the following documents to HSA for each lot of imported vaccines prior its release onto the market:
    - Lot Release Certificate from NRA/NCL of the producing country
    - Manufacturer's Summary Protocol
    - Certificate of Analysis
- There is no further update since the initial consultations

Malaysia

- Lot release procedure has been in place for all vaccines and blood products since 2015.
- However, prior release to the market, lot release documents are reviewed as well as cold-chain inspection.
- Currently, there is no testing to be done as part of the lot release requirements. However, the Malaysian National Pharmaceutical Regulatory Agency (NPRA) has started to test vaccines as part of their post-marketing surveillance and NPRA has started developing methods to test vaccines and have also requested for working standards.
- NPRA has started on a pilot for the implementation of lot release with testing for vaccines and plasma products since December 2019. All registered vaccines and plasma products imported between December 2019 to March 2020 are subjected to this pilot study.
- Depending on the dosage form of the finished products, different types of test are conducted.

Dosage Form	Testing
Solution / Liquid	1. Appearance 2. Particulate contamination (viable particles)
Freeze Dried / Lyophilised	3. Appearance 4. Solubility 5. Particulate contamination (visible particles) on reconstituted finished product

- Full implementation of the lot release with testing is currently set on April 2020.

Vietnam

- As initiated by the Drug Authority of Vietnam (DAV), the National Institute for Control of Vaccines and Biologics (NICVB) do carry out analytical testing on batches of imported vaccines and blood products before releasing into the market.
- This requirement was implemented before 2010 and was mentioned in Circular 09 on Drug Quality management issued in Apr-2010 and related regulations. The requirement is still maintained in the new Pharma Law issued in 2016 and the revised Circular on Drug Quality Management (now referred as Circular 11) issued in May-2018

Thailand

- The Thai Food and Drug Administration released the Guidance for the Control of Biological Products for Human Use Before Release onto the Market B.E.2543 in 2000for lot release of controlled biological products. The contents covered active immunizing agents, passive immunizing agent, blood product, diagnostic agents, immunomodulator that are used directly on humans. This was further emphasised by the Ministry of Public Health in 2012
- Institute of Biological Products (IBP) from the Department of Medical Science, has been designated to conduct the lot release.
- For imported products: Documents required are Summary Production Protocol, Certificate of Lot release from NRA of producing countries, Transport Information from manufacturing sites to the local warehouse, Temperature Record during transportation as well as Product Samples are required for lab testing (test for appearance). Reference Standard could be requested when applicable. The standard lead time which is the time of submission of documents and samples to the issuance of the lot release certificate by the Thai FDA is 10 working days.
- Biological Institute Department of Medical Science will perform some test mainly on physiochemical testing.

Indonesia

- The Health Authority of Indonesia, National of Agency Drug and Food Control (NADFC), issued the 'Regulation of Head of NADFC No. HK.03.1.3.12.11.10692' in 2011 which provides guidance on the monitoring of products imported into Indonesia.
    - Article 11: Imported vaccines for human use can only be distributed after sampling, evaluation and lab testing by BPOM (BPOM's Laboratory)
    - Article 12: For vaccines that already have lot release certificate form the Country of Origin's authority will be evaluated for its summary batch protocol, Certificate of Analysis, Label, and conformity to the specifications. Timeline for lot release by BPOM's laboratory is 10 working days.

Status in Other ASEAN Countries

- So far there is no information around implementation of Lot Release testing in Brunei, Myanmar, Cambodia & Laos. Though there is a possibility that based on practices by other NRAs in ASEAN this could change.

3. Possible Consequences & Challenges

Independent batch release testing is important to ensure the quality and safety of human vaccines and we believe all batches should be tested by a testing laboratory certified by a stringent health authority before release to the market. NRAs wanting to perform lot release is a positive initiative which will enhance the public trust in medicinal products and is a necessary requirement for locally manufactured products and for monitoring distribution in the country (surveillance testing). However, there are many potential challenges and consequences to public health because of increasing number of countries requiring local lot release testing for imported products that have been previously released by other agencies

- Increased complexity of supply chain:
  - Risks are introduced to patient due to interruptions to consistent supply;
  - Potential delays in product distribution and patient access to medicine;
  - Shortening of remaining shelf-life due to prolonged cycle time caused by import testing;
  - Unnecessary increase of quarantined material which can also strain capacities of cold storage facilities
- Testing is expensive, time and resource consuming for NRAs
  - Increased consumption of product specific reagents
  - Installation of company/product-specific equipment and training and transfer of these methods to NRA.
  - Several of the key tests for vaccine release are product specific and not applicable to other types of vaccines or even similar products. This creates an issue on training technicians to perform an assay they may only use a few times (or once) per year. Further complicating the capacity to perform the assay correctly in a timely fashion, which may even result in losing compliant lots due to user error.
  - When testing few batches per year, it is not feasible for NRAs to monitor the manufacturer's consistency
- Regulation of testing standards
  - Studies should be conducted with similar test parameters to ensure comparability between manufacturer and NCL test methods and results.
- Import testing does not address the concern with respect to counterfeit products.
- For supply critical situations e.g. disease outbreak, pandemic situations, additional requirements for lot release testing may slow down patient access to much needed vaccines
- Duplicative testing by multiple local authorities needlessly wastes time and resources, including excess consumption of samples, reagents and use of laboratory animals for testing. Most importantly, there is no increased benefit to patient safety if the batch was already certified by another NRA and it can potentially prevent or delay access for patients.
- World Health Organization (WHO) guidelines encourage a thoughtful approach to testing decisions: “The decision to repeat tests on a lot that has already been tested by another competent authority should be carefully considered in light of all available information”

4. Recommendations

- Full waiver of local lot release testing for mature products with manufacturing consistency demonstration as already recommended by FDA and Health Canada, if possible. Paper review or reliance on trusted NRAs as advocated by WHO for batch release activities, e.g. allow submission of NRA/NCL/OMCL certificates as adequate documentation to provide assurance for lot release can be undertaken. If full waiver is not possible, a partial waiver where the number of tests is reduced, i.e. choosing appropriate test like identification testing, and not carrying out all the release tests. Several companies have experienced the exemptions from lot release testing on a case by case basis after discussion with US FDA and Health Canada.
- Industry welcomes NRAs to obtain WHO recognition as NRA/NCL, but recommends NRAs to also apply to become a member of the WHO-National Control Laboratory Network for Biologicals (Link WHO-NNB)[5]. This Network provides a platform to collaborate and exchange technical knowledge on quality control and quality assurance of vaccines or other biological medicinal products, and build up to fostering reliance. Joining the Network is a good way to develop capabilities through cooperation, networking and sharing of best practices. Furthermore, the main objective of the Network is to share quality information in order to facilitate access to prequalified vaccines through recognition by recipient countries of the lot release decision of the responsible NRA. It is intended that this will reduce redundant testing, promote development of harmonised common standards and facilitate the sharing of best practices[6].
- To encourage officials from an NRA to visit the manufacturing site for a demonstration of the testing facilities and observe the testing of the products, thereby validating testing for all batches, and avoiding any further duplicate testing at the NRA facilities.
- To adopt risk-based approach which focuses testing on vaccines that have not yet established a track record of quality and safety, such as new products, and vaccines associated with adverse reactions or manufacturing failures. The risk-based approach is recommended by the WHO and major health authorities, including US and Canada, have successfully implemented this model.
    - Testing for a period of time to gain local confidence in the release process of the manufacturer importing products and their local NRA release. Then allowing a waiver from testing after that point in time.
    - Exempt established vaccines from lot release certification requirements and/or apply these requirements for random lots (not for every imported lot)
    - Exempt some vaccines from lot release certification requirements where supply shortage or delay in supply have major health impact e.g. Rabies. MMR. Varicella, Hepatitis B.

5. Supportive Materials & Links

1. Regulatory System Strengthening – https://www.who.int/medicines/regulation/rss/en/
2. WHO Benchmarking Tool for NRA – https://www.who.int/medicines/regulation/benchmarking_tool/en/
3. GBT- NRA Lot Release (LR): Indicators and Fact Sheets - https://www.who.int/medicines/regulation/09_GBT_LR_RevVI.pdf?ua=1
4. 2010 WHO guidelines on lot release of vaccines by NRA – Annex 2 - https://www.who.int/biologicals/TRS_978_Annex_2.pdf?ua=1
5. WHO-National Control Laboratory Network for Biologicals (WHO-NNB) - https://www.who.int/immunization_standards/vaccine_quality/who_nnb/en/
6. WHO Expert Committee on Biological Standardization; 69th report; WHO Technical Report Series, No. 1016 - https://www.who.int/biologicals/expert_committee/WHO_TRS_1016_web.pdf
7. IFPMA VSRG: Position paper on the appropriate control strategies eliminate the need for redundant testing of pharmaceutical products (Feb-2016) - https://www.ifpma.org/resource-centre/import-testing-position-papers/
8. Health Canada; Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs - https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/release/guidance-sponsors-program-schedule-biologic-drugs.html
9. US FDA 21 CFR 610 Subpart A – Release Requirements (link)
10. US FDA (Federal Register, Vol 58 (1993), 137, pages 38771) (link)

6. Identified Stakeholders & Target Audience

a. List of Stakeholders/Target audience

- ASEAN Health Authorities
- ASEAN Local Trade Associations
- APRIA (ASEAN Pharmaceutical Research Industry Association)

7. Glossary

- APRIA - ASEAN Pharmaceutical Research Industry Association
- BPOM – Badan Pengawas Obat dan Makanan (the Indonesian name for NADFC)
- DAV – Drug Authority of Vietnam
- FDA-CSL - Food and Drug Administration-Common Services Laboratory, Philippines
- GBT – Global Benchmarking Tool
- HSA – Health Sciences Authority, Singapore
- IBP - Institute of Biological Products, Thailand
- IDP - Institutional Development Plan
- NADFC - National of Agency Drug and Food Control, Indonesia
- NCL – National Control Laboratories
- NICVB - National Institute for Control of Vaccines and Biologics, Vietnam
- NPRA – National Pharmaceutical Regulatory Agency, Malaysia
- NRAs – National Regulatory Authorities
- OMCL – Official Medicines Control Laboratories
- RSS – Regulatory Strengthening Systems
- SRA – Stringent Regulatory Authority
- WHA - World Health Assembly
- WHO – World Health Organisation
- WLA – WHO-Listed Authority

8. Acknowledgment

a. Working Group Composition

- Aziza Ahmed, Regulatory Affairs CMC Director APAC, MSD International GmbH
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