



Position Paper

29 February 2016

Appropriate Control Strategies Eliminate the Need for Redundant Testing of Pharmaceutical Products

Background

To help ensure drug product quality and safety, national medicines regulatory authorities (NMRAs) in many countries have implemented, or are considering implementing, import testing requirements for pharmaceuticals, biological/biotechnology and vaccine products entering their countries. Historically such testing requirements may have been necessary to prevent the distribution of unsafe or non-conforming drug products. Today, however, pharmaceutical, vaccine, and the biotechnology industries have developed and implemented robust quality management systems to ensure the identity, safety, purity and potency of its drug products throughout its manufacture and international distribution channels, thereby eliminating the need for this redundant testing.

Key Messages

The repetition of quality control testing for pharmaceutical, biological/biotechnology and vaccine products at the country level, or 'import testing', is unlikely to increase public health protection. It can delay batch release, reduce remaining shelf life and therefore increasing risk for a potential drug shortage. Also it does not prevent the entry of counterfeited products. Finally, it creates an avoidable burden for NMRAs, the pharmaceutical industry and the national healthcare systems, as recognized by several competent authorities who have taken measures towards reducing import testing.

Import testing should not be routinely required for the following reasons:

1. Manufacturers have established appropriate control over their production through in-process controls, validation of the manufacturing process and release testing of the finished drug products, in line with internationally recognized good manufacturing practice (GMP) standards.
2. Robust quality management systems (QMS) are in place and enforced, including appropriate validation, control and risk management strategies for the handling, storage, transportation and distribution of the finished drug products under good distribution practice (GDP) standards.
3. The adequacy of a manufacturer's quality oversight is ensured through reporting requirements as well as regular internal audits and inspections by competent NMRAs confirming the adequacy of the established processes and the compliance with the product license.
4. Import testing does not increase patient safety. Practical implementation of import testing showed that the rejection rate induced by this local re-test is negligible, if any.
5. Import testing introduces risks for the patients due to interruptions of the legitimate supply chain and potential delays in product distribution and patient access to important medicines.

6. The prolonged cycle time, caused by import testing, results in significant shortening of the remaining product shelf-life and unnecessarily increases the stock of quarantined material.
7. Import testing does not address the concern with respect to counterfeit products. Where there is an increased risk or concern regarding counterfeit products this can be addressed by post-marketing surveillance testing (not a topic for discussion within this publication).

Where import testing is required by law, NMRAs should establish waiver procedures. Risk-based approaches, such as the assessment of satisfactory inspection results from competent domestic authorities at the manufacturing site, should be considered sufficient to eliminate redundant import testing.

This position paper outlines the scientific and regulatory basis for not requiring import testing and highlights the problems with this practice; including the potential for significant delays in supplying important therapeutic and preventative medicines and further associated patient risks.

Uninterrupted Control through Good Quality Practices

In recognition of the quality gaps in the past, modern pharmaceutical manufacturers now maintain tight controls over the production of their products through more advanced process understanding, proper in-process controls, extensive process and product validation efforts, advances in analytical techniques and modern change control systems as part of a holistic QMS. These control strategies extend beyond the manufacturer's own facility by qualifying/validating, for example, the cold chain including the impact of potential temperature incursions on the shelf-life specifications of the drug product (e.g. transportation stability studies). Finally, the distribution of the products is well controlled by implementing, for example, serialization and tamper evidence measures. All these efforts ensure the compliance of the drug product to its registered specifications throughout the entire supply chain from the time of production in the exporting country through the import, storage and distribution of the product in the importing country.

Understanding the value of the successive controls across the entire supply chain, several NMRAs, including those in Brazil (ANVISA), the US (US FDA) and the Ukraine (Ministry of Health of Ukraine) have eliminated redundant testing for certain biological products. Likewise, China (SFDA) has eliminated redundant import testing for small molecules as part of the Clinical Trial Authorization.

When discussing its policy change to eliminate redundant testing (lot-to-lot release), US FDA regulators determined that "once a company has demonstrated its ability to consistently produce acceptable lots, it is not necessary to verify that each manufactured lot is acceptable for release" [1]. The agency noted that eliminating this testing requirement would result in "significant savings of time and resources for both the industry and agency" without adding any "significant risk to public health" [2].

Recognized Regulatory Oversight

In addition to the manufacturer's internal oversight (self-inspections and auditing guided by the QMS), external oversight (regular inspections by the domestic NMRA) certifies the adequacy of a manufacturer's QMSs and thus compliance with the product release specifications registered in the respective countries as well as the robustness of their legitimate supply chain.

Several reports, including the presentation to the World Health Organization (WHO) on behalf of IFPMA [3] highlight that inspections across the globe have increased in the last decade as more and more countries begin to regulate pharmaceutical, biological/biotechnology and vaccine products in

their jurisdiction. Based on inspections, NMRAs can be confident that a manufacturing site and the relevant QMS with its related processes (including product distribution) are under control. This oversight provides confidence that the manufactured products are safe and of high quality standard according to licensed requirements and specifications. As a result, manufacturing practices, product release procedures (including release testing) and legitimate distribution chains are under more scrutiny by NMRAs than ever before. In addition, the increasing requirements for annual reporting and adverse event reporting as well as enforcement actions and the increased communication between NMRAs give regulators much greater confidence in a manufacturer's practices and QMSs.

Furthermore, many industry groups (e.g. EFPIA, ISPE, PDA [4, 5]), NMRAs, and global organizations (e.g. WHO, PIC/S, ICH, ASEAN, APEC) complemented by regulators have worked together to harmonize and standardize the medicinal products approval and control process as well as GMPs and GDPs (including good storage practice – GSP). Because of these harmonization and collaboration efforts, submission, manufacturing and distribution practices across the globe are becoming more standardized allowing greater information flow and understanding of risks and their controls between NMRAs.

Repeated Testing: Challenges, Issues and Risks

Supply chain integrity and resilience are important components of patient access to products [6]. Disruptions can quickly lead to drug shortages or the introduction of counterfeited products [7, 8]. Import testing may significantly impact the product supply chain.

1. Repeated testing means less time for the distribution and administration of the medicines to patients [9]. Not surprisingly, import testing takes significant time and may result in a lack of access or delayed access of medicines to patients. A recent study on import testing disclosed delays of up to 22 weeks (approximately five months) [10]. The time taken to locally test and release a product batch effectively shortens the time the product is able to be distributed before its expiry date is reached. Consideration should also be given to the time consumed in the event of a false out of specification result, thus potentially causing interrupted product supplies, drug shortages, and stock outs.
2. Import testing may result in significant supply chain issues for a country, including product inventory and sample management concerns. Moreover, a less stringent chain of custody for test samples may increase the risk for samples to be lost or diverted¹. This risk is minimized when robust GDPs are not interrupted [11]. Thus, the complexity in the legitimate product supply chain and less stringent chain of custody for test samples may lead to an increased risk to patients.
3. Import testing only controls the legitimate supply chain at the time of product import. However, risk to patients is caused by illegally imported products through many different routes (e.g. parallel trade and parcel shipments). In addition, in-country distribution channels to the pharmacy or drug dispenser and finally to patients are not controlled by import testing.
4. Additional product testing may be expensive, difficult to implement and to perform, especially for biotechnology and vaccine products. Consequently, where government testing is required, each country will need to allocate significant resources for equipment and personnel to perform this testing, which may be extremely complex given the nature of many assays (e.g. biological potency assays). Government laboratories may not have the proper equipment (e.g. method

¹ In cases, where sampling, storage (e.g. in customs warehouses) and/or testing is outside the control of the manufacturer.

specific in-house apparatus) and biological-originated materials (e.g. indicator cell, antibody). Many of these assays are subject to variation if not accompanied by a proper analytical method technology transfer to the receiving laboratory.

Need for Waivers

It is recommended, that NMRAs either eliminate import testing requirements or establish exemptions from import testing under well-defined conditions, employing timely waiver processes where appropriate manufacturing and distribution controls have been demonstrated. Where the legal framework does not allow for waivers, it is suggested that the legislative requirements should be amended to enable exemptions from import testing. Detailed rationale and proposed documentation to support a waiver from import testing is shown in the [Appendix](#).

It is understood, that identification testing upon import is a good practice. In case the current legislation requires repeating the release testing upon importation, an applicant should be able to agree with the NMRA on a reduced import specification focusing on identification tests.

Import Testing: An Outdated Practice?

In light of globally harmonized good quality practices (e.g. GMP and GDP) and comprehensive oversight by QMSs and NMRAs, import testing appears to be an outdated practice [12]. Findings from a recent study illustrate that import testing does not add benefit to the quality or safety of drugs, provided that the products are uninterruptedly controlled according to GMPs and GDPs [10]. The authors found a batch rejection rate of 0.005% (18,616 re-tests performed in one year resulted in one batch rejection).

Moreover, import testing does not detect counterfeit products, as testing occurs at the point of entry into a country and does not reflect additional risk related to illegal distribution channels. These threats, however, represent today's dominant concern [13], which is also emphasized in the above mentioned negligible rejection rate of the quality check upon import. Fortunately, these threats are already addressed by post-marketing surveillance testing. This testing category, which is not a topic for discussion within this publication, offers the possibility to detect counterfeit products as well as unauthorized or alternative imports (e.g. internet pharmacies, parallel trade) as it covers local distribution channels [14,15].

Conclusions

In many cases, import testing is redundant. Therefore, under circumstances where a manufacturer or a manufacturing facility of a pharmaceutical, biological/biotechnology or vaccine product

1. provides evidence that their product manufacturing, testing and storage/distribution systems are well controlled and validated;
2. has implemented a proper QMS [16,17] to assure compliance; and
3. is under regular control of independent auditing and globally recognized inspectorates (e.g. PIC/S members) or the inspectorates of other competent NMRAs (e.g. as described in the WHO Certificate of Pharmaceutical Product – CPP – procedure [18])

there should be confidence by the importing country's NMRA that the product is safe, of high quality and complies with registered specifications. As a consequence, the manufacturer should be given the opportunity to obtain a waiver for redundant import testing.

References

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Supporting Information

1. Pharmaceutical Inspection Cooperation Scheme (PIC/S), www.picscheme.org
2. International Conference on Harmonization (ICH), www.ich.org
3. World Health Organization (WHO), www.who.int
4. Association of South East Asian Nations (ASEAN), www.aseansec.org
5. Asia-Pacific Economic Cooperation (APEC), www.apec.org
6. IFPMA Import Testing Portal, www.ifpma.org

Appendix: Rationale and documentation to support a waiver from import testing

A rationale for a waiver application may contain, but is not limited to:

- Current control strategy at site(s) of manufacturing, packaging and testing activities and that each location is currently authorized to deliver product(s) meeting relevant Good Manufacturing Practices (GMP) and Good Distribution Practices requirements and regulatory commitments.
- Overview of national medicines regulatory authorities which have inspected the specified locations and authorize the supply of the product(s) in scope provided by an independent authorized person/ responsible person/ qualified person.
- Control strategy for transport and distribution of goods to and in the country, in which the application is being made, which ensures the integrity of product quality throughout the supply chain.
- Checks made to consignments on arrival and mechanisms for assessing the impact of unexpected events (e.g. temperature incursions, if applicable) to deliver a conclusion that the integrity of shipment(s) has been maintained in the shipping channel and the quality attributes of product(s) have been maintained as confirmed in the Certificate(s) of Analysis (CoA) from the exporting manufacturing site.

Potential documentation to support the application may be, but is not limited to:

- Specifications for the final product (country specific example).
- CoA for product(s) reflecting registered limits (country specific example).
- GMP certificates for the sites of manufacture, testing, packaging and release; further certificates (e.g. WHO Certificate of Pharmaceutical Product – CPP), as applicable.
- Summary of shipping container/system qualification used or risk assessment to support shipping under non-controlled conditions.
- Quality checks performed on in-bound shipments.

A copy of the *Import Testing Waiver Application Template* can be accessed [online](#).

About IFPMA

IFPMA represents the research-based pharmaceutical companies and associations across the globe. The research-based pharmaceutical industry's 2 million employees research, develop and provide medicines and vaccines that improve the life of patients worldwide. Based in Geneva, IFPMA has official relations with the United Nations and contributes industry expertise to help the global health community find solutions that improve global health.

IFPMA manages global initiatives including: IFPMA [Developing World Health Partnerships](#) initiative studies and identifies trends for the research-based pharmaceutical industry's long-term partnership programs to improve health in developing countries and the IFPMA [Code of Practice](#) sets standards for ethical promotion of medicines.