Pharmaceuticals Policy and Law 18 (2016) 141–156
DOI 10.3233/PPL-160439
IOS Press

Import testing turned into an unnecessary limitation of patient access to medicines as risks are managed effectively

Stephan K. Rönninger[a] and Joerg H.O. Garbe[b,*]
[a]*External Affairs, International Quality, AMGEN (Europe) GmbH, Switzerland*
[b]*Global Quality Manager In-Country Testing, F. Hoffmann-La Roche Ltd., Basel, Switzerland*

The presented facts suggest that import testing does not protect patients. On the contrary, it introduces potential risks to access of medicines and reduces the remaining shelf life time of medicines driving possible drug shortage. In the absence of data proving the evidence that import testing is decreasing risk to patients, if manufacturers comply with the evolving Good Manufacturing Practices (GMPs) and Good Distribution Practices (GDPs) regulations, including secure supply chains with documented controls, import testing should be waived. In these cases, importing country's Health Authorities should be confident the product is safe, of high quality, and in compliance with registered specifications.

This article presents risk assessments demonstrating that product quality is continuously controlled. Moreover, import testing does not detect counterfeit or substandard products nor reduces the additional risks related to local distribution channels, as testing occurs at the point of entry into a country.

Keywords: Import testing, importation, testing, Good Manufacturing Practices (GMPs), Good Distribution Practices (GDPs), risk assessment

1. Introduction

This article reviews the developments in the regulatory environment since import testing was introduced in the European Union (EU) legal framework as well as other countries and postulates that such import testing introduces additional risks to patients.

Prior to being accessible to patients, pharmaceutical products undergo well defined procedures on registration according to regulatory requirements (Fig. 1). If the marketing authorization is granted, manufacturing and packaging is performed in accordance with regulations specific to GMPs. Finally the product is tested to assure it meets approved product specifications prior to its release to the market. The legal requirements for the release formally differ from country to country. However the market release decision is a holistic decision by an 'independent quality unit',

*Corresponding author: Stephan K. Rönninger, External Affairs, International Quality, AMGEN (Europe) GmbH, Dammstrasse 23, CH-6301 Zug, Switzerland. Tel.: +41 41 369 2521; Fax: +41 41 369 0200; E-mail: stephan.roenninger@amgen.com.

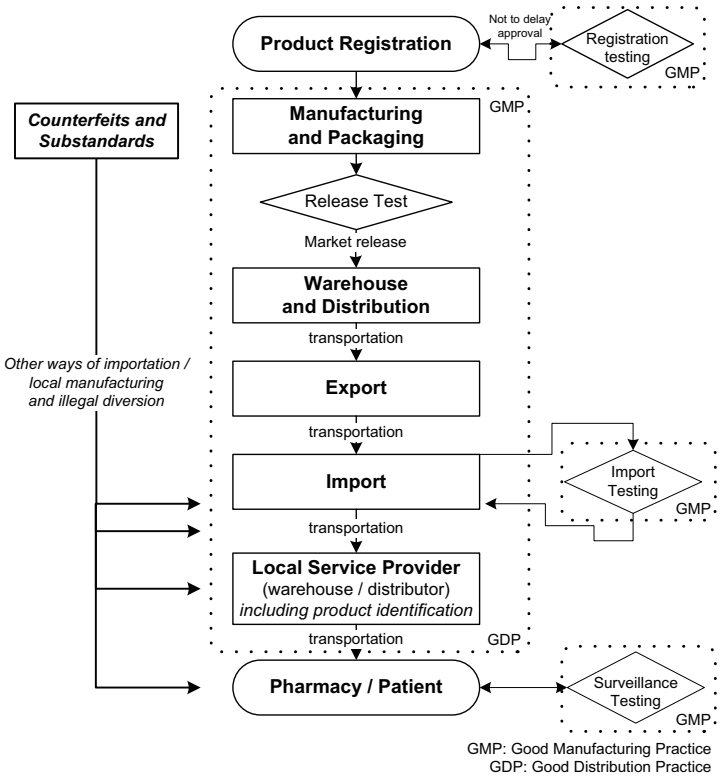

Fig. 1. Product flow and related testing activities.

which can be represented by an 'authorized person' (AP – World Health Organization (WHO) terminology)/ 'responsible person' (RP – Pharmaceutical Inspection Co-operation Scheme (PIC/S) terminology)/ 'qualified person' (QP – EU terminology). The decision to release considers all available information on the performance of the operation during a given cycle of manufacture for final disposition.

After the release, the product is stored in a warehouse, ready for distribution. Recent changes in legislation added additional supply chain oversight assuring appropriate storage and transport conditions to maintain product quality in accordance with GDPs requirements (e.g., in the EU [1]). In addition, repackaging/relabeling operations follow GMPs. During transport the product is exported from country A and imported into country B. A Local Service Provider (LSP) or a manufacturer's own local operation performs the product identification and quality check of the inbound shipment (e.g., based on monitoring data) and organizes the transport of the product to a hospital/pharmacy to be available for the patient (Fig. 1).

Throughout this very well controlled and regulated process for the legitimate supply chain, safe and efficacious medicines are delivered in a timely manner to patients.

A series of additional controls are required in several countries/markets before marketing (registration testing) and at the end of the supply chain (surveillance testing) to protect patients (Fig. 1).

In spite of full compliance with current regulations, good quality practices, all the procedures and controls mentioned above, an additional test is required in many countries: the repetition of the release testing upon importation – referred to as 'import testing' [2]. This article demonstrates, to the best of our knowledge, the lack of documented evidence that import testing reduces risk or uncovers any additional risks, which usually occur later in the supply chain (e.g., manufacturing steps performed in the country of destination) or identifies counterfeits and/or substandard products introduced by using different means of importation (e.g., parcel post).

2. History of import testing

In 1975, the EU introduced the requirement to repeat all tests, when a drug (medical) product is imported (see 75/319/EEC Article 22 [3]). It is recognized that import testing requirements may have been necessary in the 1970s as a result of the limited development of regulations, alertness and enforcement procedures in the supply chain of pharmaceutical products. Since then, many countries outside the EU have implemented, or are considering putting into place, import testing requirements.

The pharmaceutical industry is following contemporary and enforced GMPs and GDPs regulations published and maintained by, e.g., the EU [1] and the United States (US) [4] as well as WHO [5] and PIC/S [6]. Holistic controls are introduced into the supply chain, e.g., in the EU with the Falsified Medicines Directive [7]. Furthermore, industry develops and implements robust quality management systems describing all procedures and additional holistic controls [8]. These defined and controlled procedures contribute to assure supply chain integrity, safety, purity, and potency of drug products.

Today, increased regulatory supervision and enforcement of the manufacturers by frequent regulatory agency inspections [9] are in place. The AP/RP/QP in a quality unit with independent oversight, also makes the requirement of import testing in the middle of the supply chain irrelevant. The objective of ensuring product quality and patient safety at the end of the supply chain when delivered to the patient is not affected. Thus, import testing can be regarded as redundant and unnecessary step, a view shared in the position paper developed by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) [10].

More and more countries are now, however, requiring and/or enforcing import testing by implementing additional regulations. This trend does not correlate with the increasing understanding by National Regulatory Authorities (NRAs), of the need for globally harmonized requirements and procedures following best practices and

continued improvements based on experience. There is no data available demonstrating any real patient impact if the additional requirement of import testing is implemented. To understand this contradictory development, the research-based pharmaceutical industry gathered data on testing, requirements, efficacy of import testing and the associated business impact. This analysis includes obvious and hidden costs related to import testing [2].

3. Current legal situation

The requirements for importation testing are described in the legislation of the EU and other countries. Opportunities applied for waivers and implemented flexible approaches show the uncertainty of the need for an import testing requirement.

3.1. EU legislation

The Article 51 (1b) of the EU Directive 2001/83/EC [11] sets a requirement for import testing and states: "In the case of medicinal products coming from third countries irrespective of whether the product has been manufactured in the community, that each production batch has undergone in a member state a *full qualitative analysis*, quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of the medicinal products in accordance with the requirements of the marketing authorization (MA)." [11].

Article 51 (2) [11] allows exceptions to import testing by stating: "In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community, and to ensure that the controls referred to under point (b) of the first subparagraph 1 [see above] have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls" [11]. A respective "appropriate arrangement" is already established in the EU Directive 2011/62/EU [7]. Upon request, exporting countries are included in the list referred to in Article 111b, if the "country's regulatory framework applicable to active substances exported to the Union and the respective control and enforcement activities ensure a level of protection of public health equivalent to that of the Union".

Subsequently the EU-GMP directive 2003/94/EC [12] and related guidelines in EudraLex Volume 4 (EU-GMP) [1] further specify the expectation on implementation of import testing requirements according to article 51 (1b) [11].

3.2. Import testing requirements in other countries/regions

Markets other than the EU adhere to import testing requirements potentially without considering the progress industry and regulatory requirements have made by

implementing risk control measures and following international quality standards. Garbe et al. [2] describe 34 countries (the EU market is counted as one country) with import testing requirements, and the several types of waivers applied for following legal, regulatory, compliance and practical approaches.

3.3. Related registration testing requirements

In many countries, additional registration tests have to be performed prior to the Marketing Authorisation (MA). Registration testing is often used to establish product specific infrastructures, including test methods for import testing or for market surveillance studies (MSS) in governmental laboratories. In some countries, this testing can delay the approval process of new medicines up to 22 weeks [2]. Similar delays may re-occur in the case of assessing post-approval changes and when licenses/authorizations are renewed. Moreover, registration testing results in administrative bureaucracy with its respective financial impact.

3.4. Applied opportunities for flexible interpretation in regulatory statutes

Waivers from import testing may be possible even in countries where routine import testing is the rule. Allowing flexible interpretation within the legal environment could enable the regulatory statutes and guidelines to focus resources on patient protection. The EU-GMP Annex 16 [13] and the draft concept paper on a guideline on importation of medicinal products (potentially Annex 21) [14] are demonstrated examples of using the EU regulations to potentially support waivers by flexible interpretation.

Trade relationships between the EU and US increased for the benefit of both economies. Considerable changes are required in the EU to consider that the regulatory oversight is equivalent in other regulatory jurisdictions [15]. In the EU *"appropriate arrangements"* (e.g., Mutual Recognition Agreements – MRA) are operational and include the waiver of import testing for products imported from Australia, Canada, Israel, Japan, New Zealand and Switzerland [16].

4. Additional risks introduced by import testing

Today, risk-based approaches are required to control the quality of medicines. This risk assessment looks at the risks associated with import testing: *"Does import testing reduce the risk for patients receiving medicines?"*.

4.1. Challenges in meeting demands – A practical example

The start of the drug product manufacturing defines shelf life time, i.e., time period for which a drug can be stored or used, for a batch of the medicinal product.

Table 1
Examples of RSTs required by selected countries, e.g., used in tender orders

Remaining Shelf Life Time [RST]	Countries
75%	Bahrain, Kazakhstan, Kuwait, Oman, Russia, Saudi Arabia, Ukraine
70%	Iraq
66%	Algeria, Egypt, Iran, Jordan, Lebanon, Lydia, United Arab Emirates, Morocco, Qatar, Tunisia, South Africa (depending on products types)
50% or less	Bosnia & Herzegovina, Israel, Macedonia, Turkey
More than 6 months	China, EU (most countries)

Subsequently the primary manufacturing itself, release testing, batch release process and the secondary manufacturing has to be performed. The drug is ready for patient usage when, as an example, two months of the shelf life time has already passed. In order to prevent drug shortage situations, a manufacturer must build up considerable safety stock throughout the supply chain. Since the best practice in warehouse management utilizes a "first in – first out" principle, safety stock will have used up these four months from the shelf life time of the product (Fig. 2).

The health care systems in the countries where governments are responsible for ordering and importation of pharmaceuticals are acting more and more with 'tender orders' (e.g., in the Middle East/Africa region, by hospital pharmacies). These special orders are usually placed by a government to obtain a high volume of drugs by a specific date. Certain requirements apply and can be predefined by local laws. Generally, these requests are placed on an annual basis and require up to 75% Remaining Shelf Life Time (RST – Table 1).

Industry generally understands the reason for the RST requirements in tender orders. However, this practice has a huge impact on the supply chain management of products with a shelf life time of less than 36 months. Extra resources are allocated and principles/good practices (e.g., "first in – first out") are typically violated in order to meet these demands in the supply chain for delivery to patients.

4.2. Barriers to access due to stock in quarantine

On average, import testing takes about four weeks to complete [2]. As a consequence, blocked stock in the specific country reduces the RST as time elapses in quarantine. In some instances, this loss could be longer than the four weeks, if there is additional handling of goods (e.g., sampling). Experience shows that at least six weeks lead time must be added for manufacturing (secondary packaging), release testing by the manufacturer and forward shipping. This lead time can translate up to a delay of 10–12 weeks during which the finished product cannot be used. Additional delays occur, if secondary manufacturing is also performed in a third country requiring import testing, or even if such a country is used as a distribution hub for a region (Fig. 2).

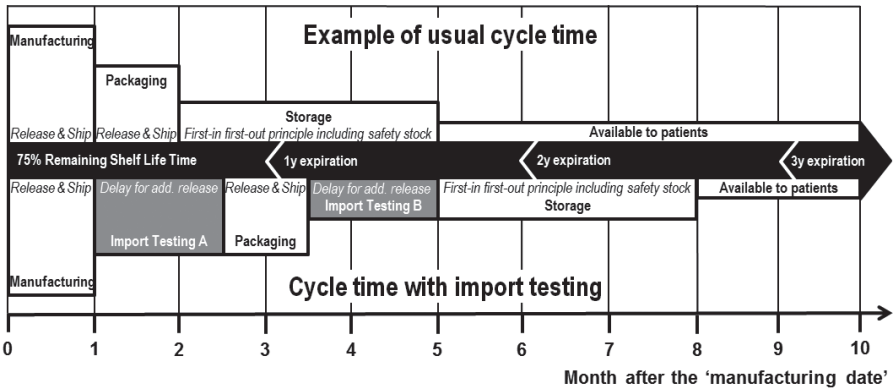

Fig. 2. Example of cycle time in the supply chain with and without import testing in relationship to the RST.

These circumstances are additional, but unnecessary, factors to be considered when evaluating risks of drug shortages [17]. Consequently, the root cause for drug shortages of more stock under quarantine can only be avoided by using time consuming planning, preventing unnecessary quarantined stock and by intensive communication with health authorities in affected countries. These block resources on industry and regulators side, which can be used better for controls which more efficient demonstrate patient safety.

4.3. Risk of drug shortage

By the very act of the import testing, drug products are blocked in quarantine and therefore are not readily available for delivery to patients in a timely manner. Furthermore already released drug product is consumed in the testing process. In addition to the testing itself, reserve and retention samples reduce the availability of the drug product to the legitimate supply chain. These samples can accumulate up to a loss of 1,020 packs per batch of medicinal product. This sample volume is calculated as follows: 1) it is assumed that a company serves all the 34 countries/regions requiring import testing [2] and two of these countries have a site for secondary manufacturing and/or are used as a hub for regional deliveries; 2) five packs are used per import test; and 3) an additional ten reserve/retention samples are required, e.g., for repeated testing in the scope of investigations. In some cases even considerably more sample packs are required, especially for inhaled products. If an individual shipment contains drug product from multiple batches, the amount of testing and samples is increased.

The value chain of a commodity needed as starting material for an Active Pharmaceutical Ingredient (API) and/or the final drug product may take up to two years. If the demand increases, it can take that long until additional drug products can be

delivered in the supply chain to patients. As a consequence, additional resources have to be spent by regulators and industry to develop and agree on exceptions (e.g., allowing supply of registered products from other markets, parallel trade).

4.4. Missed chances in ecological risk management

Any ecological benefits are lost as repeated testing requires resources such as reagent, equipment, and power. The environmental impact is negatively increased by the use of electrical power, water, and disposable plastics as well as toxic/radioactive materials. Most of these materials cannot be recycled and additional waste is created.

4.5. Economic risk management for a better protection of patients

In a competitive environment, economic benefits are of importance to companies, and an import testing waiver could decrease overall manufacturing costs. The resources spend for import testing today could be re-absorbed, bring more efficiency to the supply chain and regulatory processes and better used to control and combat the illegitimate supply chain (e.g., detection of counterfeits and substandard products), for example, by extending Market Surveillance Studies (MSS) using identification tests to better protect patients in the local market.

To estimate the financial expenditures used to comply with import testing, a survey was conducted by the European Federation of Pharmaceutical Industry and Associations (EFPIA) in 2015. As an example, imports from the US to the EU were assessed along with the number of batches subjected to retesting in one year. 15 multinational EFPIA member companies (i.e., Almirall, Amgen, BMS, Chiesi, GSK, J&J, Les Laboratoires Servier, Merck-Serono, MSD, Novartis, NoviPharma, Novo Nordisk, Pfizer, Roche, UCB) responded. In addition, the survey covered the cost for analytics as well as administrative and overhead costs associated with import testing (also refer to [2]). Ten companies reported 8,495 affected batches with five companies not importing any batches on the EU-US route.

The following calculations for the estimated financial expenditures are based on the reported average direct costs of €2,950 per imported batch [2]. These costs include resources for the analytical testing of every imported product.

In general, the resources for maintaining an import testing program can be broken down as follows (approximate figures):

- 65% Direct costs spent for the analysis and technical personnel (see [2])
- 25% Costs for additional administration (e.g., Quality Management System owners/managers, sample management, record and document management, IT/Laboratory Information Management Systems (LIMS) maintenance)
- 10% Overhead costs for people management, training and audits/inspection management

The second and third bullets above (25% and 10%) represent additional costs, which were not considered in the survey [2]. For the total cost assumption, further costs are detailed as companies have to provide additional support for the import testing when contract or government laboratories are used (e.g., the Official Medicinal Control Laboratories – OMCL – network organized by the European Directorate of Medicines – EDQM). These additional resources can include, for example, on-going activities and consumable items such as:

- Analytical method transfer and method validation (including implementation of changes in pharmacopoeias)
- Reference standards (including preparation, certification and supply)
- Reagents (including qualification prior to use)
- Test equipment (e.g., high performance liquid chromatography columns) including calibration/maintenance
- Training of testing staff (agency and/or contractor)
- Additional in-country stability testing, as required
- Shipping costs of samples
- Managing the importation of all required materials according to specific country requirements
- Need for additional material in the supply chain for a specific country to compensate shortened Remaining Shelf life Time (RST)
- Materials on the market with a low level of RST and potential need for replenishment
- Laboratory infrastructure

What if these additional costs are also taken into account? On average, the costs estimated for the above activities is around €1,100 per re-test (full analysis) and has to be added to the reported [2] direct average cost of €2,950.

What if the costs of blocked capital are included? Nine companies reported the loss of €37,672,259, representing 18,616 analyses, due to the prolonged quarantine (e.g., quarantined in warehouses, at customs, etc.) of medicinal products. These figures may be used to estimate blocked capital of an additional €2,024 per batch analysis, even though no direct correlation has been made. The impact of all of these costs per analysis, i.e., direct cost of €2,950, plus indirect and hidden costs of €1,100, plus the losses due to blocked capital of €2,024, accumulates to €6,038 overall cost per analysis.

Overall, considering the analysis of the 8,495 batches reported, this represents resources equivalent to €50,970,000. This significant sum is what these 10 companies reportedly spent on import testing in one year. This estimate covers only the import testing from US into the EU. These companies represent about 31% of the market value of the research-based pharmaceutical industry [18]. Assuming the relative trade is constant among pharmaceutical businesses and these companies are a representative portion of the overall market, the estimated total costs for import testing aggregates to €164,419,355. Considering this amount represents the cost of import testing for products imported from the US into the EU only, the global spending for import testing is assumed to be inestimably higher.

4.6. Further risks in the supply chain

To some extent sampling and storage may occur in the legitimate supply chain where GMP and GDP may not be applied to all aspects on the supply chain (e.g., under quarantine in customs/bonded warehouses). As a consequence, a less stringent chain of custody may increase the risk for test samples to not be representative, lost or diverted. In addition security/tamper-evident seals of the products may need to be broken. As a consequence, replacement of seals is not traceable and a risk for contamination is presented. Furthermore, interim storage in warehouses may increase the risk for temperature deviations [2]. However, the consistent oversight of the manufacturers ensures the detection of any transport deviation, if occurred. If not covered by stability data, a deviation will result in a rejection of the material, even very late in the supply chain.

4.7. Outcome of the risk assessment

The assessment of the hazards associated with import testing demonstrates that routine import testing is not an appropriate control to be considered in the light of global supply chains and implementation of best practices (e.g., GMP and GDP).

5. Risk controls implemented to facilitate waivers for import testing

Modern pharmaceutical manufacturers are implementing risk reduction measures as part of their continuous improvement programs [19]. They established comprehensive oversight mechanisms for compliance and patient safety along their supply chain. Emerging requirements such as GDPs are also more and more enforced on distributors, traders, and local service providers.

5.1. Compliance risk management in manufacturing and supply

Manufacturing and distribution occur in a highly regulated environment. There are hazards addressed by NRAs and others, when waiving of import testing is considered, such as:

- Failure to detect issues with the original product quality
- Inadequate release testing
- Failure to detect deterioration on transportation
- Loss of public confidence in imported medicines
- Failure to detect counterfeit finished products
- Potential for disreputable suppliers to provide substandard product
- Loss of economic value in a country/region through the provision of employment

NRAs might try to address risks supposedly coming from these hazards by additional rigid regulations and increasing oversight with additional testing and/or inspections including certification audits. However for these companies complying with the procedures described in a quality management system [19] the remaining risks are considered to be 'very low' for all of the provided hazards as presented in Table 2.

5.2. Controls of patient safety risk

Scientific evaluations [2] demonstrate that patient safety is not enhanced by import testing because of the well-established and effective quality management systems employed by industry in the manufacture and supply of medicines. There is no evidence that import testing has any added value to further control imports. In fact, this is supported by analyzing the rejection rate in import testing analyses. This rejection rate was identified to be 0.005% (one rejected batch out of 18,616 tested batches) [2]. It is concluded, that the probability of detecting residual product non-conformance by import testing is very low.

5.3. Additional effective risk controls are established

As a result of the survey, assessments of hazards and implemented controls, it is concluded, that import testing – provided manufacturers comply with good practices (GMPs/GDPs) – does not provide additional control of risks to patients and is therefore considered redundant.

5.4. Potential for refocus of import testing resources

Import testing has a very limited scope and does not reflect the existing situation of the products available to patients in a country or region. Uncertainty about the quality of the domestic distribution system can exist until the product reaches patients. This uncertainty can be better controlled when authorities focus on implementing or extending Market Surveillance Studies (MSS) [20–22]. MSS can be considered the best use of resources for a company, if performed, e.g., for products subjected to a high risk for counterfeits and substandard products. The MSS testing approach represents the unique opportunity to detect quality issues of products on the market. In addition, MSS can detect counterfeits and substandard products before the medicines are delivered to patients, and it does not cause any delays in access of medicines to patients like import testing does. Those countries that carry out MSS testing already have the benefit of still being able to assess product on the market rather than promoting more countries adopting this approach. Import testing, in contrast, considers only lots in the legitimate, established supply chain.

Table 2
Risk assessment and control grid to support the elimination of import testing requirements

Risk assessment		Risk control	
Hazard	Anticipated risk	Implemented and functioning risk reduction measures	Residual risk[3]
Loss of public confidence in imported medicines because of the perception that a control step has been removed.	High	Limited effect because the general public is largely unaware of the current control strategies in the supply chain.	Very low
Due to counterfeiting issues this may be perceived as a necessary "barrier" by politicians.	High	Appropriate identification testing is implemented upon receiving at the point of importation or at the warehouse.	Very low
Failure to detect counterfeit finished products, e.g., EU, MRA country are safe countries (with IP laws in place) others may be non-safe countries.	High	Typically a counterfeiter would not introduce product for import testing. Most examples show counterfeit product infiltrates the supply chain during local distribution. These risks might be better tackled through GDP enforcement and serialization and/or surveillance testing. However, the distribution chain via parcel post orders in small portions and/or internet orders provides additional risks. Theses supply chains are anyway not subjected to import testing.	Very low
Concern that removal of the retesting activity would mean loss of economic value in a country/ region through the provision of employment.	High	This would have an impact but on a very limited number of jobs in any country. An increase of surveillance testing would be more patient focused and even create jobs.	Very low
Potential for disreputable suppliers to provide substandard product as they know it will not be retested.	High	This should be controlled by the Quality Management System (QMS), GDP and due diligence processes done for all customer supplier relationships.	Very low
Issues with the original product quality that may not be found.	Medium	Low failure rate for import testing so expected limited impact providing a strong QMS release testing procedures and oversight on all stages of manufacturing processes is in place. Quality has to be produced into the product, not tested at the end only.	Very low
Failure to detect deterioration on transportation.	Medium	Implemented GDP practices such as temperature monitoring, stability programmers, validated distribution and shipping routes, choice of appropriate packaging components incl. seals/tamper evidence etc. are more effective mechanisms to ensure quality than retesting a small non	Very low

Table 2, continued

Risk assessment		Risk control	
Hazard	Anticipated risk	Implemented and functioning risk reduction measures	Residual risk[3]
		representative sample of a batch.	
An increased number of testing sites would need to be inspected by the authorities – resource risk.	Medium	Inspectorate resources are known to be limited and this could lead to delays in granting import licenses, if an inspection is mandatory for the license. Gaining trust (e.g., via PIC/S) among inspectorates facilitates recognition/reliance opportunities. Reasonable waivers of import testing requirements are implemented and could be better used, as applicable.	Very low
The elimination of import testing proposal is rejected but awareness has extended oversight to other areas, e.g., stability, API testing.	Medium	Control processes are based on scientific rationales. Import testing is considered as not adding benefit.	Very low
More emphasis would be placed on regulatory inspections and there may be a concern that a frequency of every two years is insufficient to provide adequate control.	Low	The oversight of the export site is covered by legislation (e.g., EU QP). Consequently the regulatory inspections and the firm's QMS and internal audits should be sufficient to provide assurance. Furthermore these processes are getting more focused and risk based.	Low

[3]With regards to patent safety when waiving import testing.

6. Conclusions and outlook

The presented risk assessments demonstrate that it is highly questionable, wether any risk to patients is reduced by import testing. Quite the reverse, import testing increases the risks to patients by facilitating e.g.:

- Increasing the Drug Shortage risk
- Stock in quarantine
- Reducing RST
- Supply chain complexity
- Pressure on ecological effectiveness
- Misuse of resources and economic losses

The pharmaceutical industry is committed to support all requirements that contribute to reducing or eliminating risks to patients. Waivers of import testing will improve product availability and reduce lead times. A waiver of import testing is secured by manufacturers implementing GMPs/GDPs and therefore enabling uninterrupted supply of products. Keeping the requirements on import testing, which are performed in the middle of the supply chain, can decrease product availability, prolong lead times, and therefore contributes to put the uninterrupted supply of products to patients at risk. An infographic was published to visualize the topic in a simplified manner [23].

6.1. Further opportunities using the existing regulatory framework

Comprehensive oversight of manufacturing and supply is well-established. Besides performing manufacturing and release testing, industry provides additional information to regulators in the dossiers, which get approved by the competent authorities for a country or region. Inspection oversight preferably by domestic inspectorates, controls the compliance with GMP and GDP requirements.

Giving the variety of waivers implemented [2] and the results of the assessments discussed in this article, it should be considered to allow the following, for example:

- **Automatic waiver, if the product is manufactured in a recognized country**
  A list of countries is established to waive the import testing requirement based on their legal framework, controls of manufacturing and distribution as well as enforcement policies. In the EU, this approach would be similar to the equivalence of regulatory oversight for the 'written procedure' upon importation of APIs [16].
- **Waiving of import testing when shipment validation is performed**
  Shipment validations are confirming oversight of the distribution chains. The initial transport validation would cover the needs to demonstrate that the supply chain is fit for purpose and to guarantee the quality has not changed during transportation.
- **Advance specification settings for import testing**
  The release specification as part of the regulatory commitments could be separated into quality attributes: a) confirming the success of the manufacturing process; and b) confirming the identity of the product (finger print). Only the product identity in b) is tested upon importation and/or surveillance testing (reduced specification). This would be proposed and justified by the applicant in the release specification sections of the Q-CTD 3.2.P.5.1 and 3.2.P.5.6.
  In the EU such separation is already accepted under the conditions of parametric release [24]. Article 51 (1b) of the EU Directive 2001/83/EC [11], as well as Chapter 1.5.4 of the recent EU-GMP Guideline [1] Annex 16, provide a base for reduced specification, stating that a product batch must undergo testing in a Member State "*in accordance with the requirements of the marketing authorisation (MA)*". In addition, Annex 16 (scope section) states: "*The basic arrangements for batch release for a product are defined by its MA. Nothing in this Annex should be taken as overriding those arrangements"*. Hence, if a reduced specification is approved with the MA, reduced import testing is acceptable. Equally, it would be an appropriate utilization of the directive 2001/83/EC Art. 51(2) [11] to waive import testing requirements if "appropriate arrangements" are established and "equivalent" GMPs standards are applicable to the country of origin.
- **Testing upon registration, post-approval changes and license renewals, if required, is not delaying access of new medicines**
  Without import testing the knowledge can be transferred independent for the registration process to support opportunities, e.g., for MSSs.

6.2. Final note

Today, no strong rationale exists to support import testing assuming that pharmaceutical manufacturers follow international good practice standards and have implemented controls of the products and production processes throughout the entire supply chain. Waiving or removing such redundant import testing would significantly reduce product lead times, blocked inventories and the risk of drug shortages, especially on a country level. Accordingly, an uninterrupted supply of important medicines to the patients could be further ensured. Remaining risks related to import testing would be decreased as the robust GDPs would not be interrupted. Resources could be spent in activities such as improved information exchange between regulatory agencies, further reliable inspection schemes by NRAs and, if considered necessary, market surveillance testing. Moreover, continual improvement of supply chain processes can be more efficient. In addition, simplified regulatory procedures will lead to a better control of the local market.

Acknowledgements

The authors thank the Import Testing teams at IFPMA, under the leadership of Maria G. Jacobs (Pfizer), with Karl Ennis (GSK) and Guido M. Furer (AbbVie); and at EFPIA, previously active under the leadership of John Kerridge (Lilly). Thanks for discussions are expressed to Andreas Pfenninger (Interpharma), Zena Kaufman, Genevieve Lovitt-Wood as well as Amgen colleagues Douglas Gregory, Dan Latham-Timmons, Gillan Fitzpatrick, Paul Seligman, Karen White, and Martin Van Trieste.

References

All hyperlinks were accessed on April 2016.

[1] European Commission, EudraLex Vol.4 (EU-GMP), various guidelines for industry and regulators, http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm.

[2] J. Garbe, K. Ennis, G. Furer, M. Jacobs and S. Rönninger, Import Testing of Pharmaceutical Products Has Limited Safety Benefits and Can Add Risk to Patients, *Pharm. Tech. Europe.* **27**(8) (2015), s6–s20, http://images2.advanstar.com/PixelMags/pharma-tech-eu/digitaledition/08-2015-sp. html#6 and *Pharm. Tech. NA* **39**(18), s18–s26 http://images2.advanstar.com/PixelMags/pharma-tech-na/digitaledition/09-2015-sp.html#18.

[3] European Commission, Approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products, *EU Council Directive*, 75/319/EEC, 20 May 1975.

[4] US Food and Drug Administration (FDA), Legal requirements: a) US-regulation CFR title 21, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm and related guidance documents www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[5] Quality Assurance, World Health Organization (WHO), see documents listed at www.who.int/medicines/areas/quality_safety/quality_assurance.

[6] Pharmaceutical Inspection Cooperation Scheme (PIC/S), Publications, https://picscheme.org/en/publications.
[7] European Commission, Prevention of the entry into the legal supply chain of falsified medicinal products, EC of the European Parliament and of the council directive, 2011/62/EU, 8 June 2011; amending Directive 2001/83/EC on the Community code relating to Medicinal products for human use.
[8] International Conference on Harmonisation, Pharmaceutical Quality Systems, *ICH Q10*, 05 June 2008.
[9] International Conference on Harmonisation, Quality Risk Management, *ICH Q9*, 09 November 2005.
[10] European Federation of Pharmaceutical Industry and Association (EFPIA), Annual inspection survey, please contact EFPIA, www.efpia.eu.
[11] Appropriate Control Strategies Eliminate the Need for Redundant Testing of Pharmaceutical Products, *International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Position Paper*, 29. February 2016, www.ifpma.org/wp-content/uploads/2016/04/IFPMA-Position-Paper-on-Redundant-Testing.pdf. See also Strengthening Regulatory Systems: Import testing, *IFPMA Homepage*, www.ifpma.org/subtopics/import-testing, and [23].
[11] European Commission, Community code relating to medicinal products for human use, EC of the European Parliament and of the council, directive 2001/83/EC, 6 November 2001.
[12] European Commission, Community code relating to medicinal products for human use, EC of the European Parliament and of the council, *directive 2001/83/EC*, 06 November 2001.
[13] European Commission, Principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use, *directive 2003/94/EC*, 08 October 2003.
[14] European Commission, Certification by a Qualified Person and Batch Release, *EUDRALEX Vol. 4 (EU-GMPs), Annex 16*, Ref. Ares (2015) 4234460–12/10/2015, 12. October 2015, 1–12.
[15] European Commission, Importers of medicinal products, *EUDRALEX Vol. 4 (EU-GMPs)*, Concept Paper Annex 21, EMA/238299/2015, 13. May 2015, 1–4.
[16] European Commission, Quality of medicines and Good Manufacturing Practices (GMP), see applied waivers for the 'written procedure' at 'Status of current and past applications', http://ec.europa.eu/health/human-use/quality/index_en.htm.
[17] European Commission, *Mutual Recognition Agreements (MRAs) and Conformity Assessment Bodies (CABs) with Australia, Canada, Japan, New Zealand, the USA, and Switzerland*, see: http://ec.europa.eu/growth/single-market/goods/international-aspects/mutual-recognition-agreements/index_en.htm.
[18] E. Ramnarine, M. Jornitz, M.A. Long, K. O'Donnell, S. Rönninger, C. Smalley and A. Vinther, Risk based approach for prevention and management of drug shortages, *PDA Technical Report* **68** (2014), 1–45.
[19] Based on IMS Health Market data. Assessed and provided by Interpharma, Basel www.imshealth.com/portal/site/imshealth.
[20] EDQM, Official Medicinal Control Laboratories (OMCL), The advantages and benefits of the CAP surveillance project, general documents, *PA/PH/CAP (13) 32 2R*, November 2013, www.edqm.eu/medias/fichiers/the_advantages_and_benefits_of_the_cap_surveillance_project_paphcap_13_32_2r.pdf.
[21] Guidelines on the conduct of survey of the quality of medicines, World Health Organization (WHO), Working document QAS/15.630, draft, June 2015.
[22] U. Paulsen-Sörman, R. Wanko and J-M. Spieser, Market Surveillance of Centrally-authorised Products, *Regulatory Affairs Journals* **11** (2000), 409–13.
[23] J. Garbe and S. Rönninger, The Value of Import Testing versus Surveillance Testing, Infographic, *PDA Letter* **LI**(8), 34. www.ifpma.org/resource-centre/the-value-of-import-testing-vs-surveillance-testing.
[24] European Commission, Parametric Release, *EUDRALEX Vol. 4 (EU-GMPs) Annex 17*, ENTR/6270/00, July 2001, 1–5.