The Pandemic situation has created challenges and opportunities in the inspection landscape. The aim of the inspection is to make the case of assuring the overall state of control. Opportunities for risk-based inspection planning follow a simple qualitative tool provided by PIC/S. Reliance on inspection results is possible based on understanding of the principles to protect patients to waive import testing. Risk-based approaches seem to gain broader acceptance for waiving foreign inspections by LA countries. The value is to serve patients but inspections and in-country testing can negatively impact on-time access.
‘RELIANCE’ ON INSPECTIONS - A REAL OPPORTUNITY (?)

Perceived Problem
- Restrictions of the pandemic

Issues to be resolved
- Patients have continued access to medicines
- Regulatory boundaries appear to be inflexible

Background to the proposal

Work to be done
- Make use of alternative inspection tools

The overall state of control is maintained

THE PANDEMIC SITUATION HAS CHALLENGES AND OPPORTUNITIES IN THE INSPECTION LANDSCAPE

Regulatory oversight was maintained supporting public health
- Virtual approaches helped as an enabler and have a role
- But companies report delay of approval by postponing Pre-Approval-Inspections, when applicable

Gain efficiency in the use of different tools
- Hybrid inspection (virtual & on-site) – locally / joint inspections
- Standardise the package of documents to streamline efforts

Increasing use of reliance will be beneficial
- Enabled by waivers, mutual recognition by agencies and using various tools
- Experience demonstrated feasibility and value in decision making

The overall state of control is maintained
RISK-BASED APPROACHES SEEM TO GAIN BROADER ACCEPTANCE FOR WAIVING FOREIGN INSPECTIONS BY LA COUNTRIES

<table>
<thead>
<tr>
<th>Year</th>
<th>Mexico/COPESRIS</th>
<th>Brazil**</th>
<th>USA*</th>
<th>Singapore*</th>
<th>Austria*</th>
<th>France*</th>
<th>Germany*</th>
<th>Switzerland*</th>
<th>Belgium*</th>
<th>Chile</th>
<th>China</th>
<th>Canada</th>
<th>Italy*</th>
<th>Norway*</th>
<th>Peru/DIGEMID</th>
<th>Colombia/INVIMA</th>
<th>Argentina/ANMAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Inspections of a firm’s manufacturing operation are essential to evaluate

- Capability of commercial manufacturing,
- Adequacy of production and control procedures,
- Suitability of equipment and facilities, and
- Effectiveness of the quality management system

Combining to ensure the overall state of control.

Notably, pre-approval inspections include the added evaluation of authenticity of submitted data and link to dossier

ICH Q-IWG training, October 2011
AIM OF ANY INSPECTION IS TO MAKE THE CASE OF ASSURING THE OVERALL STATE OF CONTROL

Agencies are using different inspection tools

- Sometimes in combination
- They are not equivalent - each tool has advantages and disadvantages

OCCURRENCE FOR RISK-BASED INSPECTION PLANNING TO FOLLOW A SIMPLE QUALITATIVE TOOL

Elements
- Knowledge of the GMP-compliance history of the site
- Footprint of history of critical and major deficiencies
- Type of inspection i.e., routine, for cause, pre-approval

Hazard to consider
- Intrinsic risk
- Complexity of site, Processes and Products, Criticality to availability
- Compliance-related risk
- GMP/GDP / CMC, regulatory status (incl. e.g., number of deficiencies)

Output
- Risk ranking ('Quality metrics')
- Inspection frequency
- Required number of inspectors and competence / expertise
- Scope, focus, depth & duration of the next routine inspection

Fulfill the legal requirement for ‘Inspections’
THE VALUE IS TO SERVE PATIENTS BUT INSPECTIONS AND IN-COUNTRY TESTING CAN NEGATIVELY IMPACT ON-TIME ACCESS

Process for registration of drugs

Product Dossier → Approval Process → Authorisation

Verify usually 1-12+ months

Manufacturing Capability & GMP → Registration and Import Testing

‘The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk’

Quality Risk Management Principle (ICH Q9, 2005)

QUALITY IS MAINTAINED IN THE LEGITIMATE SUPPLY CHAIN BY MAKING USE OF ESTABLISHED CONTROLS NOWADAYS

Achievements in managing risk since the 1970s

Registration
- Common Technical Document (CTD)
- Stability studies (ICH Q1/Q5C; WHO, Climatic zone III&IV)

GMP
- Independent product release
- QMS for managing distribution
- Inspections & audits

GDP
- Import / Export controls
- Transport validation
- Quality check by the recipient

Consider waiving import testing (see back up material incl. IFPMA Position)

Mandatory import testing
- Reduces remaining shelf-life time
- Misuse of resources
- Negative environmental footprint
- Economic losses

Patients are waiting 4-133 days per import
RELIANCE IS POSSIBLE BASED ON UNDERSTANDING OF THE PRINCIPLES TO PROTECT PATIENTS

- Regulatory process are quite different between countries
  - Assessment
  - Inspections
  - Testing regimes
- They follow similar principles*
  - Quality Systems for inspectorates
  - Handling rapid alerts and recalls arising from quality defects
  - GMP-Inspection reliance
  - Risk-based inspection planning
  - Notification of foreign inspections
  - Team inspections
  - Classification of GMP Deficiencies
  - Inspection report format

* Best practices for inspectorates provided by PIC/S www.picscheme.org

PANDEMIC SHOWCASES DEMONSTRATE OPPORTUNITIES TOWARDS AN IDEAL STATE OF RELIANCE

* For inspections performed in a 3rd country, no legal barriers assumed

PATIENTS RECEIVE THE SAME MEDICINE WHEREVER THEY ARE

It is time for reliance

Acknowledgement
• Joerg Garbe, Roche

FOR FURTHER READING
♦ References
THE WORLD HEALTH ORGANIZATION NOW RECOMMENDS THE KEY CONCEPTS OF RELIANCE GLOSSARY

- **Recognition**
  - Acceptance of the regulatory decision of another regulator or trusted institution
  - Recognition should be based on evidence that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority
  - Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement

- **Reliance**
  - The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision
  - The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others

**ADDITIONAL REFERENCES ON INSPECTIONS**

- **Guidance for regulators incl. inspectors**
  - PIC/S, A recommended model for risk-based inspection planning in the GMP environment, Guideline PI 037-1, 01. Jan 2012
  - PIC/S, GMP Inspection reliance, Guideline No PI 048-1, 01. June 2010
  - PIC/S, Classification of GMP Deficiencies, Guideline No PI 040-1, 01. January 2010

- **Scientific Papers**

- **Industry Position Papers**
## FOR FURTHER READING

♦ Inspection process

### INSPECTIONS BY A LOCAL INSPECTORATE CAN BE MORE EFFICIENT AND MATURE THAN AN INSPECTION FROM A 3RD COUNTRY

<table>
<thead>
<tr>
<th>Prerequisite</th>
<th>Advantage</th>
<th>Transparency</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High quality standards embraced and supported by the local government&lt;br&gt;• Evaluation of national regulatory systems by an independent control / maturity metrics e.g., PIC/S member inspectorates, WHO Global Benchmarking Tool</td>
<td>The local inspectorate has&lt;br&gt;• Flexibility regarding coming back and following up on issues&lt;br&gt;• Knowledge on the site specific history&lt;br&gt;• Insight on culture i.e., do/don’ts in the local area&lt;br&gt;• Optimisation of resources&lt;br&gt;• Benefit from improved inspection logistics e.g., no language barrier, less travel / environmental friendly</td>
<td>• A non-compliant local site may put the integrity of the local inspectorate at risk&lt;br&gt;• Direct access for feedback on CAPAs&lt;br&gt;• Inspectorates may not like to see their local manufacturing sites in the headlines</td>
</tr>
</tbody>
</table>
COLLABORATION, RELIANCE, DELEGATION ARE POTENTIAL STRATEGIES TOWARDS THE FUTURE

Plan inspections based on risk

Consider
- Basics: compliance history, product criticality, etc.
- Coordination of inspections among agencies
- Expired GMP certificates may impact regulatory procedures
- Flexibility by using alternative tools including virtual inspection (also for PAIs) instead of postponing
- Coordination of certification audits by different notified bodies (note: privacy agreements)
- Support by a tool to coordinate inspections worldwide (e.g., by PIC/S)

Evolve the traditional on-site approach

Adopt
- A hybrid approach with a focused on-site presence
- A clear, defined and followed timetable
- Using surveillance inspection to build in PAI elements, as applicable
- Allowing reliance on domestic inspections for license renewals or use virtual tool especially in 3rd countries

Build reliance

Leverage
- Complete inspection history
- Reliance on domestic inspections especially if performed by PIC/S members
- Regional certificates (e.g. EAEU)
- MRAs: implement and extend

FOR FURTHER READING

♦ Import Testing
IN THE 1970s IMPORT TESTING WAS INTRODUCED IN THE EU AND OTHER COUNTRIES TO CONTROL HAZARDS

• Historically, re-testing requirements may have been necessary
  (EU directive 75/319/EEC Article 22, 1975)
  – Mistrust of having quality products imported
  – Limited development of regulations and enforcement procedures - outside the EU

• Arguments made to control hazards; for example:
  – Issues with the original product quality that may not have been found
  – The release testing was not performed adequately
  – Potential for disreputable suppliers to provide substandard product
  – Loss of economic value in a country/region through the provision of employment
  – Failure to detect deterioration on transportation
  – Loss of public confidence in imported medicines
  – Failure to detect counterfeit finished products

IN A REGULATED ENVIRONMENT TODAY THE REQUIREMENT FOR IMPORT TESTING IS REGARDED AS BEING REDUNDANT

Additional regulations introduced additional controls; for example:

1. Development: Quality is built in
   – Filing and approval of manufacturing process including release specification

2. Manufacturing: According to current good manufacturing practices (GMPs)
   – Quality management systems (QMSs) are in place
   – Supplier management including quality agreements, audits and domestic inspections
   – Validated process and analytical methods

3. Supply Chain: Quality is controlled and maintained
   – Shipping is under good distribution practices (GDPs) - including validation, qualification, monitoring, stability studies
   – Additional requirements, controls and enforcement (e.g. EU Falsified Medicines Directive, inspections)

4. Safe and efficacious product for the patient
   – Uninterrupted control through the whole supply chain
REALITY WITH IMPORT TESTING TODAY WHILE QUALITY IS MAINTAINED IN THE LEGITIMATE SUPPLY CHAIN

- Delay in delivery to patients
  - Bounded stock in quarantine
- Delay in registration and license renewals
  - Testing is often established during product registration to later support import or surveillance testing
- Managing a variety of waivers
  - Legal, regulatory, compliance and technical approaches implemented
  - Not allowing, refusal of, and/or time it takes to obtain a waiver
- Increasing the drug shortage risk
  - Blocked stock reduces the remaining shelf-life time (RST)
- Misuse of resources
  - Redundant tests occur along the global supply chain in an isolated manner
  - Import testing does not reveal any additional risks to quality: 0.005% batch rejection rate*  
  - Economic losses
  - Environmental aspects of testing and waste creation

*IFPMA survey: 1 out of 18'616 analysis; may be explainable by transport monitoring data

PROGRESS IN DISCUSSIONS REGARDING WAIVING OF REGISTRATION AND IMPORT TESTING

- Refocusing in the area of registration and import testing
  - Discussed in Argentina, Chile and Paraguay
  - COFEPRIS in Mexico are about updating process and guidelines (NOMs). However waving of Import testing for biological products if the manufacturing, packaging and tests sites only if are certified by COFEPRIS
- Reliance on reference countries in the Central America region (CAC)
  - Costa Rica implemented a waiver from first batch testing for biological products approved in a SRA country in 2020 - Circular MS-DRPIS-009-05-2020
  - Guatemala grants waivers from first batch testing for products approved by a WLA ML4 as of 2018 - Acuerdo Gubernativo No. 104-201, 12 June 2018
  - Panama implemented a waiver from registration testing for biological products approved in a SRA country in 2017 - Gobierno De La República De Panamá (2017): Abbreviated procedure to register products approved by Health Authorities with high standards. Resolution No. 58.
- Major markets stopped routine import testing
  - EU when importing from countries were Mutual Recognition Agreements (MRA) are established with e.g., Japan, Australia, Israel, Switzerland and US
  - ASEAN member economies have established and MRA when in the inspectorate in countries
  - China replaced routine import testing for chemical products by post-marketing surveillance testing in 2018. The change was justified by a very low rejection rate (0.16%) confirming that the established controls are efficient - NMPA Announcement on matters related to customs clearance and import testing of imported chemical drugs, 2018.
IMPORT TESTING: FOR FURTHER READING

- IFPMA Position Papers
  http://www.ifpma.org/subtopics/import-testing/

- J. Garbe, S. Rönninger
  The Value of Import Testing versus Surveillance Testing,
  Infographic, PDA letter, September, 2015, 34.
  http://journals.sagepub.com/doi/10.1177/2168479017701980

- J. Garbe, K. Ennis, G. Furer, M. Jacobs, S. Rönninger
  Import Testing of Pharmaceutical Products Has Limited Safety Benefits and Can Add Risk to Patients,
  Pharm. Tech. Europe, September, 2015, s6-s20 including knowledge base: Import testing requirements by country

- S. Rönninger, J. Garbe,
  Import testing turned into an unnecessary limitation of patient access to medicines as risks are managed effectively,
  Pharmaceuticals Policy and Law, 18, 2016, 141-156

- J. Garbe, M. Jacobs, S. Rönninger,
  Import Testing: An Outdated Practice? Opportunities for Improved Access to Safe and Efficient Medicines,
  Therapeutic Innovation and Regulatory Science 2017, 1-5.
  http://journals.sagepub.com/doi/10.1177/2168479017701980

Import Testing
https://www.ifpma.org/subtopics/import-testing/