‘RELIANCE’ ON INSPECTIONS: NOT JUST A BUZZWORD BUT A REAL OPPORTUNITY

CMC STRATEGY FORUM LATIN AMERICA
12 AUGUST 2021

DR.-ING. STEPHAN RÖNNINGER
DIRECTOR QUALITY EXTERNAL AFFAIRS
AMGEN (EUROPE) GMBH

1

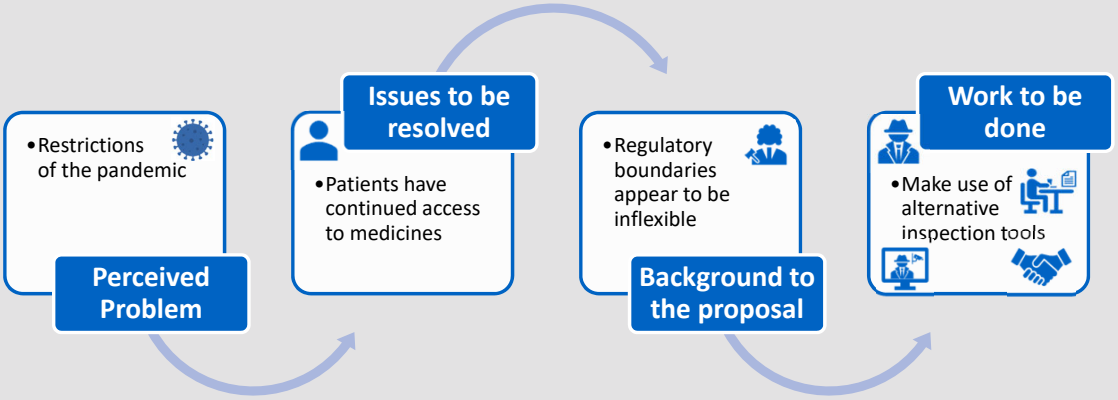
ABSTRACT

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.

2

2

‘RELIANCE’ ON INSPECTIONS - A REAL OPPORTUNITY (?)



3

AMGEN

3

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

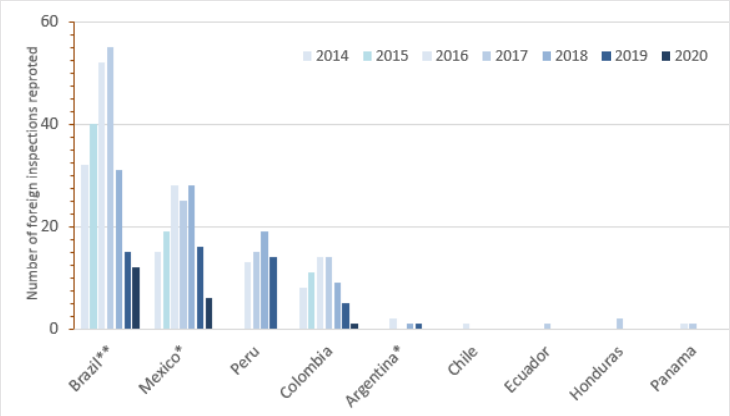
Increasing use of reliance will be beneficial
- Enabled by waivers, mutual recognition by agencies and using various tools
- Experience demonstrated feasibility and value in decision making

The overall state of control is maintained

AMGEN

4

RISK-BASED APPROACHES SEEM TO GAIN BROADER ACCEPTANCE FOR WAIVING FOREIGN INSPECTIONS BY LA COUNTRIES



Reported LA countries which performed foreign inspections

Mexico / COFEPRIS	**16**
Brazil**	5
USA*	4
Singapore*	3
Austria*	1
France*	1
Germany*	1
Switzerland*	1
Brazil / ANVISA	**15**
USA*	7
Japan*	2
Belgium*	1
Chile	1
Germany*	1
Italy*	1
Norway*	1
Singapore*	1
Peru / DIGEMID	**14**
Slovenia*	4
Brazil**	3
USA*	2
Austria*	1
Chile	1
Mexico*	1
Romania*	1
Turkey*	1
Colombia / INVIMA	**5**
Mexico*	2
Brazil**	1
Chinese Taipei*	1
USA*	1
Argentina / ANMAT	**1**
Ireland*	1

efpia Annual Inspection Survey 2020, May 2021
data bases: 25 multinational companies; 7 local manufacturers
https://www.efpia.eu/media/602634/efpia-2020-reg-inspection-survey_v1a.pdf

* PIC/S member inspectorate
** PIC/S accession inspectorate

5

efpia Annual Inspection Survey 2019, May 2020
data bases: 26 multinational companies; 10 local manufacturers
https://www.efpia.eu/media/547447/efpia-2019-reg-inspection-survey-v1-public.pdf

AMGEN

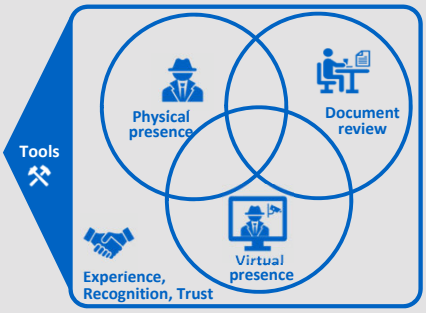
5

AIM OF THE INSPECTION IS TO MAKE THE CASE OF ASSURING THE OVERALL STATE OF CONTROL

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

- **C**apability of commercial manufacturing,
- **A**dequacy of production and control procedures,
- **S**uitability of equipment and facilities, and
- **E**ffectiveness 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

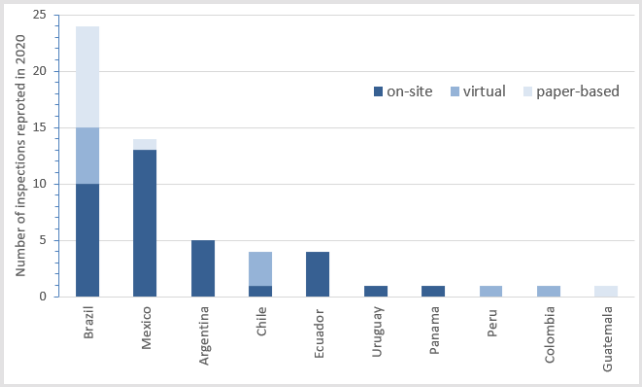
6

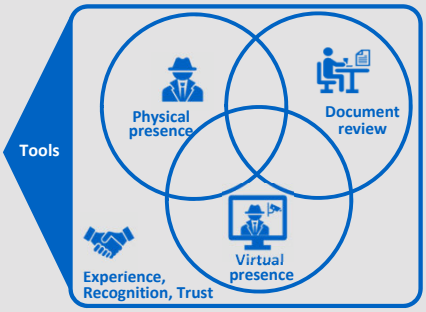
AMGEN

6

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

efpia Annual Inspection Survey 2020, May 2021
data bases: 25 multinational companies; 7 local manufacturers
https://www.efpia.eu/media/602634/efpia-2020-reg-inspection-survey_v1a.pdf

7

AMGEN

7

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

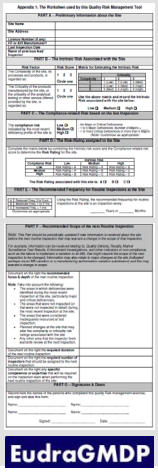
Elements
- Knowledge of the GMP compliance history of the site
- Footprint of history of critical and major deficiencies
- Type of inspection i.e., routine, for cause, pre-approval

Hazards 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

Experience, Recognition Trust

Fulfill the legal requirement for 'Inspections'



EudraGMDP

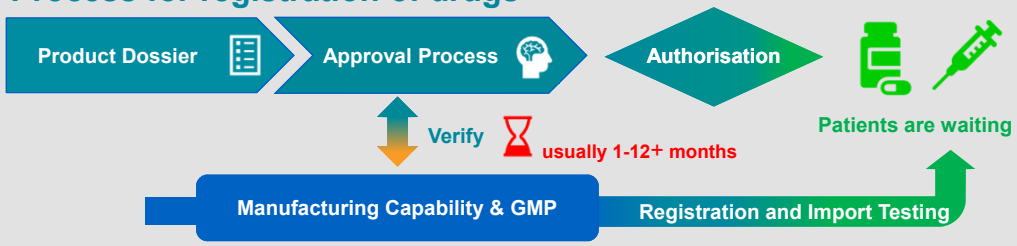
PIC/S **RISK-BASED INSPECTION PLANNING**, PIC/S GUIDELINE PI 037-1, 1 JANUARY 2012

AMGEN

8

THE VALUE IS TO SERVE PATIENTS BUT INSPECTIONS AND IN-COUNTRY TESTING CAN NEGATIVELY IMPACT ON-TIME ACCESS

Process for registration of drugs



'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)

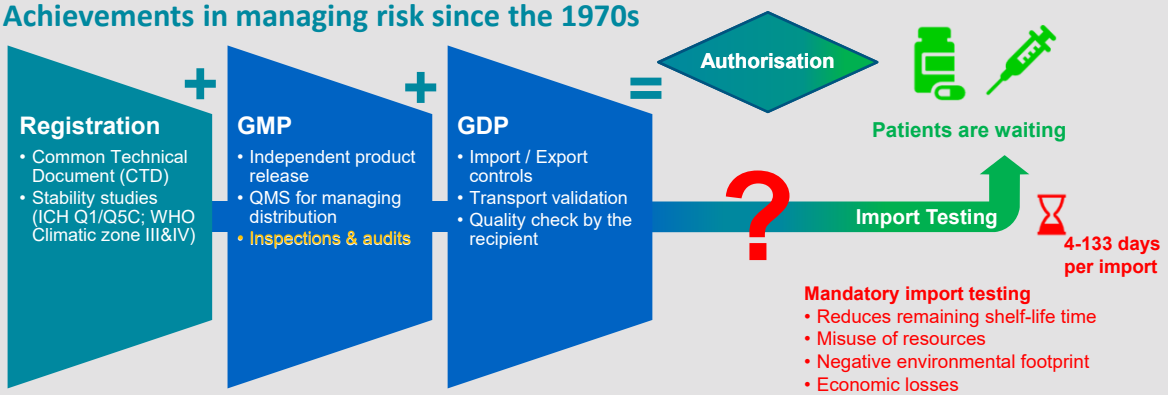
9

AMGEN

9

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

Achievements in managing risk since the 1970s



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

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

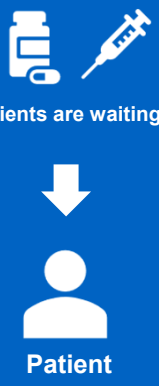
10

AMGEN

10

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**
  - **Handing 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**



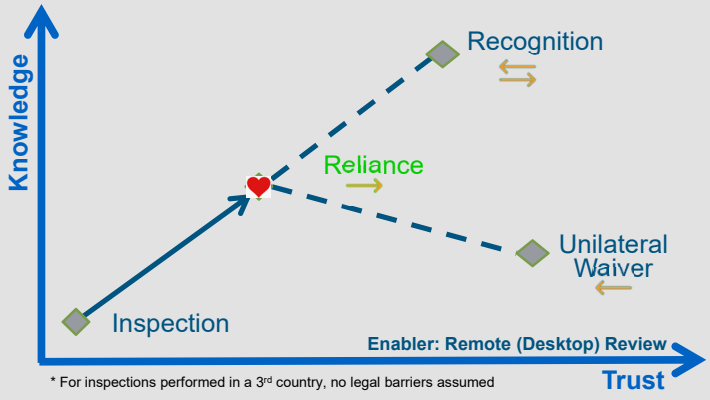
* **Best practices for inspectorates provided by PIC/S www.picscheme.org**
Good reliance practices in the regulation of medical products: high level principles and considerations, WHO, *TRS 1033, Annex 10,* **2021,** 237-267.

11

AMGEN

11

PANDEMIC SHOWCASES DEMONSTRATE OPPORTUNITIES TOWARDS AN IDEAL STATE OF RELIANCE



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

Good reliance practices in the regulation of medical products: high level principles and considerations, WHO, *TRS 1033, Annex 10,* **2021,** 237-267.

- **Risk-based inspection planning,** PIC/S guideline PI 037-1, 1 January 2012
- **GMP-Inspection reliance,** PIC/S guideline PI 048-1, 1 June 2018
- **Classification of GMP Deficiencies,** PIC/S guideline PI 040-1, 1 January 2019

Convergence of GMP standards and Related Inspections, IFPMA Position paper, January 2020
S. Rönninger, P. Gough, V. Davoust, **Opportunities for Saving Resources in the Regulatory Inspection Process: Mutual Recognition Agreements (MRA) Example EU/US,** *Pharm. Tech. Japan*, 35, **2019,** 15-25..

12

PATIENTS RECEIVE THE SAME MEDICINE WHEREVER THEY ARE

It is time for reliance

Acknowledgement
- **Joerg Garbe, Roche**

*Picture by Lale Ayanoglu Seher, Amgen

AMGEN

13

FOR FURTHER READING

- **References**

AMGEN

14

THE WORLD HEALTH ORGANIZATION NOW RECOMMENDS THE KEY CONCEPTS OF RELIANCE *GLOSSARY*

- **Recognition** must
  - 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** may
  - 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

Good reliance practices in the regulation of medical products: high level principles and considerations, WHO, *TSR 1033, Annex 10,* **2021**, 237-267 – chapter 4: glossary

15

AMGEN

15

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 2018**
  - **PIC/S, Classification of GMP Deficiencies, *Guideline No PI 040-1*, 01. January 2019**
  - **WHO, Good regulatory practices in the regulation of medical products, WHO Technical Report Series, *1033, Annex 10,* 2021, 237-267.**
- **Scientific Papers**
  - **S. Rönninger, P. Gough, V. Davoust, Opportunities for Saving Resources in the Regulatory Inspection Process: Mutual Recognition Agreements (MRA) Example EU/US, *Pharm. Tech. Japan*, 35, 2019, 15-25.**
  - A. Meshkovskij, S. Rönninger, **National GMP Inspection Practice for Biotech Pharmaceuticals: Commonalities, Differences, Opportunities,** CIS GMP News, **2018**, *1,* 26-31. https://gmpnews.net/magazine/gmpnews-eng-2-1-2018/#page/26
  - H. Jin, N. Carr, H. Rothenfluh, TGA, **Medicines Regulations: Regulating Medicines manufacturers: Is an onsite inspection the only option?**, *WHO Drug Information*, 31/2, **2017**, 153-157. https://www.who.int/medicines/publications/druginformation/issues/WHO_DI_31-2_RegMedManufs.pdf
  - EMA, WHO, TGA, US-FDA, EDQM, Council or Europe, ANSM, DMA, HPRA AIFA, MHRA, **Report on the International Active Pharmaceutical Ingredient Inspection Programme 2011 – 2016, March 2018,** 1-13.
  - S. Rönninger, J. Berberich, V. Davoust, P. Kitz, A. Pfenninger**, Landscape of GMP/GDP inspections in research-based pharmaceutical industry, Part I: Data,** *Pharm. Tech. Europe*, **January, 2017,** 6-10.http://www.pharmtech.com/gmpgdp-inspection-landscape-part-i-data ; **Part II: Considerations and Opportunities,** *Pharm. Tech. Europe*, **February, 2017,** 5-9. http://www.pharmtech.com/gmpgdp-inspections-landscape-part-ii-considerations-and-opportunities
  - A. Meshkovskij, S. Rönninger**, GMP Inspection practice: a case for global benchmarking, convergence and mutual reliance/recognition,** *The GMP News*, ***2017,*** 2-9 (Rus).
  - EFPIA Annual Inspection Survey, results 2018 https://www.efpia.eu/media/361849/_efpia-2018-reg-inspection-survey_public-summary.pdf
- **Industry Position Papers**
  - **EFPIA: Annual Regulatory GMP/GDP Inspection Survey's** https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/regulatory-affairs/
  - **EFPIA: Enhanced Good Manufacturing and Good Distribution Practices (GMP/GDP) Inspection Efficiency, 19. May 2014.**
  - **EFPIA / PhRMA: A Concept for Harmonized Reporting of Inspections, 29. May 2015;** ***addendum of the PhRMA White Paper: 'Mutual Recognition of Drug GMP Inspections by U.S. & European Regulators'*****, 15. May 2015.** http://www.efpia.eu/uploads/EFPIA_Position_Paper_A_Concept_for_Harmonized_Reporting_of_Inspections_final.pdf
  - **IFPMA: Convergence of Good Manufacturing Practice (GMP) standards and Related Inspections, IFPMA Position paper, June 2017; update January 2020.** https://www.ifpma.org/wp-content/uploads/2017/06/IFPMA-Position-on-GMP-Convergence-Final-_9June2017.pdf
  - **IFPMA Infographic:** https://www.ifpma.org/wp-content/uploads/2018/02/GMP_IFPMA_02-20-2018-WEB.pdf
  - IFPMA: **Points to consider for virtual inspections, 2021** https://www.ifpma.org/tag/gmpgdp-inspection/

16

AMGEN

16

FOR FURTHER READING

♦ Inspection process

AMGEN

17

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

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

PIC/S **GMP-INSPECTION RELIANCE**, PIC/S GUIDELINE PI 048-1, 01 JUNE 20, CHAPTER 5.2 – as basis

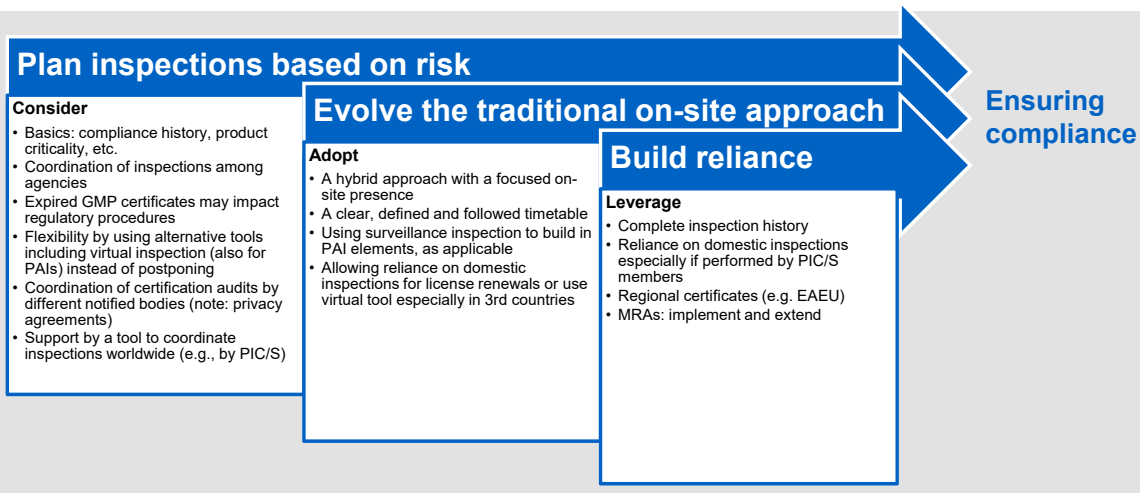
♦ Inspection process

18

AMGEN

18

COLLABORATION, RELIANCE, DELEGATION ARE POTENTIAL STRATEGIES TOWARDS THE FUTURE



♦ Inspection process

19

AMGEN

19

FOR FURTHER READING

♦ Import Testing

AMGEN

20

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

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

21

AMGEN

21

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

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

22

AMGEN

22

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

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

23

AMGEN

23

PROGRESS IN DISCUSSIONS REGRADING 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-909-05-2020 "Empresas-Fabricantes-Importadoras y Distribuidoras de Medicamentos, 25 May 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
  - Honduras introduced waivers from registration testing dependent on the product approval by a reference authority (WLA ML4 and South Korea) in 2018 - Comunicado C-003-ARSA-2018, 22 March 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.
  - Russia completely replaced routine import testing by risk-based post-marketing surveillance testing in 2019 - Russian Federation: Federal Law N 449-FZ "On Amendments to Certain Legislative Acts of the Russian Federation on the entry into civil circulation of medicines for medical use, 28 November 2018.

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

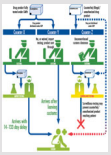
24

AMGEN

24

IMPORT TESTING: FOR FURTHER READING

- **IFPMA Position Papers**
  Appropriate Control Strategies Eliminate the Need for Redundant Testing of Pharmaceutical Products, Feb. 2016
  http://www.ifpma.org/wp-content/uploads/2016/02/IFPMA-Position-Paper-on-Redundant-Testing-vF.pdf
  Best Practices for In-Country Testing and Sample Management, Oct 2020.
  www.ifpma.org/resource-centre/position-paper-best-practices-for-in-country-testing-and-sample-management
- **J. Garbe, S. Rönninger**
  The Value of Import Testing versus Surveillance Testing,
  Infographic, PDA letter, September, 2015, 34.
  http://www.ifpma.org/resource-centre/the-value-of-import-testing-vs-surveillance-testing/
- **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**
  http://images2.advanstar.com/PixelMags/pharma-tech-eu/digitaledition/08-2015-sp.html#12
- **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
  http://www.ifpma.org/wp-content/uploads/2016/11/13.-Import-Testing.pdf
- **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/

25

AMGEN

25