MINISTRY OF INDUSTRY AND TRADE OF RUSSIA

GMP VIII ALL-RUSSIA GMP CONFERENCE

50 years GXP SID& GP

Typical nonconformities identified during the GMP Inspection Classification of nonconformities DIGEMID's experience

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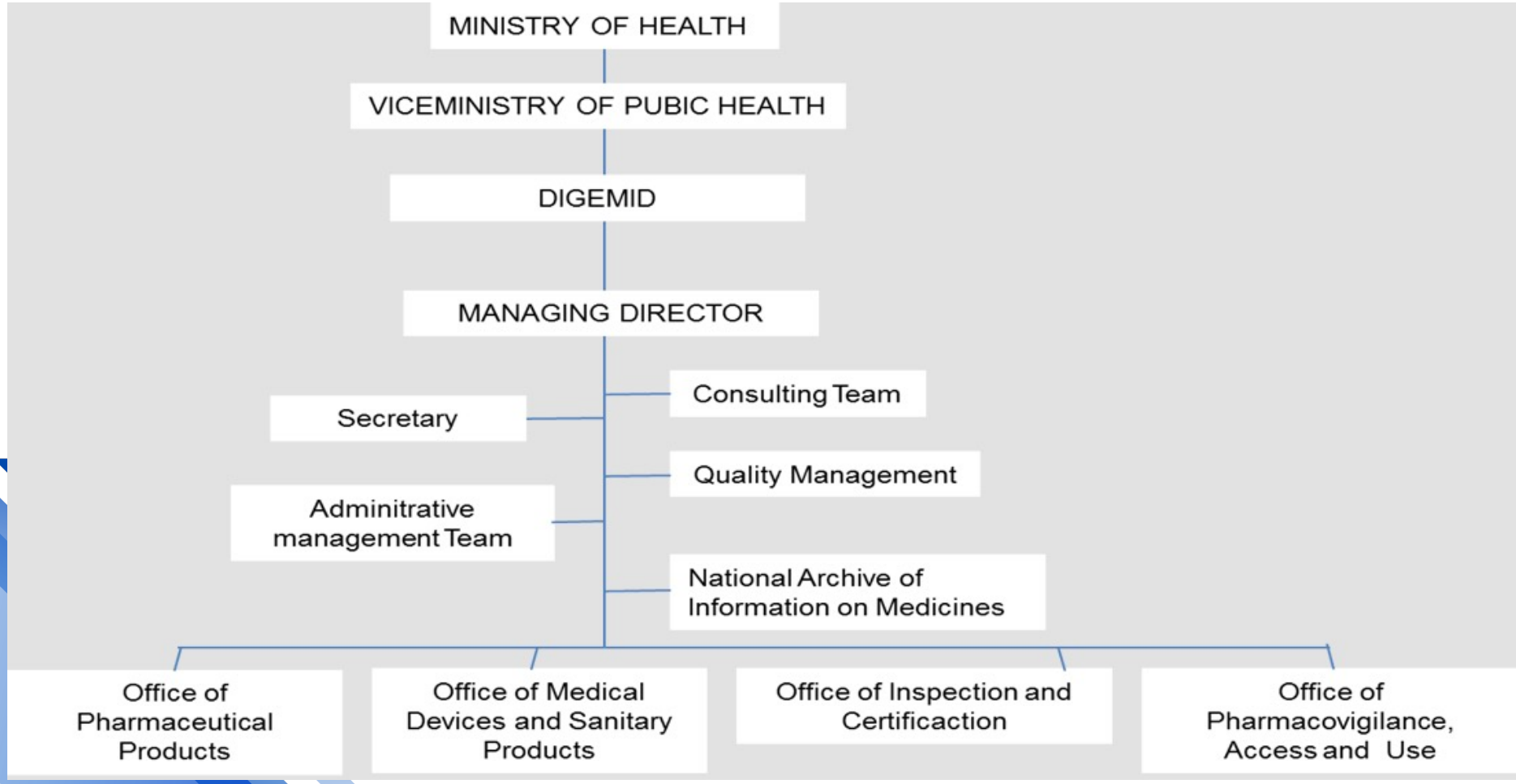
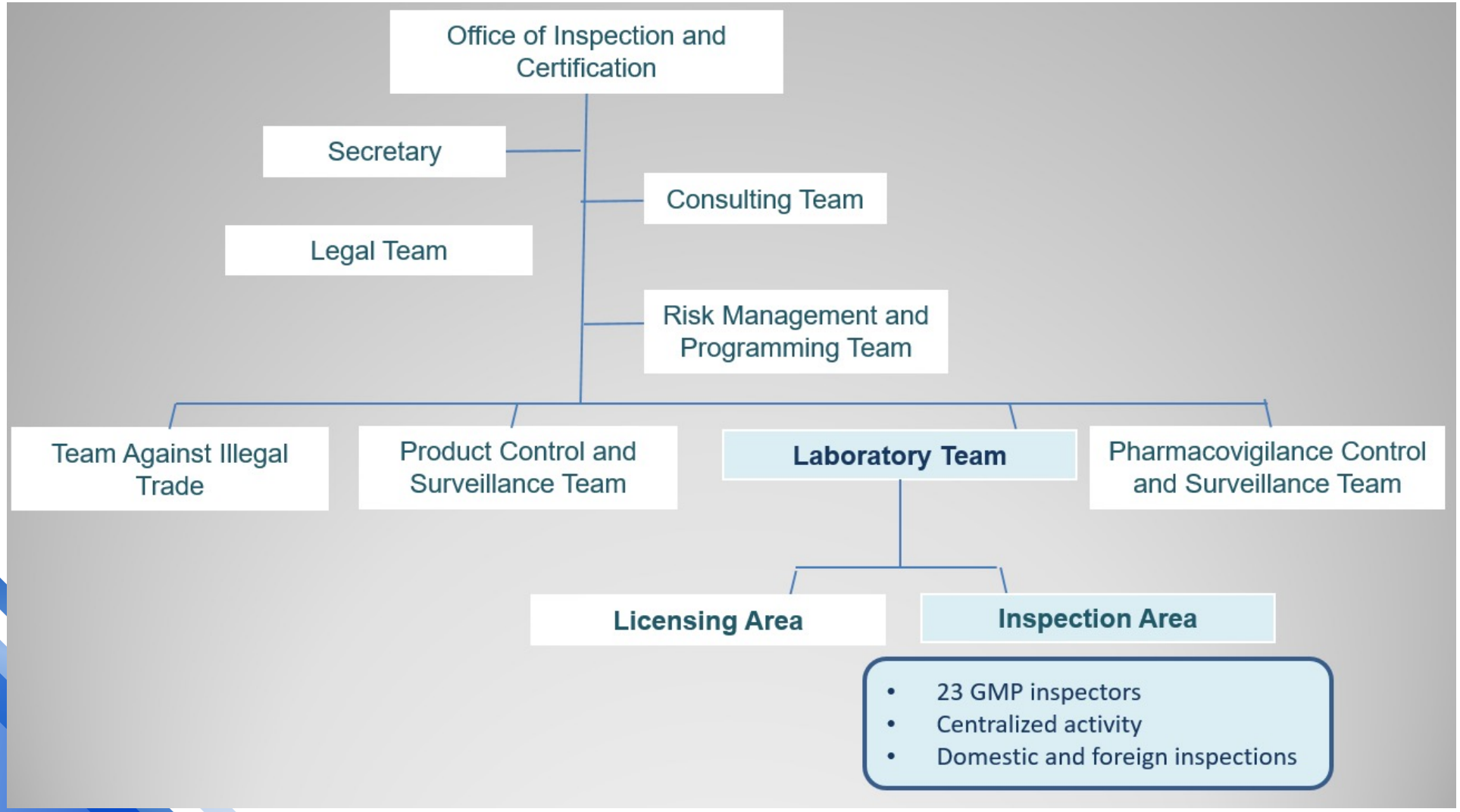
Agency: General Office of Medicines, Supplies and Drugs (DIGEMID) - Organization Chart



Organization Chart - II



Evolution of the regulatory framework and medicine policy in Peru

1990

The General Office of Medicines, Supplies and Drugs (DIGEMID) is a line body of the Ministry of Health, created with Legislative Decree No. 584 of April 18, 1990.

1997 1998

The General Health Law No. 26842-1997 is approved in 1997, which simplifies the approval of marketing authorization.

The first National List of Essential Medicines was approved in August 1998.

2005

The first "Directive for the Certification of Compliance with Good Manufacturing Practices" was approved in 2005 - National

GMP compliance verification inspections began at national manufacturing laboratories

2009

The Law of Pharmaceutical Products, Medical devices and Sanitary products N° 29459, was published in November 2009

This law gives DIGEMID authority to inspect manufacturing plants not only national but also foreign.

2010

Administrative Directive for the Certification of Good Manufacturing Practices in National and Foreign Laboratories was approved.

Importers began to apply for GMP certification

2011

The "Regulation of Pharmaceutical Establishments" was approved by Supreme Decree No. 014-2011-SA.

The "Regulations for the marketing authorization of pharmaceutical products" was approved by Supreme Decree No. 016-2011-SA.

The first GMP inspection abroad was carried out

Peruvian GMP regulatory framework

1992

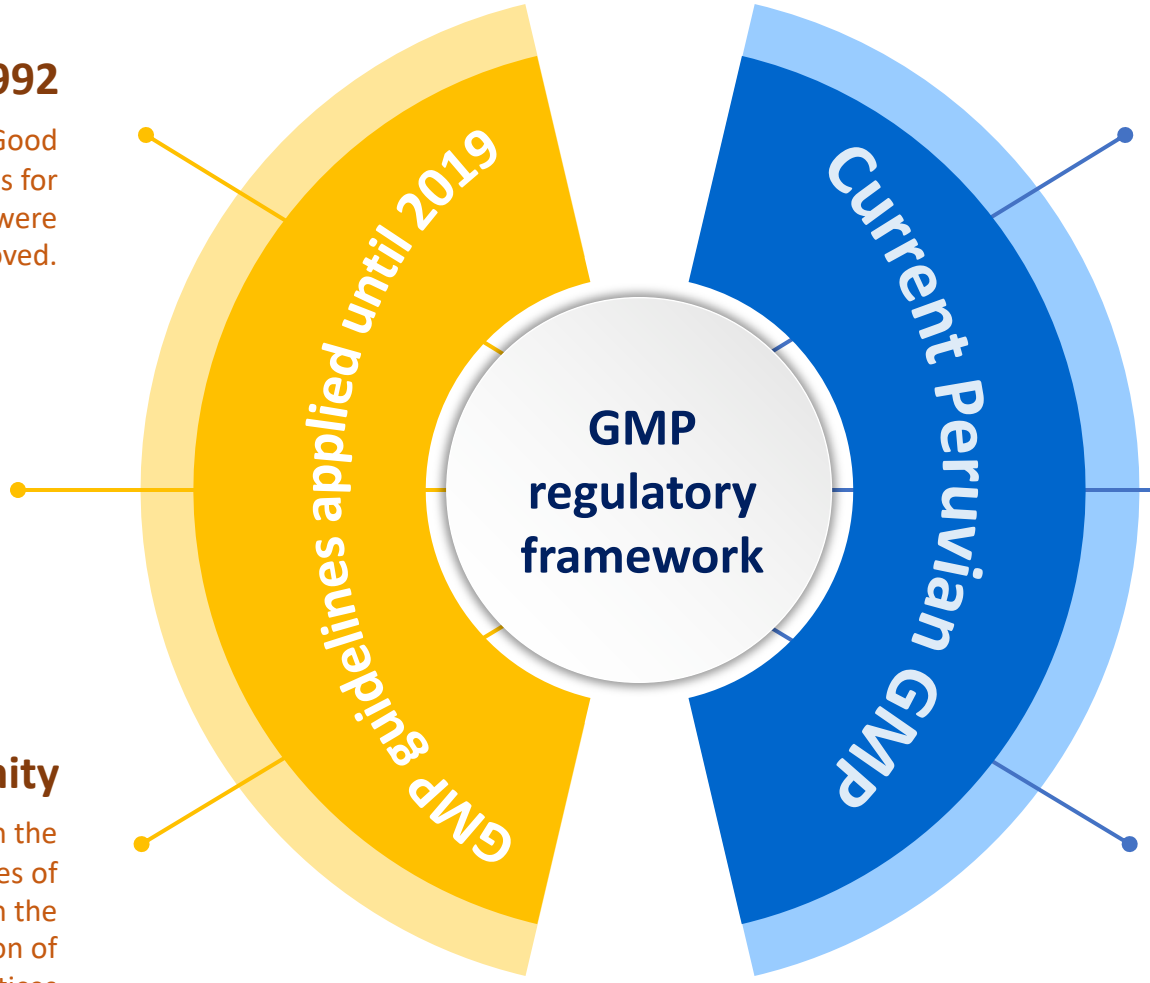
The Guidelines for Good Manufacturing Practices for Pharmaceutical Products were approved.

Reference

WHO Technical Report Series 823 – Thirty second Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations

CAN –Andean community

In compliance with the commitments with the countries of the Andean Group within the framework of harmonization of Good Manufacturing Practices



2018

The Guidelines for Good Manufacturing Practices for Pharmaceutical Products were updated and improved.

Reference

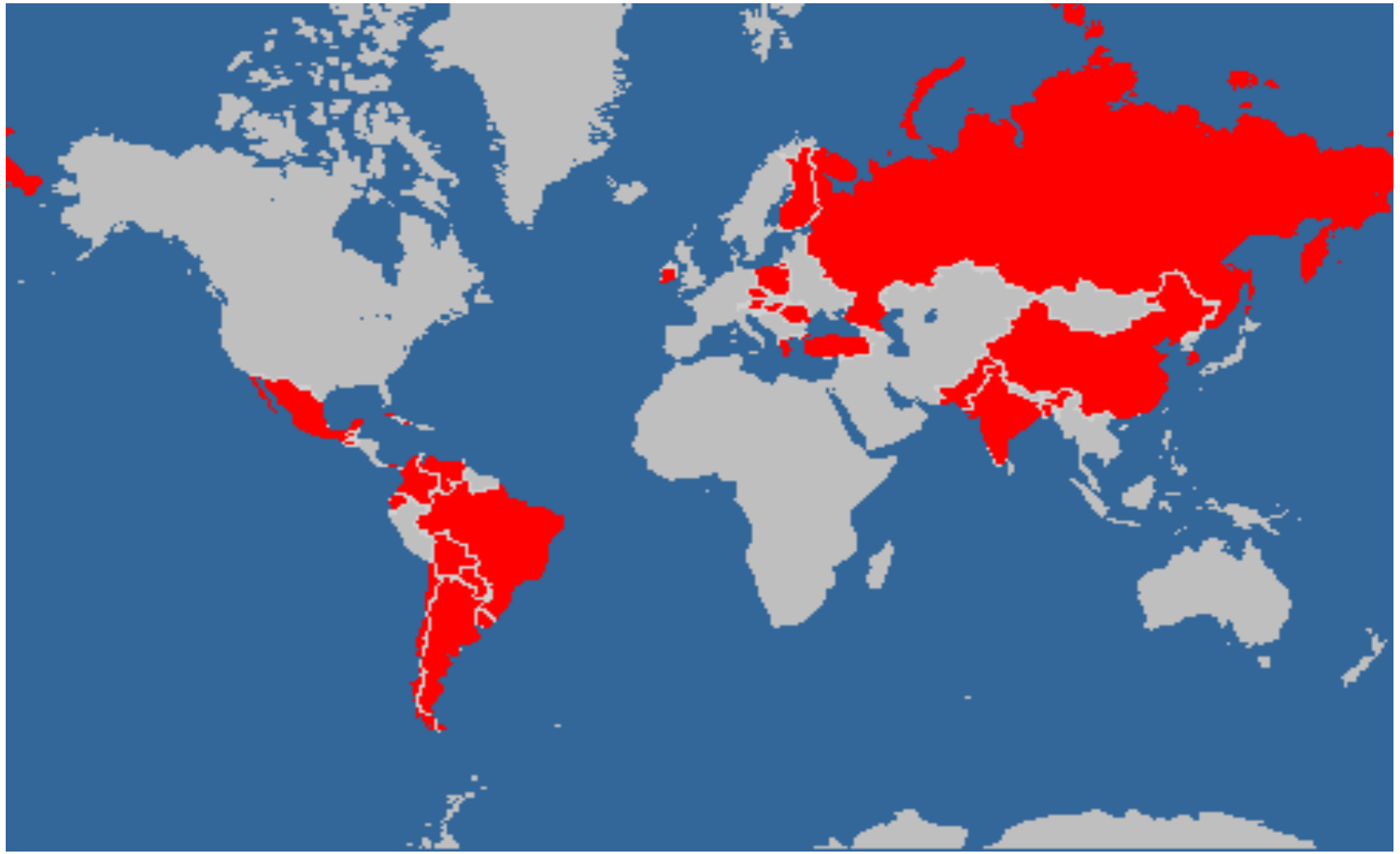
WHO Technical Report Series 957 – 44th Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations

WHO Technical Report Series 961 – Forty-fifth Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations

Inclusions

The current guidelines establish for the first time requirements for specific categories, such as segregated or highly dangerous products, radiopharmaceuticals, medicinal gases, investigational products and biological products….

GMP compliance inspections of foreign manufacturers



358
Inspections worldwide

35
Countries inspected

Number of GMP compliance inspections of foreign manufacturers

358
inspections worldwide

America

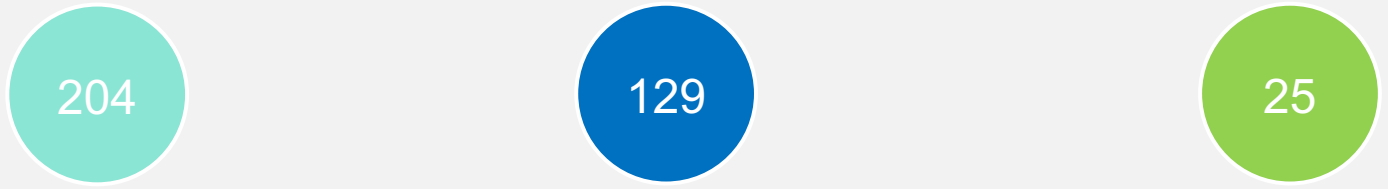
Argentina, Bolivia, Brazil, Chili, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Guatemala, Mexico, Panama, Paraguay, Puerto Rico, Dominican Republic, Uruguay and Venezuela.

Asia

Bangladesh, China, India, Korea, Pakistan and Singapore.

Europe

Austria, Slovenia, Finland, Hungary, Ireland, Poland, Malta Republic, Czech Republic, Hellenic Republic, Romania, Russia and Turkey.



Classification of GMP deficiencies

Critical

That which leads or may lead to the production of a non-compliant product, representing a significant immediate or latent risk to the patient and/or involving fraud, adulteration or falsification of products and/or data. It can negatively influence data integrity.

Major

That which may lead to the production of a non-compliant product, but does not represent a significant immediate or latent risk to the patient. It can negatively influence data integrity.

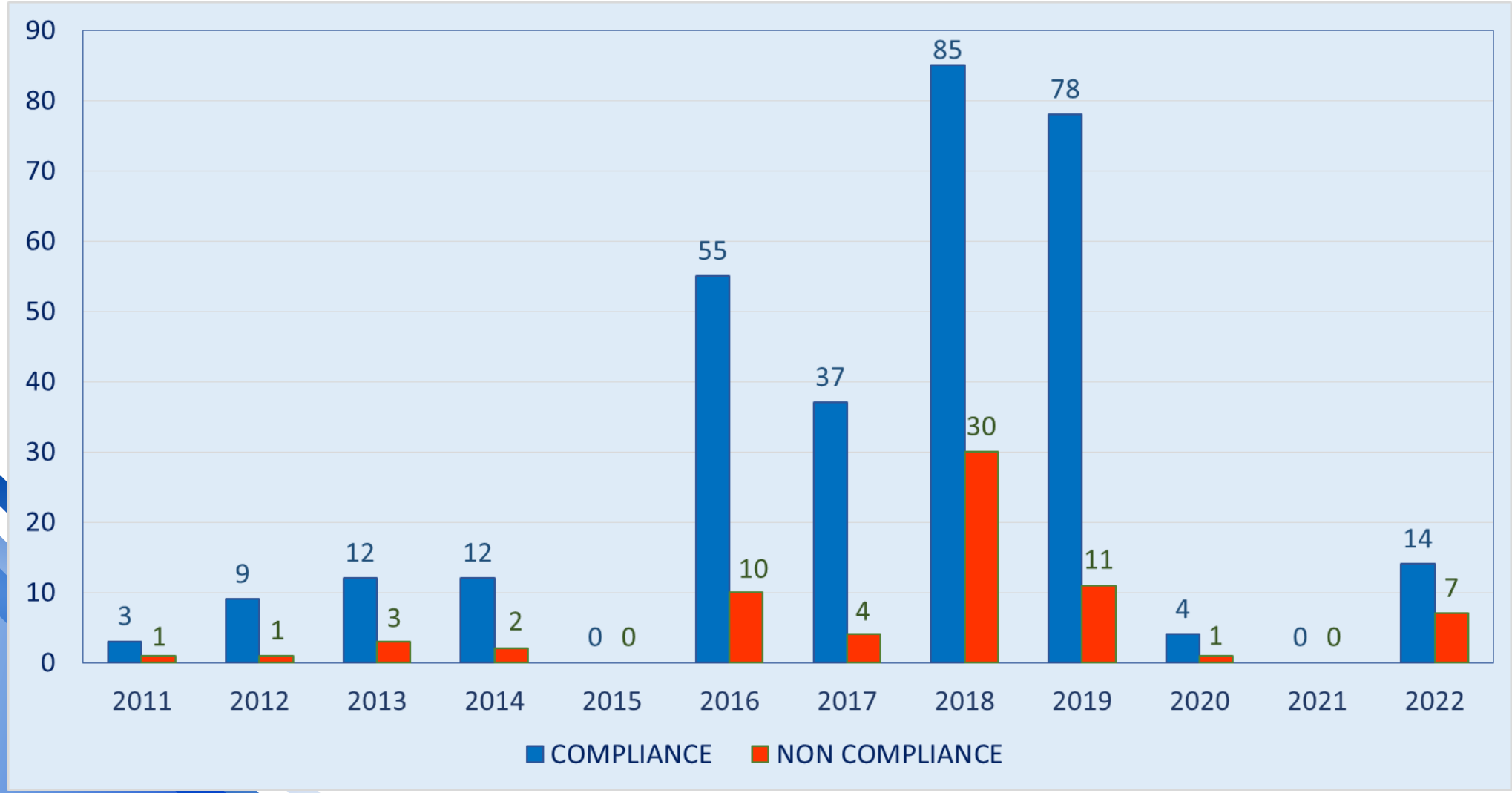
Minor

That which is not classified as critical or major but that indicates a non-compliance with good manufacturing practices

In 2019, the Technical Guide: Inspection Guide for Good Manufacturing Practices for Pharmaceutical Products was approved. The purpose to develop this guide was the harmonization of the classification and reporting of GMP deficiencies across inspectors.

Reference: Risk Classification of Good Manufacturing Practices Observations (GUI0023), February 28, 2018

Results of GMP compliance inspections of foreign manufacturers



Statistics of Non-conformities found with Reference to GMP Section for 2019

SECTION	MAIN NON-CONFORMITIES	QUANTITY	%
SECTION VI	QUALIFICATION AND VALIDATION: Processes and procedures are not established based on the results of validation studies	22	24
SECTION XXVIII	CONTAMINATION CONTROL: Risk of cross contamination	18	20
SECTION IV	EQUIPMENT: The equipment is not qualified / The equipment is inadequate as it does not have a sanitary finish	12	13
SECTION XXII	QUALITY CONTROL: They do not verify that raw materials and finished products meet their specifications	11	12
SECTION XXII	QUALITY CONTROL: They use techniques not declared in their marketing authorization for the analysis of raw materials and finished products	7	8
SECTION XXII	QUALITY CONTROL: They do not carry out stability studies and holding time studies	7	8
SECTION III	FACILITIES: The design of the facility is not suitable for the pharmaceutical products they manufacture	6	7
SECTION III SECTION IV	FACILITIES AND EQUIPMENT: They do not have the facilities or equipment necessary to carry out manufacturing	3	3
SECTION II	PERSONEL: They do not have evidence of personnel qualifications	2	2
SECTION XVIII	PRODUCT RELEASE: Incomplete manufacturing batch records	2	2
	TOTAL	**90**	**100**

Examples of non-conformities

Ref.	Section XXX	Compliance		Classification	Notes
Ítems	XXX	Yes	No		
11.4	Simulations are carried out to demostrate the effectiveness of the product recall process at least once a year?			Minor	
6.68	The need for a new qualification or validation is evaluated and determined when trends in results from any of the systems are detected that may affect the quality, safety and efficacy of the product as well as the traceability of the data? **Systems: Calibration, Maintenance, cleaning and sanitation, personal qualification, deviations, self inspections and quality audits, environmental monitoring, periodic product review**			Major	
20.5	Documentation ensures the existence of evidence, traceability and availability, in the event or any intestigation at any of the manufacturing stages of the pharmaceutical product?			Critical	

- During the content analysis by chromatographic method of the raw material ABC Lot: XYZ, three standards and three samples (M1, M2 and M3) were prepared, however for the report just the data of samples 2 and 3 were considered, the report didn't establish the reason for the elimination of the results (sample 1), however the investigation (OOS) is not available and the final result of the analysis is considered valid.
- During the review of the protocol and validation report of the analytical methodology for determining the absence of traces of ABC (XXX-00-000 and YYY-00-000), it was observed that the 10 data reported as a result of the analysis performed on the HPLC equipment for the swab recovery assay (two injections from five samples), come only from two injections coded as 04102713 (Area 148.53094) and 04102714 (Area 147.94843), being evident the inconsistency in the analysis that supports the validation study.

Examples of non-conformities

- In the incubator of the Microbiology Area, plates were found with water analysis samples from point No. 12, which showed characteristic growth of E. coli on MacConKey Agar and atypical growth on Cetrimide Agar. A Plate Count Agar was also found with the presence of yellow colonies at points No. 22 and No. 25, without a report of out-of-specification results having been generated or the corresponding investigation having been carried out.

- During the review of the analytical reports corresponding to the raw material GEMCITABINA Batch ABC, it was evident that two drums entered the warehouse, however, the HPLC identification analyzes were not carried out for each container, performing these as a pool, likewise, the analysis corresponding to the identification test A “IR Spectroscopy” is not evident. In addition, they use an C18 250 X 4.6 mm, 5 um HPLC column which differs from what is described in the monograph where it states that the column to be used is a 4.6 mmx 25 cm, 5 um L7 (C8). Likewise, the development of the analysis of residual solvents (Methanol, Acetone and Isopropanol) is not evident, since they do not have the necessary resources within the laboratory, because the gas chromatograph acquired to date has installation qualification and is not is operational for analysis.

- During the manufacturing process of the product Doxorubicin Batch ABC for 3500 vials, it was evident that the filling system is a semi-closed system, with gloves installed in the filler for handling the materials, the same ones that are used to: lift fallen vials during the process, align the vials, among others; been in contact with the depyrogenated vials, however, the gloves were not sterilized by steam, dry heat or other methods whose effectiveness is demonstrated through validation.

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