Hosting Inspections from foreign countries:
PMDA (Japan)
ANVISA (Brazil)

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First Russian GMP Conference
20. – 22. September 2016

Agenda

- General information about the authority
- GMP Regulations
- Inspection
  - ➢ Recommendations for successful preparation
  - ➢ Examples for Deficiencies

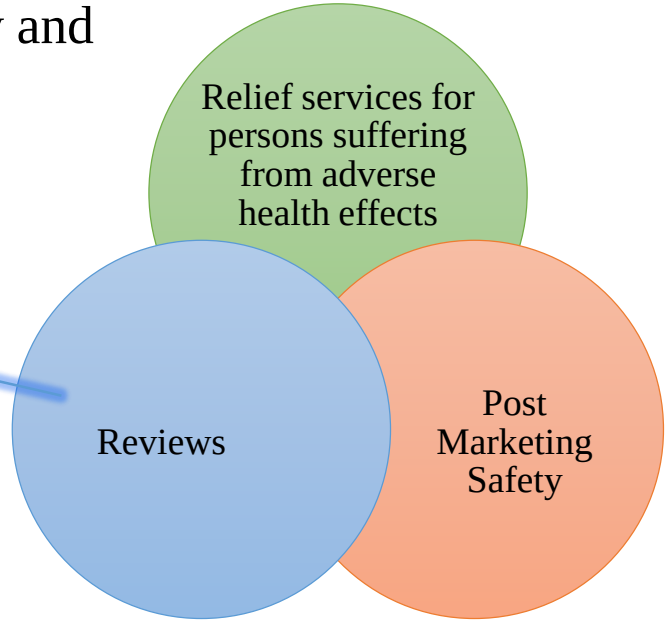
……What looks alike turns out not to be the same!

Although general GMP requirements are set,
you might see deficiencies during third-party audits

General information about the authority

- PMDA (Pharmaceuticals and Medical Devices Agency) is the Japanese regulatory agency
- 2004, April 1st: Pharmaceuticals and Medical Devices Agency (PMDA) was established and came into service under the Law for the Pharmaceuticals and Medical Devices Agency
- Collaboration with Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labor and Welfare (MHLW)
- General obligation is to protect the public health by assuring safety, efficacy and quality of pharmaceuticals and medical devices by a three pillar system
- Active role in harmonization process, Accession to PIC Scheme July 2014

Auditing of manufacturers to ensure they conform to Good Manufacturing Practice (GMP) and have a suitable Quality Management System (QMS)



General information about the authority

- National Health Surveillance Agency or ANVISA (Agência Nacional de Vigilância Sanitária)
- Established by Law 9782, enacted in January 26, 1999
- Independently administered, financially autonomous regulatory body
- Managed by a Collegiate Board of Directors composed of five members
- In the federal public administrative structure, the agency is connected to the Ministry of Health, a periodic management contract is signed
- The agency is connected to the Ministry of Health (Ministério da Saúde)
- Protect and promote public health
  - Coordination, Approval and health surveillance for
    - Pharmaceuticals, medical devices, food, cosmetics, tobacco
    - Health services, processes and technologies
    - Health control in ports, airports and borders
  - Cooperation with the Ministry of International Affairs and foreign institutions for health surveillance related topics

GMP Regulations

- Key Elements of GMP System

Manufacturing Control & Quality Control by Manufacturer

Quality Assurance by Marketing Authorization Holder

GMP Inspection by Competent Authority

- Current GMP Ordinance has resulted from former GMP Ordinance (No. 16, 1999), harmonized with ICH Quality Guidelines
  - GMP Ordinance (MHLW Ministerial Ordinance No. 179, 2004)*
  - Requirements for Manufacturing of Medicinal Products (including APIs)
  - Accreditation of Foreign Manufacturers incl. Guidance documents**
  - Master File System (=Drug Master File)
  - Japanese Pharmacopoeia (JP)

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- *Quality Assurance for Drugs, Quasi-drugs, Cosmetics and Medical Devices*
- ***Manufacturing Control and Quality Control for Drugs and Quasi-drugs***
- *Regulations for Buildings and Facilities of Pharmacies, etc.*

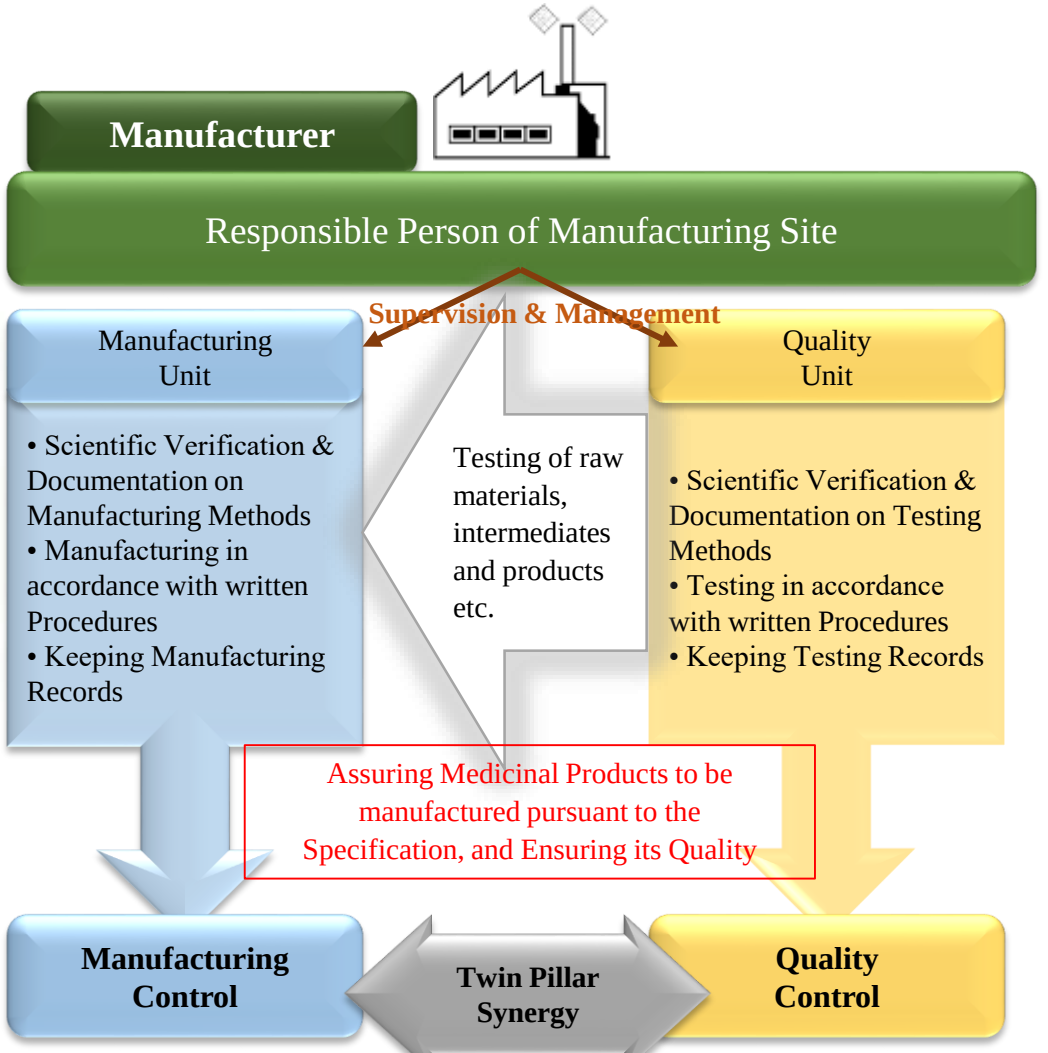
**
- *GMP Compliance Inspection concerning Pharmaceuticals (including APIs)*
- *Management of Computerized Systems*
- *Manufacture of Sterile Pharmaceutical Products*
- *Manufacture of Sterile Pharmaceutical Products by Aseptic Processing*

GMP Regulations

Concept of Manufacturing Control & Quality: MHLW Ministerial Ordinance No. 179, 2004

Manufacturer's Responsibility according to Ministerial Ordinance (MO)

- Routine Manufacturing Control & Quality Control
- **Product Quality Review**: Article 5 , ref. **ICH Q7 2.5**
- **Periodic Review** of Validated Systems: Article 13, ref. **ICH Q7 12.6**
- **Internal Audits (Self Inspection):** Article 18, ref**. ICH Q7 2.4**
- **Training**: Article 20, ref. **ICH Q7 3.1 ICH Q7 2.11**
- Quality Risk Management for Manufacturing Process and continuous improvement of manufacturing process & the product quality.
- **ICH Q9; Quality Risk Management**



GMP Regulations

- First Brazilian GMP guideline was published in 1995
- Incorporation of **WHO** pharmaceutical quality assurance guidance into national health legislation system
- Present edition, RDC no. 17/2010 derived from the 2003 edition of the basic **WHO GMP guide: GMP for pharmaceutical products** or upon guidance from other regulatory bodies
- Defines Brazil‘s minimum GMP requirements are established regarding manufacturing medicinal products in Brazil and outside the country for the local market
  - **WHO “Supplementary guidelines on GMP for heating, ventilation and air conditioning systems for non-sterile pharmaceutical dosage forms, exh. 02 of technical report No. 937(2006)**
  - Resolution 249-05 – GMP API Manufacturing

- General practice in the standardization and guidelines literature is to use the term "should" for the individual determinations
- ANVISA guidelines give preference to "must" determinations

- **Counterfeiting:** Initially the implementation of Track & Trace coding (2D Matrix) was planned for 2016
  - ANVISA has undertaken a review of the Regulation to implement the existing serialization law, considering significant changes to the existing requirements
  - Timelines extended through 2020/21 and requirements moving closer to aligning on the use of GS1 Standards.

GMP Regulations

RESOLUTION - RDC Nº 17, OF 16.04.10	
TITLE I	INITIAL PROVISIONS
TITLE II	QUALITY MANAGEMENT IN THE MEDICAMENT INDUSTTRY: PHYLOSOPHY AND ESSENTIAL ELEMENTS
TITLE III	STERILE PRODUCTS
TITLE IV	BIOLOGICAL PRODUCTS
TITLE V	VALIDATION
TITLE VI	WATER FOR PHARMACEUTICAL USE
TITLE VII	COMPUTER INFORMATION SYSTEMS
TITLE VIII	GOOD PHYTOTHERAPIC MEDICAMENTS MANUFACTURE PRACTICES
TITLE IX	FINAL AND TRANSITIONAL PROVISIONS

- „QUALITY MANAGEMENT“: Close to corresponding WHO GMP guideline
  - Each Article focusses on a single determination which can be numerically referred to in inspection reports and enforced
- Production in exclusive and closed areas
- Computerized systems: ANISA established guide in co-operation with Brazilian Chapter of ISPE
  - No Risk based approach!
- Detailled GMP Guideline for raw materials published in 2012
- Risk based approach only acceptable for the extend of validation activities
  - Prospective validation - risk assessment should be used to determine scope and extension
  - Frequency / extension of periodic revalidation based on risk assessment, review of historical data (periodic review program)

Inspection: 5 Years Validity

Input Information

- Submitted documents
- Reported adverse events and recalls
- Records of previous QMS inspections etc.

Risk Assessment

- Complexity of manufacturing processes
- Risk associated with the use of products
- Previous nonconformities and recalls
- Results of the previous on-site inspections
- Certificate of ISO13485 etc.
- ~ 4 months to evaluate the documentation and inform if paper based or on site inspection is required

Decision of on-site or desktop

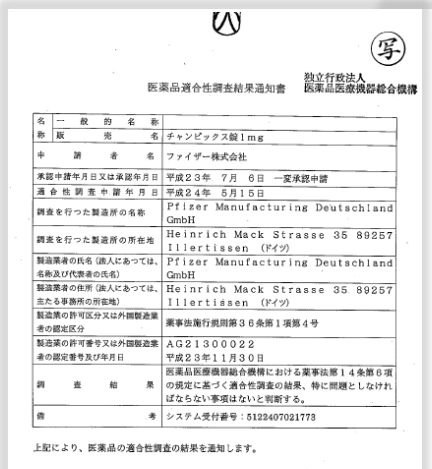
Manufacturing sites located in countries with Mutual Recognition agreement (MRA) or Memorandum of Understanding (MOU) are generally subjects for document reviews

On Site Inspection

- Typically two Investigator
- 4 to 5 days
- Inspection language: Japan
- ~ 14-30 days to issue the official report
- Based on the outcome manufacturers are graded for compliance only if **all manufacturing sites involved are in compliance**

Expectations for CAPA Implementation:

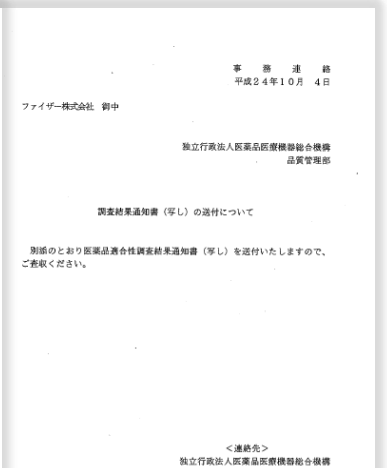
Deficiency	Response	CAPA's Implementation	Confirmation of Effectiveness	Evaluation
Minor	Improvement Report/Plan	~ 30 days	Next inspection	Conformity
Major	Improvement Report	≤ 30 days	Next inspection	Conformity
		≥ 30 days		Non-Conformity
Critical	Improvement Report	≤ 15 days	Next inspection	Conformity
		≥ 15 days		Non-Conformity


医薬品適合性調査結果通知書

独立行政法人
医薬品医療機器総合機構

名称 一般的名称	
名称 販売名	チャンピックス錠1mg
申請者名	ファイザー株式会社
承認申請年月日又は承認年月日	平成２３年　７月　６日　一変承認申請
適合性調査申請年月日	平成２４年　５月１５日
調査を行った製造所の名称	Pfizer Manufacturing Deutschland GmbH
調査を行った製造所の所在地	Heinrich Mack Strasse 35 89257 Illertissen （ドイツ）
製造業者の氏名（法人にあっては、名称及び代表者の氏名）	Pfizer Manufacturing Deutschland GmbH
製造業者の住所（法人にあっては、主たる事務所の所在地）	Heinrich Mack Strasse 35 89257 Illertissen （ドイツ）
製造業の許可区分又は外国製造業者の認定区分	薬事法施行規則第３６条第１項第４号
製造業の許可番号又は外国製造業者の認定番号及び年月日	AG21300022 平成２３年１１月３０日
調査結果	医薬品医療機器総合機構における薬事法第１４条第６項の規定に基づく適合性調査の結果、特に問題としなければならない事項はないと判断する。
備考	システム受付番号：5122407021773

上記により、医薬品の適合性調査の結果を通知します。


事務連絡
平成２４年１０月　４日

ファイザー株式会社　御中

独立行政法人医薬品医療機器総合機構
品質管理部

調査結果通知書（写し）の送付について

別添のとおり医薬品適合性調査結果通知書（写し）を送付いたしますので、ご査収ください。

＜連絡先＞
独立行政法人医薬品医療機器総合機構

Inspection: 2 Years Validity (Bi-annual Re-certification)

Input Information

- Submitted documents
- Major Changes (e.g. new facility/area, new technology or product)
- **Anvisa Inspection Check-list**
- Site Master File
- GMP certificate issued by the local agency
- Periodic Product Review

Risk Assessment

- Anvisa will evaluate based on their risk assessment process if a GMP inspection will be necessary
- ~ 4 months to evaluate the documentation and inform if paper based or on site inspection is required

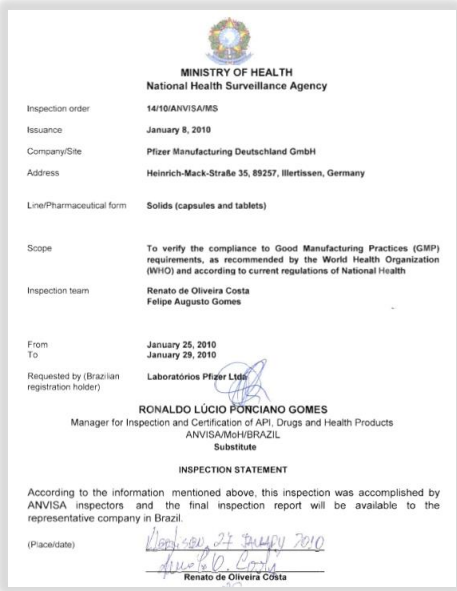
Decision of on-site or desktop

On Site Inspection

- Typically two Investigator
- 5 days
- Inspection language: English, Portuguese
- ~ 30 days to issue the official report
- Based on the outcome facility is “approved”, “On Query” or “Rejected”

Expectations for CAPA Implementation:

Outcome	Actions
Approved	GMP certificate will be issued within 30 – max. 120 days.
On Query	Improvement Report must be submitted within 30 days Can be extended on request to max. 3 months ANVISA response to Improvement plan in 60 days if acceptable.
Rejected	Improvement Report to address deficiencies from the inspection must be submitted. Certification must start again. ANVISA response to Improvement plan in 60 days if acceptable.



MINISTRY OF HEALTH
National Health Surveillance Agency

Inspection order	14/10/ANVISA/MS
Issuance	January 8, 2010
Company/Site	Pfizer Manufacturing Deutschland GmbH
Address	Heinrich-Mack-Straße 35, 89257, Illertissen, Germany
Line/Pharmaceutical form	Solids (capsules and tablets)
Scope	To verify the compliance to Good Manufacturing Practices (GMP) requirements, as recommended by the World Health Organization (WHO) and according to current regulations of National Health
Inspection team	Renato de Oliveira Costa Felipe Augusto Gomes
From To	January 25, 2010 January 29, 2010
Requested by (Brazilian registration holder)	Laboratórios Pfizer Ltda.

RONALDO LÚCIO PORCIANO GOMES
Manager for Inspection and Certification of API, Drugs and Health Products
ANVISA/MoH/BRAZIL
Substitute

INSPECTION STATEMENT

According to the information mentioned above, this inspection was accomplished by ANVISA inspectors and the final inspection report will be available to the representative company in Brazil.

(Place/date)

Renato de Oliveira Costa

Inspection: Recommendations for successful preparation

- All documents to comply with
  - Product application/dossier submitted to PMDA
  - Japanese GMP Ministry Ordinance
  - JP Pharmacopoeia
- Apply and Document Quality Risk Management (QRM)
- Ensure all operators are trained and supervised
- Management of the entire supply chain
  - Ensure a robust System for management of suppliers and third parties
  - Have a robust Incoming Reduce testing program based on the supplier certification

Inspection: Examples for Deficiencies

- Quality System:
  - Deviations
    - Process of checking of deviations was not incorporated in the final product release procedure
  - Training
    - Operators did not understand what a “deviation” is
  - Document Control
    - Management Control System not implemented
    - Deviation in packaging documented in a operation memorandum instead of a GMP System
  - Change Control
    - No documentation about who decided the importance of changes and background for decision
    - Quality unit only checked the content of deviation during approval, no assessment of influence on quality, no check of the appropriateness for change results
- Cross-Contamination/Cleaning Validation
    - No evaluation on the appropriateness of cleaning method / No evaluation on the appropriateness of an on-site visual confirmation after cleaning
    - No evaluation on the cross-contamination risk with multiple products at a common facility
    - Powder drifting workroom was positively pressurized
    - There was no cleaning validation of a shared chamber dryer

Inspection: Recommendations for successful preparation

- Review the Brazil GMP requirements in advance and have them available during the inspection
- ANVISA inspectors focused on compliance with Brazil GMPs
  - Anvisa spends time on the facility and shopfloor when manufacturing process is executed
  - Anvisa witness operation and if instructions are followed for each step by the operator
  - Prepare operators and ensure training of all SOP's is in place and effective
- Pre- Inspection - Information (Anvisa Audit Check – List)
  - Production information for each product in sampling, weighing, storage, HVAC, production equipment/rooms, in/out material and personnel should be prepared as handouts
  - Very strict regulations for Sharing level with Penicillin's, Cephalosporin's, carbapenem, monobactamic, cytotoxic, biologicals (live), veterinary, devices, cosmetics, radiopharmaceuticals, disinfectants, hormones – hormones included the ATC/DD code

Inspection: Examples for Deficiencies

- No Separation of areas for production of hormones
  - HVAC System was not independent from production of other material
  - Personnel flow was not separated for operators involved in manufacturing of cytotoxic substances
  - High potent drugs were produced using the same area as non-toxic drugs
  - No clear separation of material flow for toxic-drugs and non-toxic drugs
- No Confirmation that the plant does not produce animal products in the same line that human products are produced
- Non-pharmaceutical products are produced in areas or used equipment in use for pharmaceutical drugs production

Thank you for your attention

Спасибо за внимание!

Kathrin Abelein, PhD
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Director Quality Operations
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