
# Introduction and Case Sharing of FDA CGMP Inspections

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# Agenda

- Principles and rules of FDA CGMP inspections
- How to be prepared for FDA CGMP inspections?
- USA-EU Mutual Reliance Agreement on CGMP inspections
  - How it was decided?
  - What was done?
  - What will be done?

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***DISCLAIMER**: The views and opinions expressed in this presentation are those of the authors and do not necessarily represent official policy or position of Novo Nordisk or other organizations, e.g., US FDA*


# Principles and rules of FDA CGMP inspections

- Basic structure of the US-GMP
- Case Study
  - CBER/FDA managed review and inspection programs
- Recent trend

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# Legal Bases for CGMP


- **Section 501(a)(2)(B):** “A drug... shall be deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.”

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# Legal Bases for CGMP

- **FDASIA 2012 amendment to section 501:** CGMP “includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.”


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# CGMP Legal Principles

- **Quality built into product**
  - By “taking care” in making medicine
  - Can’t ‘test’ into product the quality
- **Without / Inadequate CGMP**
  - Product(s) adulterated(defects need not be shown)
  - Firm and its management are responsible
- **Non-compliance = eventual problems**
  - Super-potency/sub-potency
  - Contamination
  - Misbranding
  - Bioavailability
  - Safety and efficacy

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# CGMP Legal Principles

- **Current = dynamic**
  - Standards evolve over time
    - **Risk and science based approach**
- **Good practices**
  - Minimal standards
  - Not “best practices”
    - **Unless “best” is, in fact, current minimal**

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# **CGMP for** Finished Pharmaceuticals
# **21 Part 211**

**Subpart A** - General Provisions

**Subpart B** - Organization an Personnel

**Subpart C** - Buildings and Facilities

**Subpart D** - Equipment

**Subpart E** - Control of Components and drug product Containers and Closures

**Subpart F** - Production and Process Controls

**Subpart G** - Packaging and Labeling Controls

**Subpart H** - Holding and Distribution

**Subpart I** - Laboratory Controls

**Subpart J** - Records and Reports

**Subpart K** - Returned and Salvaged Drug Products

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# Four Major CGMP Inspection Types

1. **Pre-approval**
2. Post-approval
3. **Surveillance (CGMP, routine)**
4. For-cause or directed

# Surveillance (CGMP, routine) Systems Based Inspections

- Quality
- Facility and equipment
- Production
- Laboratory Control
- Materials
- Packaging and Labeling

- Observations made during inspections are organized by system
- Two options for systems approach:
  - The Full Inspection Option
  - The Abbreviated Inspection Option

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# After the Inspection

- Inspections are generally classified into one of three categories
  - **NAI**-No Action Indicated
  - **VAI**-Voluntary Action Indicated
  - **OAI**-Official Action Indicated

- Expect a copy of FDA inspection report (EIR)

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# Inspections…

- An FDA inspection is a careful, critical, official examination of a facility to determine its compliance with certain laws and regulations administered by the FDA
  - Are **FACT** finding
  - Obtain **EVIDENCE**
  - Are **REGULATORY**
    - What is said could end up in court

**Be reasonable (Time, Limits, Manner) in order to achieve the objective of the inspection**

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# What Are Investigators Looking For?

- Evidence that a violation exists
  - Adulteration
  - Misbranding

- CGMP violations
  - Poor Employee Practices
  - Poor Equipment and facilities
  - Lack of process control

- Application departures
- Data integrity issues


# Principles and rules of FDA CGMP inspections

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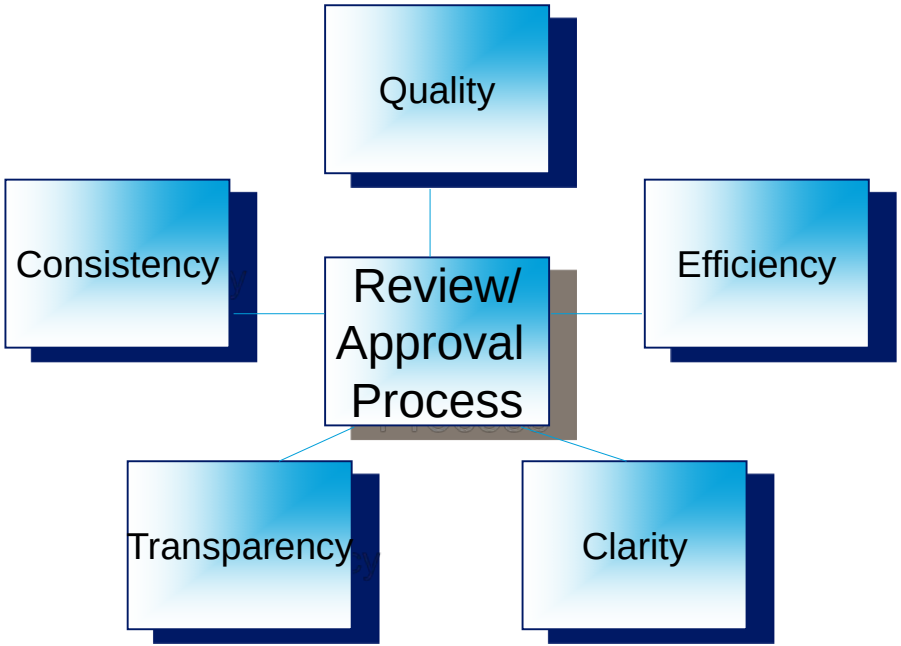
# Fundamental Values
## – Apply to All FDA Review Process

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# Clarity vs. Transparency

- Clarity → **What** does the FDA think?
- Transparency → **Why** does FDA think that way? **How** did FDA arrive at their position?

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# Operational Principles

1. Pre-submission activity
2. Submission of a complete application
3. CBER/FDA is responsible for a well-managed review
4. Applicant involvement during review process
5. Adherence to internal review timelines
6. Teamwork
7. Maximize 1st Cycle Approvals (without lowering standards!)
8. Effective and timely communication
9. Written Regulatory Action
10. Avoid discussing with applicant the planned regulatory action

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# Team Approach – Single Voice

- **The Review Committee**
  - Chairperson/Lead
  - Regulatory Project Manager
  - Discipline Reviewers
    - Medical officer
    - Statistician
    - Product reviewer
    - Pharmacology/Toxicity reviewer
    - Establishment (Facility and Equipment) reviewer and lead inspector for pre-approval
    - BIMO Person


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# Dispute Resolution

- Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level
- SOPP 8005 Major Dispute Resolution Process (2/11/99)


# Principles and rules of FDA CGMP inspections

- Basic structure of the US-GMP
- **Case Study**
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- **Recent trend**
  - New Inspection Protocol Project (NIPP)
  - Data Integrity

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# **FDA's Current Thinking:**
# Current vs. Future Inspections Programs

## Current

- Focus on evidence of CGMP violations – e.g., employee practices, equipment and facilities, lack of process control, data integrity issues, departure from application commitments, and other deficiencies
- Establishment Inspection Report (EIR) is long, in narrative format, and lacks standardized data that can be quickly and easily analyzed

## Future

- The inspection process and work products focus on measuring and describing the state of quality in the inspected facility
- The inspection includes analyzable assessments to track and improve performance
- Inspections identify and encourage excellent manufacturing practices
- A clearer set of requirements that may lead to better utilization of information by other inspection authorities

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# New Inspection Protocol Project (NIPP)

- New paradigm for inspections and reports that will advance pharmaceutical quality
- Standardized approach to inspection
- Data gathering to inform “quality intelligence” of sites and products: **both positive and negative behaviors**
- Risk-based and rule-based process using expert questions
- Semi-quantitative scoring to allow for comparisons within and between sites
- More common inspection report structure
- Knowledge from inspections can inform FDA decision-making:
  - Site selection
  - Post-approval change reporting
  - Industry outreach/training on positive manufacturing behaviors

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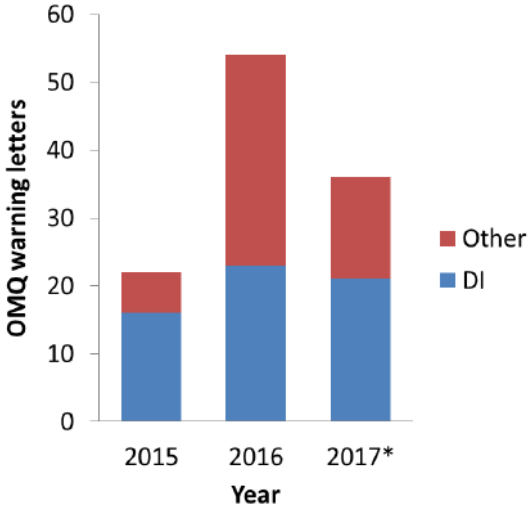
# Data Integrity Issue

- Drug Regulatory Program depends heavily on the reliability (i.e. **truthfulness, completeness and accuracy**) of data & information in records
  - Applications for approval
  - Manufacturing Controls documentation




- More than 50% of the warning letters issued and cleared by OMQ/CDER/FDA have involved data integrity lapses

*Note: data come from FDA's recent public presentation*

** Through July 15, 2017 and excludes compounding-related actions*

FDA experiences broad scale unreliability of data in records or in conduct related to records

- **non-compliance mostly observed in India, China and other countries outside US/EU**

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# Inspection as a Q process


Who does what when?

# Pre-inspection Activities

- Steering Group formed with the purpose of overseeing the inspection preparations
  - Consisting members from relevant parts of the organisation relevant to the inspection scope (PAI/PLI/routine inspection) incl. senior management
- Perform MOCK audits
- Train in how to interact professionally with investigators

# During the inspection

- War-room/staging set-up to coordinate responding to request from the investigator
- Corporate host who is the through-going person during the entire inspection securing links between different areas being inspected
- Wrap-up and feed-back on a daily basis to the site being inspected including summary mail to executive management

# Post-inspection management activities

- Daily meetings with senior management to set directions for writing the response to observations. Members from all relevant parts of the organisation; e.g. production, QC, QA, RA, development etc.
- Use of highly skilled writers with knowledge of GMP, manufacturing processes etc. and professional English skills.

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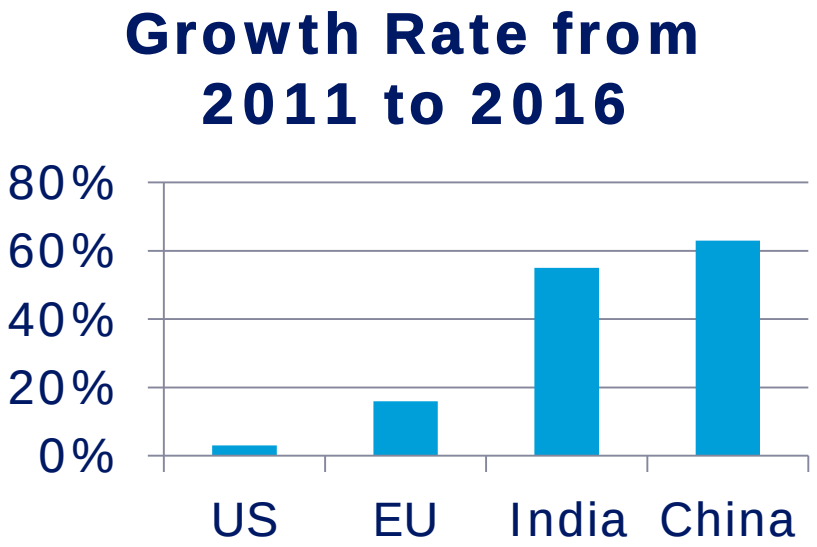
# The Basis and Rationales for the MRA

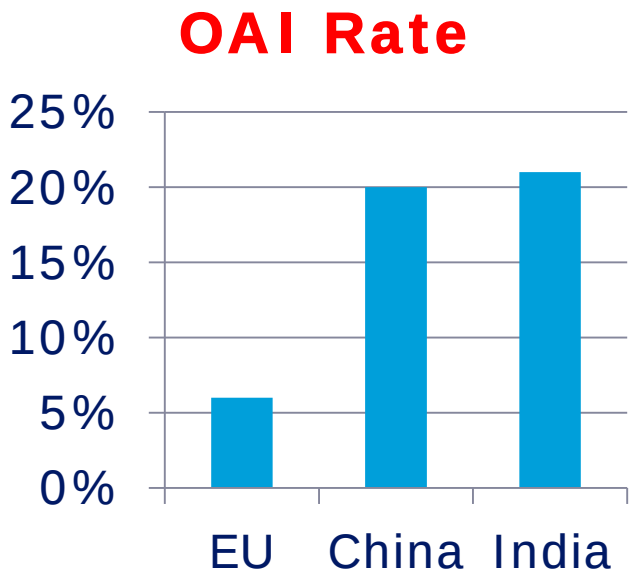
- The global drug manufacturing supply chain
- Growth of registered manufacturing facilities outside of US/EU




*Note: Data from FDA public presentations*

# The Basis and Rationales for the MRA (Cont.)

- Resource management based on risk
- Same/similar standard setting
  - ICH and PIC/s
  - QbD joint pilot program
  - Parallel scientific advice interaction
- Confidence built up in the past
  - API inspection program
  - Good clinical practices/bioequivalence inspection collaboration
- Capability assessment




*Note: 2015 inspection data - from FDA public presentations*

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# MRA: Capability Assessment

**Conflict of Interest (COI) Evaluation**

FDA evaluates the inspectorate's COI policies against EMA and FDA ethics regulations

**Joint Assessment Program (JAP) Audit Observation**

FDA experts observe EU audit of member states

**Primary Assessment**

FDA experts review the final EU audit report, the observers' reports, the inspections reports, and supporting information

**Secondary Assessment**

Representatives of FDA's senior leadership assess the primary team's conclusions and make the final capability determination.

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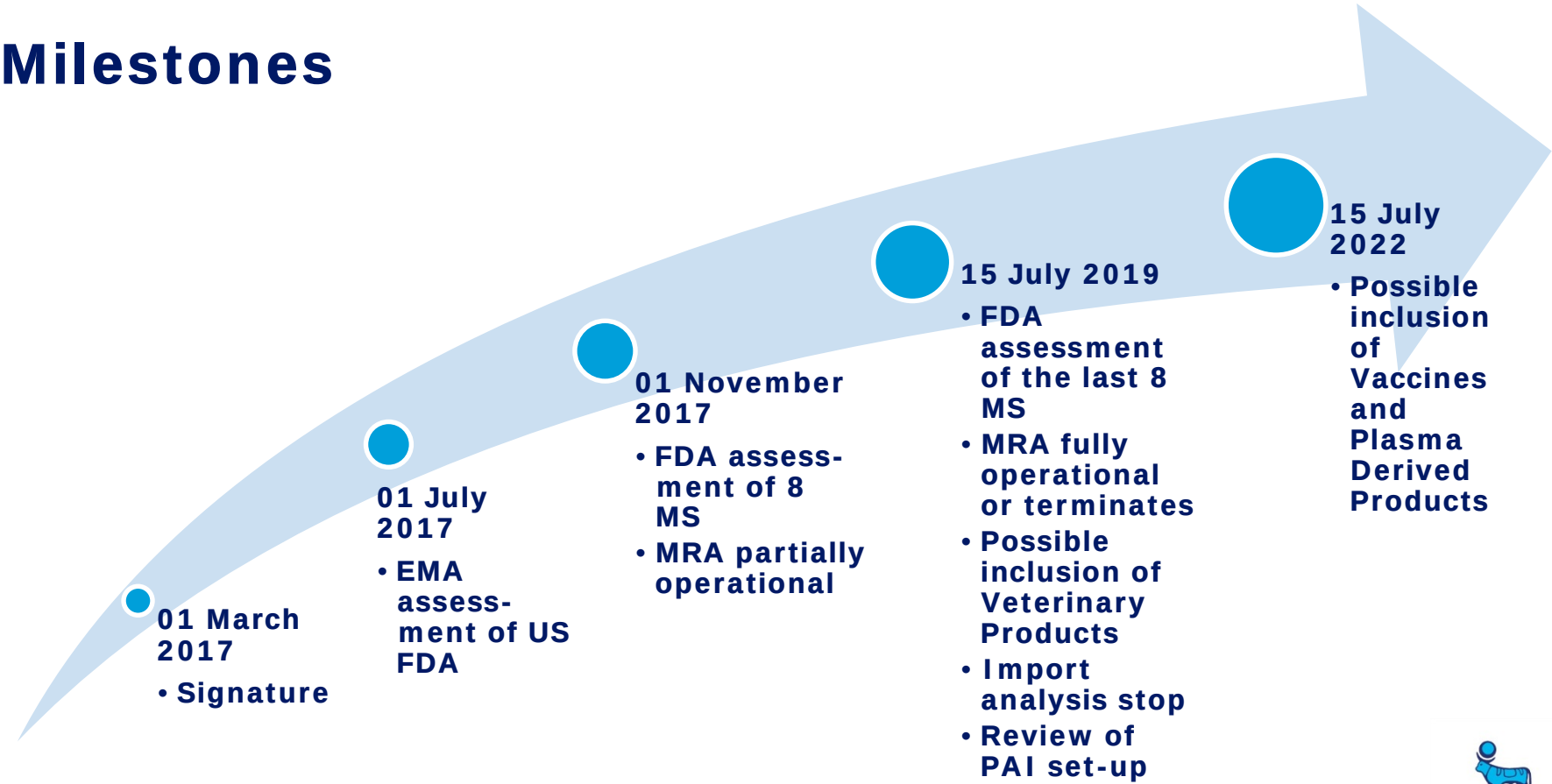
# Milestones


01 March 2017
• Signature
01 July 2017
• EMA assess-ment of US FDA
01 November 2017
• FDA assess-ment of 8 MS
• MRA partially operational
15 July 2019
• FDA assessment of the last 8 MS
• MRA fully operational or terminates
• Possible inclusion of Veterinary Products
• Import analysis stop
• Review of PAI set-up
15 July 2022
• Possible inclusion of Vaccines and Plasma Derived Products

# Major Achievements with the MRA

Based on the original agreement from 1998 the following has been agreed:

- Recognition
  - Inspections US/EU
- Reliance
  - Inspections in 3rd countries (i.e. outside US/EU)
- Waiver
  - Import testing US to EU

**Scope:**

- Includes a vast majority of drugs
- Certain products will be reevaluated in the future, such as vaccines and veterinary products
- Surveillance and, under certain conditions, pre-approval inspections of marketed human drug facilities located within the US and EU

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# MRA: Benefits

- Stronger drug inspection expertise
- Greater efficiency
- Decreased duplication inspections
- Reallocation of resources to areas with a higher public health risk

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  RA Manager


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**Thank You!**

**Спасибо!**

# Questions

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