

# **Pharmaceutical Industry Overview**

Good Manufacturing Practices (GMPs)  
Regulatory Chemistry Manufacturing & Controls  
(CMC)

Greg DiGennaro

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# TOPIC 1 - GMP Expectations

- GMPs are governed by:
  - ICH Q7 for Active Pharmaceutical Ingredients
  - Other ICH guidelines apply to Drug Products
    - <https://www.ich.org/page/quality-guidelines>
  - CFR Code in the US
    - 211.25(c), 211.63, 211.100, 211.42, 211.58, 211.67, 211.182
  - FDA Guidance documents:
    - <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>
  - EMEA (Europe)
    - <https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/quality-guidelines>
  - Many other regulatory bodies
    - Brazil (ANVISA)
    - China
    - Japan

# cGMP

## (Current Good Manufacturing Practice)

- GMP should be “*Designed*” to be flexible to allow each manufacturer to decide individually how to implement the necessary controls by using scientific sound design, processing methods and testing procedures
- The “C” in GMP means current – up to date technologies
- Overall concept
  - Quality should be built into the product
  - Testing alone cannot be relied on to ensure product quality

# cGMP Principles

- Build QUALITY in - you cannot test or inspect quality into a product – it must first be quality
  - We do X, Y, and Z – therefore we ensure final result A
- Have controls in place for each step of the process – increase the likelihood the product produced is safe and fit for its intended purpose
  - Controls are sliding scale as the step approaches the patient
    - E.g. general purpose space is acceptable for early API intermediate. Grade A space is required for sterile drug product.
- Controls, rather than testing, are required because not all potential quality concerns can be tested for.

# cGMP Principles (cont)

- Know what you are doing in advance and document what really happened (document everything)
  - Integrity of pharmaceutical data is a current hot button issue with agencies.
  - How can you PROVE the data is accurate?
  - Were there incentives to manipulate data
- Work towards consistency and control and monitor your system
  - Within the guidelines, it is up to the manufacturer to prove their control strategy is acceptable.
- Have an independent Quality Assurance Group

# cGMP Requirements

- A robust manufacturing process that consistently produces a given product at a given quality
  - A Quality System (change control, validation, CAPAs)
  - Qualified and trained personnel
  - Fit for use buildings and facilities to meet the purpose
  - Equipment that is suitable, clean, maintained and calibrated
  - Controls in place to prevent degradation or contamination of materials (raw, in process and final)
  - Production and in-process controls for performance monitoring and deviations
  - Proper packaging and labeling – ID and Protection
  - Laboratory controls – specifications , samples, testing

# Pharmaceutical Quality System

- Guidance for Industry: Quality Systems Approach to Pharmaceutical cGMP Regulations (June 2006); 21CFR210 and 211
- The six-system inspection model
  - Quality system
  - Facilities and equipment system
  - Materials system
  - Production system
  - Packaging and labeling system
  - Laboratory controls
- Robust Quality System will have
  - SPOs
  - Training
  - Records and good documentation practices

# QC vs. QA

## Quality Control vs. Quality Assurance

- The QC unit monitors specific endpoints and other measurable results against targets.
  - Testing final product results
- The QA unit supplies system oversight by auditing the functions
  - Investigates deviations
  - Approves procedures and corrective actions
  - Approves validation, training, documentation



# Records

- ALL operations must be documented and retained
  - Batch Records
  - Training records
  - Lab records
  - Microbiological Monitoring
  - Distribution records (must be maintained to aid in recalls)
- Includes both Paper and Electronic
- Control must be in place to ensure data is “ALCOA”
  - Attributable, Legible, Contemporaneous, Original, Accurate

# Facilities and Equipment System

- Areas are designated as clean and dirty,
  - Physical separation, equipment and staff for each operation
- Specify personnel protection equipment and to prevent contamination by humans
- Areas must operate to a single standard - GMP or non-GMP
- Need to have designed into areas
  - Building materials, air handling, temperature, microbiology
- Environmental Controls, Support systems, Alerts, Action Limits must be established to prevent product cross-contamination and contamination by harmful microorganisms

# Microbiology

- Effects on product
  - Causing human illness
  - Product
    - Discoloration
    - Malodors
    - Production of gasses that can lead to package swelling or busting
    - Breakdown in viscosity or elasticity
    - Otherwise unable to perform as intended
- Types: contact or airborne/ bacterial, yeast or mold
- Resistance to product preservative system or sanitizers (think antibiotic resistance)
- Classic Microbiology – takes 48-72 h for aerobic bacteria; 72-120 h for yeast or mold

# Microbiology – areas of risk

- Heat exchangers
- Air compressors
- Pumps
- Water systems (Grades of water – WFI)
- Valves
- Ancillary Equipment (O-rings, pipes, clamps, gaskets)
- Effective Cleaning and Sanitation (C&S)
  - Autoclaves, sanitizer, alcohol, steam generators
  - CIP – Conducted on assembled equipment
  - COP – Conducted on disassembled equipment
- **PEOPLE!!!!**

# Material System

- The measurement and activities to control finished products, components containers and closures
  - Inventory Control Process
  - Drug Storage
  - Distribution Controls and Records
- Written procedures for the receipt, storage, testing and approval or disapproval of raw materials components, products, containers and closures

# Production System

- Quality and manufacturing process and procedures (and changes to them) must be defined, approved and controlled.
- Batch numbering and maintaining proper traceability is required
  - Track batch, equipment use records and labeling used, personnel, raw material controls are traceable
- Verification of all steps including sign-off are required for critical process steps.
- All batch records must be reviewed and have QA approval before the product is released

# Package and Labeling System

- FDA 'recommends' as part of the design process and before commercial products that the controls for all processes within the packaging and labeling systems be planned and documented with written procedures.
  - Discriminating features of different products/strengths
  - Distribution of all labels to manufacturing unit
  - Reconciliation is performed between label issued, applied and returned (damaged) to insure 100% accountability

# Laboratory Control system

- Laboratory Controls and written documentation
  - Analytical Methods validation and laboratory equipment qualification
  - Scientifically sound stability program to support labeled expiration dating
  - Sampling program Statistical models to determine sample scheme
  - Proper training of QC staff to collect samples
    - Batch, water, microbiology, etc.
  - Retesting conditions



# Critical Elements of Subsystems

- SOPs
  - Describes how the company complies with the drug or device regulations and are critical to GMP compliance
  - See GLP review on overall view of SOPs
  - Change Control System – to prevent unintended consequences to product quality
  - Training
  - Records

# Process Validation

- Guidance for Industry: Process Validation: General Principles and Practices (January 2011)
  - Stage 1 – Process Design: The commercial process is based on knowledge gained through development and scale-up activities
  - Stage 2 – Process Qualification: The process qualification is confirmed as being capable of reproducible commercial manufacturing
  - Stage 3 – Continued Process Verification: Ongoing assurance that the process remains in a state of control during routine production. Requires an ongoing program to collect and analyze product and process data that relate to product quality (21CFR211.180(e))
    - Requires an interdisciplinary team approach (process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics)
    - “Begin with the end in mind”

# Other “Validation”

- Cleaning
- Equipment (IQ/OQ/PQ)
- Method
- Sterility
- Environmental/media fill
- Container Closure
- Stability
- Safety compliance
  - Nitrosamines, elemental impurities, extractables

Questions and Discussion of GMPs?

# TOPIC 2 – Regulatory Expectations (CMC)

- 5 Modules comprise the Common Technical Document (CTD)
  - Module 1: Administrative Information and Prescribing information
  - Module 2: Overviews and Summaries of Modules
  - **Module 3: Quality (Chemistry, Manufacturing, and Controls - CMC)**
  - Module 4: Non-Clinical Reports (pharmacology/toxicology)
  - Module 5: Clinical Study Reports
- Governed by ICH M4 standards
- In addition to an approved Dossier, a site must have:
  - manufacturing license
  - GMP Certificate
  - Certificate of Pharmaceutical Product (CPP)

# GMP documentation in dossiers- provide minimum basis for review

- Manufacturing license
  - issued by national competent authority
  - usually certifies that a given site has been authorized to perform the claimed duties
  - may or may not specify specific products but at least the authorized dosage form/line
  - important to establish the basic legal and regulatory status of the manufacturer



# GMP documentation- Contd

- GMP certificate

- Certifies that a given site has been inspected by the national inspector (in accordance with local requirements) and deemed to be of acceptable compliance.
  - Local requirement may make reference to WHO GMP requirements but does not mean that the site has been inspected by WHO
- In some jurisdictions, GMP certification is part of the manufacturing license



# GMP documentation- Contd

- Certificate of Pharmaceutical Product
  - WHO format, comprehensive
  - issued to a specific formulation
  - certifies whether the formulation has been reviewed/licensed by the country of origin and whether it is on the market
  - includes composition of the approved formulation
  - states all sites involved in manufacturing of the FPP but may not state API sites
  - may include summaries as approved by the issuing agency
    - Product information
    - Summary of basis of approval (similar to public assessment reports)





# Certificate of Pharmaceutical Product-contd

- Primarily intended to promote faster approval and speedy access to medicines by helping recipient countries to depend on sending authorities marketing authorization
- Being also used in various other ways
  - As a key criteria for registration even though the application is supported by full dossier data
  - As supporting document for tenders
  - As a substitute for mfg license and GMP certificates
- WHO's blue book provides recommendations on appropriate use of CPP in various scenarios



# Module 2 Content

- 2.1 Table of Contents
- 2.2. Introduction
- 2.3 Quality Overall Summary
- 2.4 Non-clinical Overview
- 2.5 Clinical Overview
- 2.6 Non-clinical written and tabulated summaries
- 2.7 Clinical Summary
- For more information:

<https://journal.emwa.org/regulatory-writing-basics/an-overview-of-the-common-technical-document-ctd-regulatory-dossier/article/1693/2047480614z2e00000000207.pdf>

# Module 3 Content - CMC

- Broken into 3.2.S sections for drug substance and 3.2.P sections for Drug Product
  - Also includes appendices and regional information sections
  - See M4Q
    - <https://www.fda.gov/media/71581/download>

# Module 3 Content – Outline (DS)

- 3.2.S.1 General Information
- 3.2.S.2 Manufacture
- 3.2.S.3 Characterization
- 3.2.S.4 Control of Drug Substance
- 3.2.S.5 Reference Standards or Materials
- 3.2.S.6 Container Closure System
- 3.2.S.7 Stability

# Module 3 Content – Outline (DP)

- 3.2.P.1 Description and Composition of the Drug Product
- 3.2.P.2 Pharmaceutical Development
- 3.2.P.3 Manufacture
- 3.2.P.4 Control of Excipients
- 3.2.P.5 Control of Drug Product
- 3.2.P.6 Reference Standards or Materials
- 3.2.P.7 Container Closure System
- 3.2.P.8 Stability

# Module 3 Content – DP sections

- 3.2.P.1 Description and Composition of the Drug Product
- 3.2.P.2 Pharmaceutical Development
  - 3.2.P.2.1 Components of the Drug Product
  - 3.2.P.2.2 Drug Product
  - 3.2.P.2.3 Manufacturing Process Development
  - 3.2.P.2.4 Container Closure System
  - 3.2.P.2.5 Microbiological Attributes
  - 3.2.P.2.6 Compatibility
- 3.2.P.3 Manufacture
  - 3.2.P.3.1 Manufacturers
  - 3.2.P.3.2 Batch Formula
  - 3.2.P.3.3 Description of Manufacturing Process and Process Controls
  - 3.2.P.3.4 Controls of Critical Steps and Intermediates
  - 3.2.P.3.5 Process Validation and/or Evaluation
- 3.2.P.4 Control of Excipients
  - 3.2.P.4.1 Specifications
  - 3.2.P.4.2 Analytical Procedures
  - 3.2.P.4.3 Validation of Analytical Procedures
  - 3.2.P.4.4 Justification of Specifications
  - 3.2.P.4.5 Excipients of Human or Animal Origin
  - 3.2.P.4.6 Novel Excipients

# Module 3 Content – DP sections

- 3.2.P.5 Control of Drug Product
  - 3.2.P.5.1 Specifications
  - 3.2.P.5.2 Analytical Procedures
  - 3.2.P.5.3 Validation of Analytical Procedures
  - 3.2.P.5.4 Batch Analyses
  - 3.2.P.5.5 Characterization of Impurities
  - 3.2.P.5.6 Justification of Specifications [name, dosage form]
- 3.2.P.6 Reference Standards or Materials
- 3.2.P.7 Container Closure System
- 3.2.P.8 Stability
  - 3.2.P.8.1 Stability Summary and Conclusion
  - 3.2.P.8.2 Postapproval Stability Protocol and Stability Commitment
  - 3.2.P.8.3 Stability Data

# Module 3 Content – DP sections

- 3.2.A Appendices
  - 3.2.A.1 Facilities and Equipment
    - Can be handled as a Drug Master File in the US
    - Otherwise, can be quite detailed on how the facility and equipment is controlled and fit for purpose
  - 3.2.A.2 Adventitious Agents Safety Evaluation
    - BSE/TSE or other infectious agents
  - 3.2.A.3. Novel Excipients
    - Rarely used, but allows a placeholder if necessary
- 3.2.R Regional
  - Catch all for everything else a specific market requires.
  - CoAs, vendor reports, signed letters, etc.



# New Registration Process

- Varies by country/Market
- US New filings generally take 1-2 years for approval depending on how novel the formulation is, the clinical data, and the availability of alternative treatments, and the number of queries from the particular reviewer(s).
  - Emergency Use Authorization can fast track – used for Covid Vaccine
  - May vary for small molecules versus biologics
- US, Japan, EU, China, Brazil all have major review units. Many other countries require an approval in a major market first, and then have their own 1-2 year review
  - While initial approval in a market is a milestone, full market penetration takes years

# Existing Product Variations

- Large amount of work is involved in keeping existing registrations active
  - Annual reports or period renewals
    - Require updated information such as batch data and stability as well as a summary of any minor changes
  - Administrative changes (Annual report, Type IA)
    - Company name changes, site address changes
  - Minor quality changes (CBE0/30, Type IB)
    - New supplier of a raw material, addition of an improved assay test, batch size increase
  - Major quality changes (PAS, Type II)
    - New container closure, reformulation, new synthetic route

# Examples of Variations

- Change in excipient from lactose to sucrose filing in EU in 2019. Still awaiting approvals on ~10 markets out of >100.
  - Site still forced to manufacture lactose containing product.
- Change in HPLC release method from old LC to newer UHPLC
  - Newer method separates impurities that were previously co-integrated
    - Some markets accept historical evidence indicating the impurities have always been there and are safe
    - Other markets require significant additional work on safety and toxicity of the newly visible (but always present) impurities

# Parting thoughts on Regulatory

- Complying with regulatory requirements is burdensome, but also has many benefits
  - helps ensure drug safety by ensuring detailed clinical and CMC information is available.
  - Prevents fly by night, low quality, and financially insecure entities from market entry
  - Regulatory submission expertise can be a competitive advantage no different than scientific innovation
- Also has drawbacks in the form of time and cost implications to the innovators
- Numerous firms exist to help smaller firms and startups navigate this landscape.

Questions and Discussion of the  
regulatory process?