PDA Mountain States Chapter Webinar: cGMPs for Gene and Cellular Therapies

Jul 16, 2020
11:00 AM - 12:00 PM | MST

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Connecting People, Science and Regulation®

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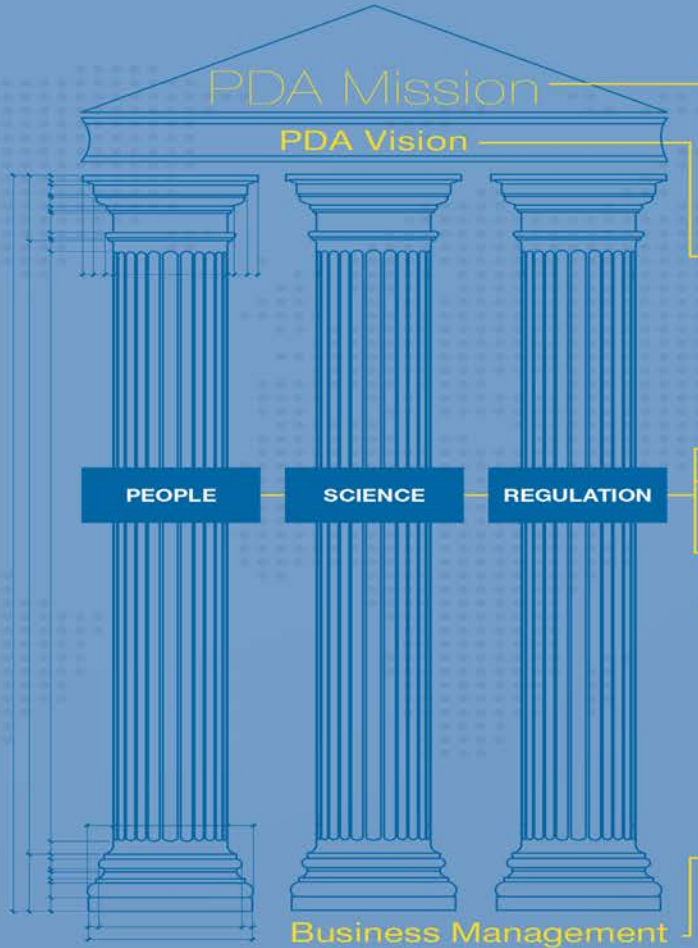

MISSION
To develop scientifically sound, practical technical information and resources to advance science and regulation for the pharmaceutical and biopharmaceutical industry through the expertise of our global membership

VISION
To be the foremost global provider of science, technology, and regulatory information and education for the pharmaceutical and biopharmaceutical community

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- **PEOPLE:** Enhance the value of PDA membership
- **SCIENCE:** Be recognized as a leading organization for manufacturing science, quality and innovation
- **REGULATION:** Our regulatory activities are scientifically and technically focused, and current information is communicated to our members

BUSINESS MANAGEMENT: Enhance business processes to provide a solid foundation and organization to sustain PDA's people, science and regulation strategies

The Mountain States Chapter of the Parenteral Drug Association (PDA) was established to provide learning and growth opportunities for scientific and technical individuals in the fields of biotechnology, pharmaceutical, and medical devices.

The Chapter provides opportunities for members to participate in educational events, peer networking, and other opportunities.

We encourage industry professionals into our membership and are open to suggestions that increase the knowledge and skills of our existing members.

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GMPs for Gene and Cellular Therapies

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Principal Consultant, Parexel

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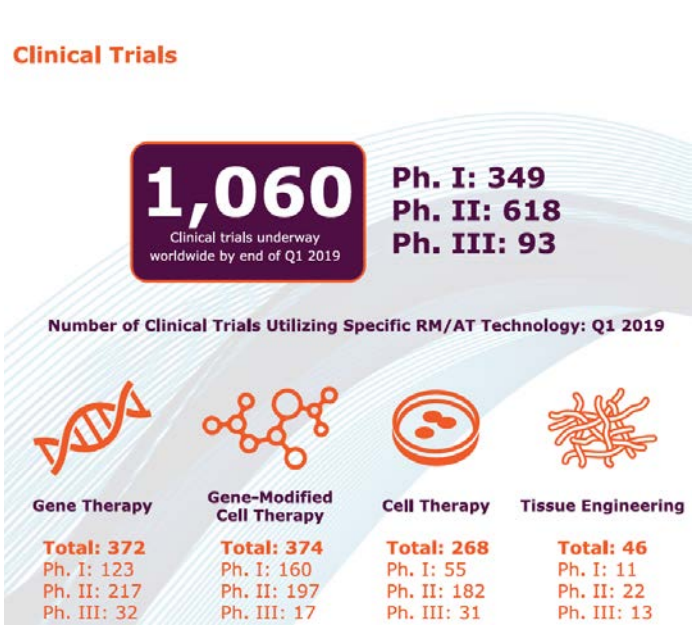
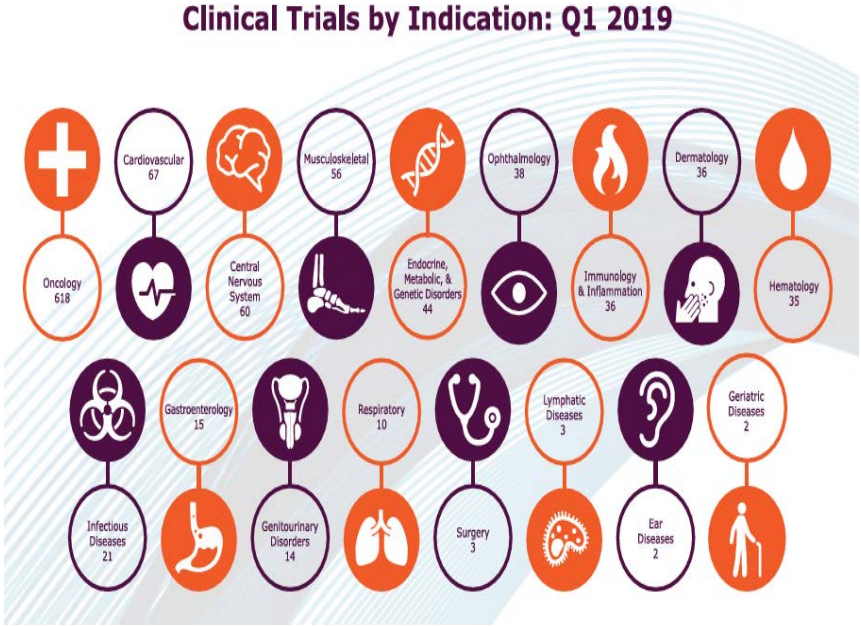
Regenerative Medicine





Quarterly Regenerative Medicine Global Data Report

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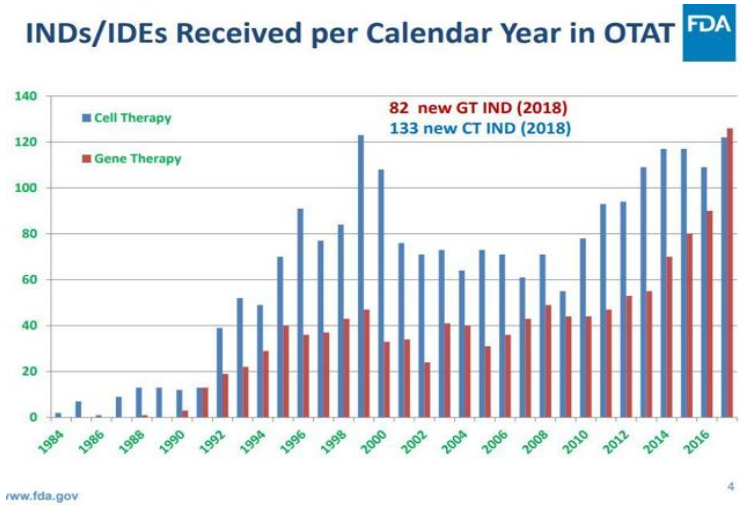
General Trends

- Remarkable **growth** in cell and gene therapy products
  - Oncology and inherited genetic disorders
- **Orphan** drug products
  - Small addressable market size for ground breaking technologies
- Potential for **curative** products
- **Flexible** Interpretation of existing regulations
- **Innovative** Trial Design
  - Single arm, small patient population, ethical considerations
  - Large treatment effects

- **High risk, high** benefit scenarios (risk mitigation strategies)
- **Manufacturing** remains a major hurdle



Source: FDA.gov

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The Accelerated Development Pathways

Breakthrough designation (BKT)
("based on substantial clinical data")

Regenerative advanced therapy designation (RMAT)
("based on preliminary clinical data")

Fast track designation
("can be based on animal data")

Accelerated approval

Orphan drug designation
Technically is not an Expedited Program
(any time before BLA submission)

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Expedited Programs

	Fast Track (FT)	Breakthrough Therapy (BT)	Regenerative Medicine Advanced Therapy (RMAT)
Criteria	-Serious condition AND -**Nonclinical** or **clinical** data demonstrate the **potential to address unmet medical need** Note: Information to demonstrate *potential* depends upon stage of development at which FT is requested	-Serious condition AND -Preliminary **clinical** evidence indicates that the product may demonstrate **substantial improvement over available therapy** on one or more clinically significant endpoints	-Serious condition AND -Preliminary **clinical** evidence indicates that the product has the **potential to address unmet medical need** Note: RMT include cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using such therapies or products (gene therapies, including genetically modified cells, that lead to durable modifications of cells or tissues)

	Fast Track (FT)	Breakthrough Therapy (BT)	Regenerative Medicine Advanced Therapy (RMAT)
Features	**Frequent meetings** Frequent written communication Eligibility for *: ✓ **Accelerated approval** ✓ **Priority review** **Rolling Review** *if relevant criteria are met	**All of FT Features +** ✓ **Intensive guidance** on an efficient drug development program, beginning as early as Phase 1 ✓ **Organizational commitment**	**All of BT Features +** ✓ **Early interactions** to discuss any potential surrogate or intermediate endpoints ✓ Statute addresses potential ways to support **accelerated approval** and satisfy post-approval requirements

CMC Readiness for Expedited Programs

- Approximately **100 BKT and RMAT** Designations
- Most **BKT** Designations (**Gene Therapy**)
- Most **RMAT** Designations (**Cell Therapy**)
- **CMC readiness** is not criteria for RMAT and BKT designation
- **Expedited program designation** is decided based on potential or substantial **clinical** benefit to patients who have **serious and life threatening** conditions
- Most expedited designations (RMAT) are awarded during very **early phase**-sometime designation is requested at the same time as IND is submitted.
- Minimal Requirement is to have an **active IND**
  - However, **minimal readiness** for initiating IND may not be sufficient demonstration of product readiness for receiving expedited designation

- Expedited programs are designed to **accelerate clinical development**
- Typically manufacturers plan to **shorten time to approval** by conducting **pivotal trials**
- **Lack of CMC readiness** delays expedited clinical program
- FDA can and have **rescinded BKT designation** due to lack of activity and readiness

https://pink.pharmaintelligence.informa.com/PS125489/CellGene-Therapy-Manufacturing-Readiness-Urged-As-A-Condition-For-US-Expedited-Designation

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It is Complicated and Manufacturing is Behind

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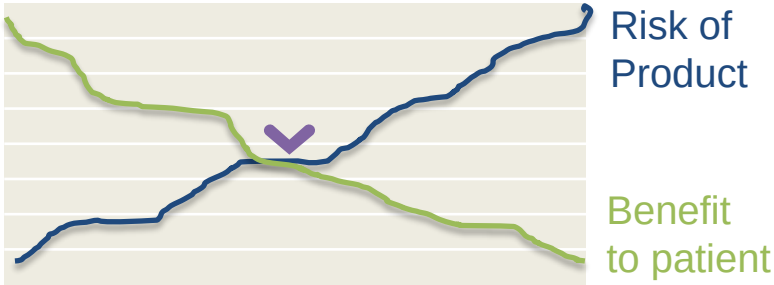
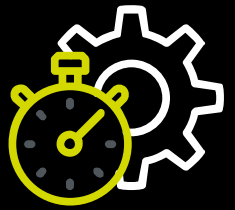
Quality Standards and CMC Requirements for Initiating IND for Expedited Programs

- Benefit to risk assessment
  - Safety considerations come first
  - Product Specific
  - Risk and science based approach
  - Institutional knowledge



IND 30-day clock:

- Cursory review
  - Is IND appropriate for submission
  - Required sections
- Gap analysis
  - Information Request
- Final assessment
  - Hold
  - Allow to proceed



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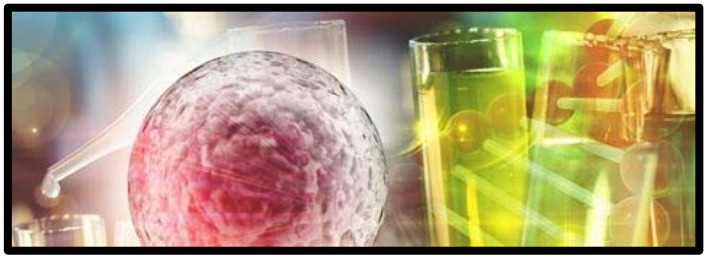
CMC Information Required by FDA for an IND

- Description of product
- Manufacturing process
- Mechanism of action
- Analytical methods qualification
- Ancillary materials (human versus animal derived)
- Master cell bank (MCB) and master virus seed (MVS) qualification
- Donor screening and testing
- In process release specifications
- Drug substance release specifications
- Drug product release specification
  - Sterility, identity, purity (endotoxin level), viability, mycoplasma if cultured and potency
  - Other list of release tests (Product Specific)
- Action plan for sterility failure when results not available prior to administration
- Container label
- Stability studies
- Shipping qualifications
- Categorical exclusion (environmental)



https://labiotech.eu/features/car-t-therapy-cancer-review/

Compliance Lifecycle Approach

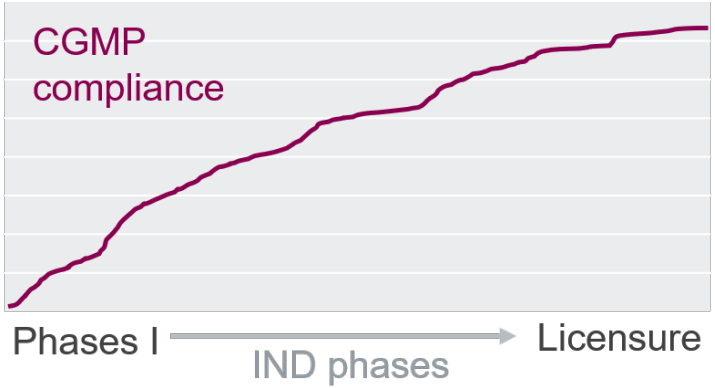
Essential elements of cGMPs

- **Manufacturing controls**
  - Prevention of **contamination** and **cross-contamination**
  - **Manufacturing consistency**
  - **Product quality**

Phase based approach:

- **Phase I** (statutory cGMPs)
- Guidance for Industry cGMP for Phase 1 Investigational Drugs (https://www.fda.gov/downloads/drugs/guidances/ucm070273.pdf)

Full **cGMPs** verified at time of pre-license inspection



Initiate FIH (Phase I)

Expedited Program

Pivotal or Licensing Trial

Licensure

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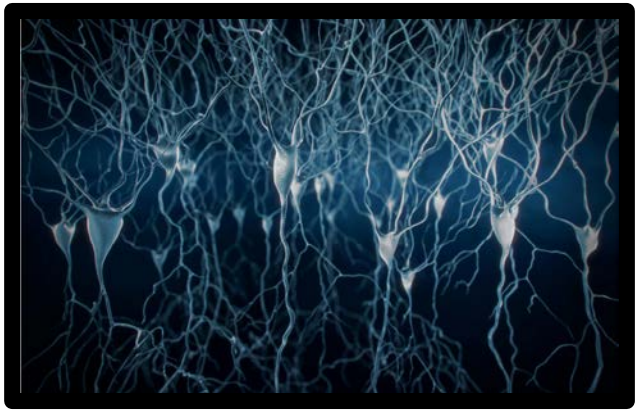
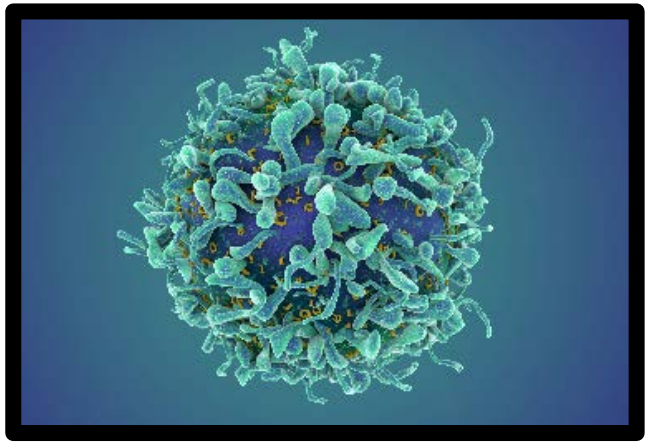
CMC Readiness for Expedited Programs



- **<u>The criteria for allowing IND to proceed focuses on safety mainly</u>**
- Receiving **expedited program designation** aims to accelerate product approval
- **Pivotal** can not be initiated without sufficient **phase-based appropriate product manufacturing control**
- CMC readiness for initiating IND **may not** be sufficient for receiving expedited program designation

CMC requirements for Expedited Programs is based on cGMPs

FDA currently considers and **may accept** clinical data generated for a **comparable product** not manufactured by the sponsor/requester (**assumption is that product manufactured by sponsor** is **comparable** to product evaluated by others referenced parties).



- Product Manufacturing should be in state of control
  - **Manufacturers should meet** the following criteria for expedited programs in addition to fulfilling the minimal requirements for initiating an IND.
    - Knowledge of **CQA/CPP and KPP**
    - Provide evidence of **manufacturing consistency at pilot scale**
      - Pilot scale process **represents the commercial scale**
      - **Qualification of the process** is necessary at minimum
      - **Release specifications** which **reflect product quality** based on empirical evidence
    - **Qualified/validated critical assays** (Potency assay)
    - **Supply chain** quality considerations
    - Plan for **manufacturing process change** and **manufacturing site change**

Consistent and High Quality Product Manufacturing

Knowledge of product:

- How it works?
  - Mechanism of action (MOA)
- What is the product?
  - Target product profile (TPP)
- Critical quality attributes (CQA)
- Critical process parameters (CPP)
- Risk assessment

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Performing a Risk Assessment

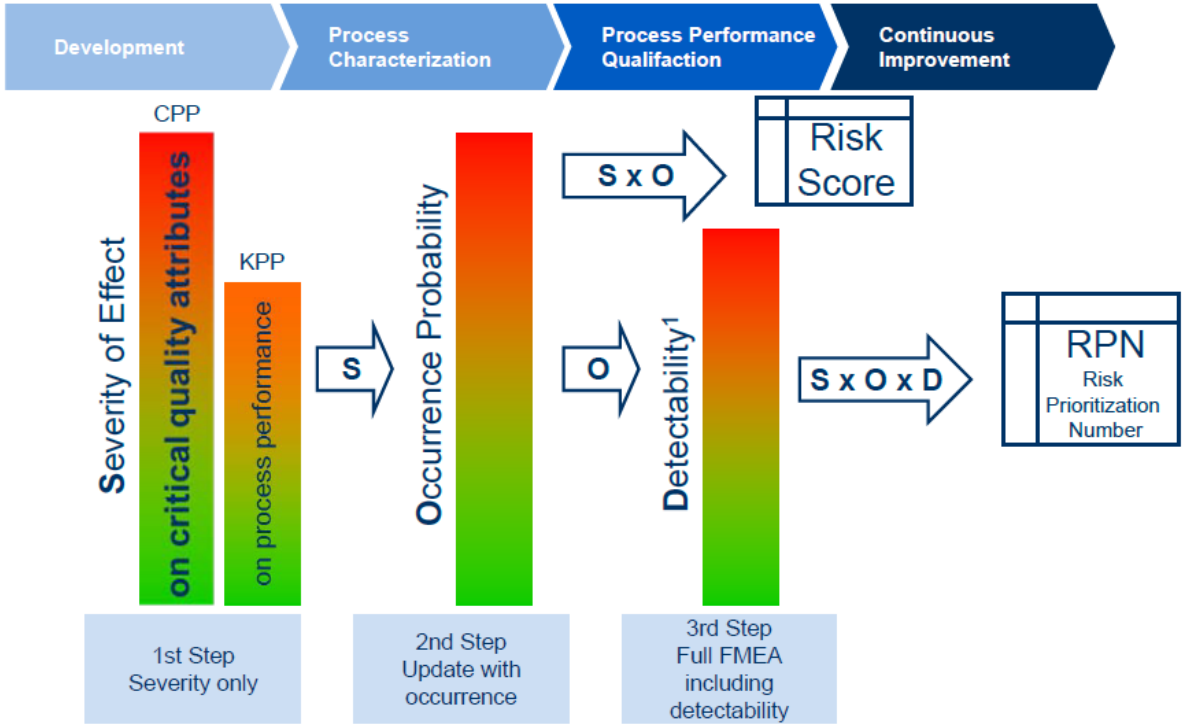
Risk assessment links the **CQA and CPP** with the product quality

- Risk assessment is **not a good substitute** for lack of product knowledge
- It is **science based**
- It is **performed early** in product development cycle and **repeated** when additional knowledge of product becomes available
- Risk assessment **tools** are found in ICH Q9
- For **expedited programs** manufacturers should have adequate knowledge of candidate **CQAs, CPP and their relationship to product quality**.

Stepwise FMEA for process risk assessment

Scoring severity, occurrence and detectability for each process parameter

Life cycle approach of the process risk assessment



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Elements in Biopharmaceutical Development

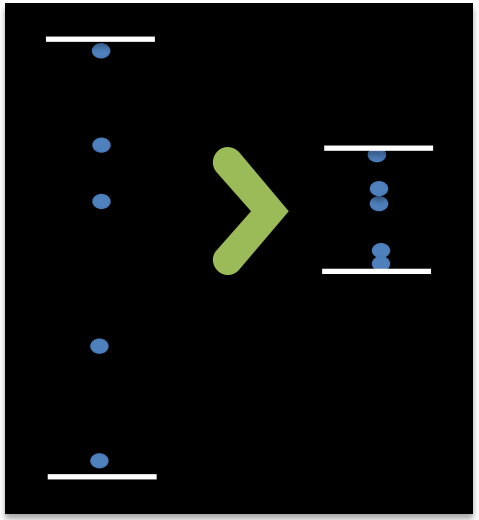
- Establish Quality Target Product Profile – the QTPP forms the basis of design for development of the product
- Determine Critical Quality Attributes – linking quality attributes to clinical safety and efficacy
- Linking process parameters and critical material attributes to CQAs – Definition of critical process parameters (CPPs)
- Optional: Define the design space – (multivariate) acceptable process parameter ranges
- Design and implement control strategy using risk management e.g. by linking CQAs to process capability and detectability
- Manage product life cycle, including continuous process verification and continual improvement

Specifications and Analytical Method Development

Specification are test method(s), procedures and acceptance criteria

- Define **specifications** as a range with **lower and upper limit**
- The boundaries are defined based on **historical data** and **inherent assay variability**
- Throughout **clinical trial identify** sources of **process** and **assay variabilities** to better define the acceptable range
- For expedited programs **specifications** should be reflective of product's candidate **CQAs (Identity, Purity and Potency)**

Example:



Analytical Assays

Qualification

- Demonstration that an assay is **suitable for measuring the analyte**
  - **Sensitive**
  - **Accurate**
  - **Reproducible** (identical sample measured at two different time in same lab give similar results)
  - Requirement for **Early Phase** for all **critical analytical methods**
  - If **compendial methods** are used you must follow the **sampling requirements**

Validation

- Demonstration that assay is **suitable for the intended use under worst condition** of use
  - **Sensitive**
  - **Accurate**
  - **Precision**
  - **Robustness**
  - **Ruggedness**
  - Assay gives similar results when identical samples are tested in **different labs**, by different **operators**

Potency Assay

- Potency assay the **most important assay**
- It is laborious and **difficult to qualify/validate**
- FDA recommends developing potency assay as **early as possible** by **evaluating multiple assays**
- Potency assay is **required to be validated for licensure**
- Should be guided by **MOA**
- Potency assay is defined in **21 CFR 600.3(s)**
- Defined as a biological assay which could be ***in vitro*** or ***in vivo*** that measure specific activity of the product
- A **qualified potency assay should be in place for INDs** with **expedited program** designation.

Supply Chain Considerations

Raw materials, ancillary materials, equipment, containers

- **Source material collection equipment**
- **Media and growth factors, others**
- **Manufacturing tools (flask, bags etc.)**
- **Container closures (bags or vials)**
- **QC test platforms**

- **Grade of materials** (cGMP) alone is not sufficient to ensure quality
- **Shipping, and storage** conditions are sometimes challenging

- **Material qualification**
  - Verify safety, identity, purity and potency
  - Certificate of analysis is not necessarily sufficient
  - Quality (fit for purpose) and reliability
  - Regulation requires that manufacturers test the incoming materials for **identity**
- **Vendor qualification**
  - Vendors of critical materials should undergo a routine qualification process which may involve audit and/or verification of their good manufacturing practices
- **Quality agreements**
  - Manufacturer should have a quality agreement in place with key vendors particularly those that perform contact manufacturing. This agreement defines the relationship between the manufacturer and contract manufacturers
- **Alternative sources (supply chain uncertainty)**
  - Determine long term sustainability of the supply
  - Determine potential alternative sources

Plan for Manufacturing Changes

Process change is inevitable

- Scale up scale out
- Automation
- Change of critical reagents
- Manufacturing site change
- **Sponsors are ultimately responsible** to plan for change, report the change and demonstrate **product comparability** as needed

- **Product comparability** is intended to demonstrate that a change in process does not adversely impact product quality.
- Demonstrate product before and after change are **similar** not identical
- ICH Q5E states that **comparability** can be established using ***in-vitro* or non-clinical study**. In some cases if *in-vitro* or preclinical studies are **not sufficient** then additional clinical study may be required.

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Tools for establishing comparability

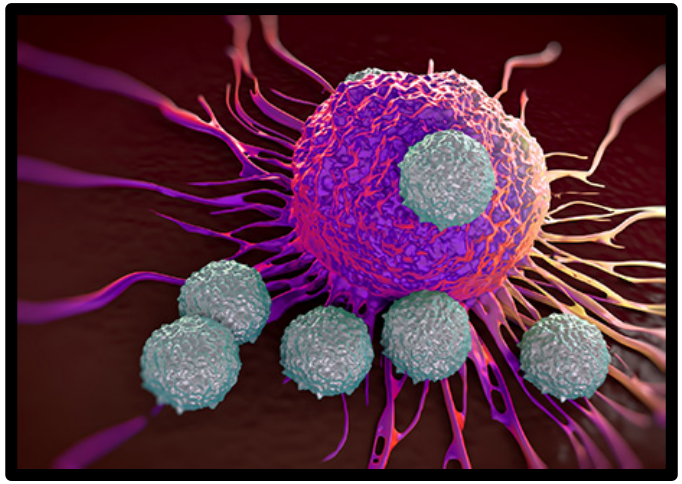
If **CQA/CPP** are well known and a correlation between **CQAs** and **product quality, safety and efficacy** can be demonstrated then testing of the product CQA **before** and **after** change may be sufficient using a **predetermined acceptance criteria for comparability**

If knowledge of CQA/CPP is **not complete** then a matrix based approach is recommended

- **Compare** all relevant **product attributes before** and **after** change (full/extended characterization)
  - **In-process** and **final release**
  - Comparing release specifications for the product before and after change **may not be sufficient**
- Manufacturing **yield** consideration
- Control of key process parameters (**KPP**)
- **Risk assessment**
- **Process qualification/validation** ensure consistency of product after major changes are introduced

Comparability study points to consider

The more reflective **CQAs** are of **clinical outcome**, the easier it is to establish product comparability

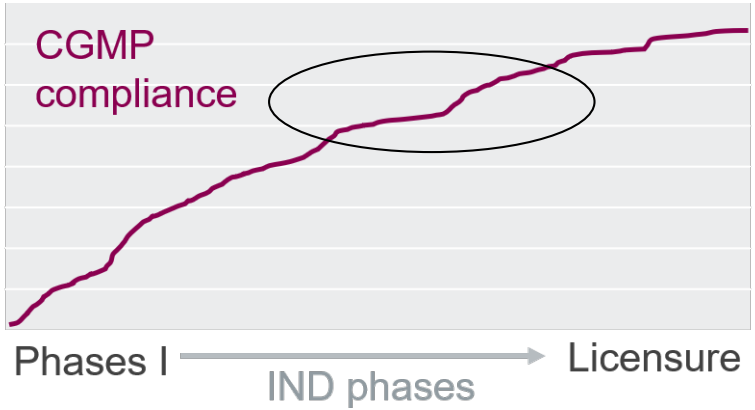


Essential aspects of the **comparability study**

- A description of proposed change
- Risk assessment
- A rationale for the proposed changes
- Comparability study designs
- Ranking of critical attributes for product safety and activity
- Comparative assessment of quality attributes before and after change
- Side by side comparison using the same biological source material is preferred
- Justification for a well defined acceptance criteria for establishing analytical comparability
- Detailed analytical procedure, sample plan and statistical method and analysis

CMC requirement for licensure

- Compliance with full **cGMP** is verified at time of licensure
- **Planning** for full cGMP compliance must start ideally **before licensing trials and continue thereafter**



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Common BLA review issues

- Lack of adequate **process validation/plan**
- Lack of sufficient **stability**
- Lack of proper **validation** for **analytical procedures**
- Insufficient information **Extractables and Leachables**
- Inadequate **SOPs**
- Lack of **retention samples**
- Lack of s**hipping validation.**
- Inadequate **donor eligibility** determination
- Insufficient information about **CQA/CPP**
- Lack of **container closure integrity** test
- Lack of validation of **starting biological material collection**
- Lack of detailed information about **formulation**
- Lack of validation of dilution or thaw and wash step at **clinical site**
- Inadequate **instruction for use**
- Deficient content of **label**

Examples of Inspectional Issues

- Inadequate **Quality Systems**
- Incomplete **process validation/plan** and **validation aseptic processing** (APV)
- **Batch record documentation**-lack of detailed process description
- Inadequate **material qualification**-lack of identity test for incoming materials
- Inadequate **contamination** and **cross-contamination** controls
- Inadequate segregation and **quarantine**
- Inadequate **SOP, change controls, investigations**
- Inadequate chain of **custody/chain**
- **Maximum manufacturing capacity** has not established

Preparing for Licensure

- **Validation of collection of materials** (Starting Material Qualification)
- Performing **extractables & leachables** studies
- Measuring **particulates** in the final drug product (inherent, intrinsic and extrinsic)
  - Conduct **risk assessment**:
    - Identify types of particulates and potential **source of particulates** in the final drug product
    - **Reduce introduction** of particulates in the final drug product
      - Control **manufacturing environment**
      - Control **introduction of particulates by components** specially containers with direct contact with product
      - **Develop tests for** measuring and monitoring visible and subvisible particles in cell and gene therapy products

Preparing for Licensure

The **final drug product** should be in a **single final container** if possible

- The **container quality** should be verified
  - Vendors of the final container commonly perform tests to **assess sterility, pyrogenicity, particulates and L&E studies** (Choose vendors that have performed comprehensive studies).
- **Fill and finish** are to be conducted in **ISO 5** environment
- **Aseptic process validation** is required
- The container should be **transparent** allowing **visual inspection**
- **Sampling from final container** should be possible

Process Qualification for Expedited Programs

Process Qualification for cell and gene therapy product is very challenging

- Manufacturers continuously introduce **changes to manufacturing**
- **Process Qualification** should provide evidence that a product can be **manufactured consistently** according to a **predetermined specifications** that are **reflective of product quality**

Recommended approach for process qualification

- **Complete major manufacturing changes** prior to process qualification if possible
- Process Qualification based on **critical unit operations** is recommended
- Process Qualification using **pilot/engineering runs** could be achievable if the pilot run process **represents the final process**.

https://www.fda.gov/media/71021/download, LA Times Aug 30, 2017

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Preparing for Licensure

Aseptic Process Validation

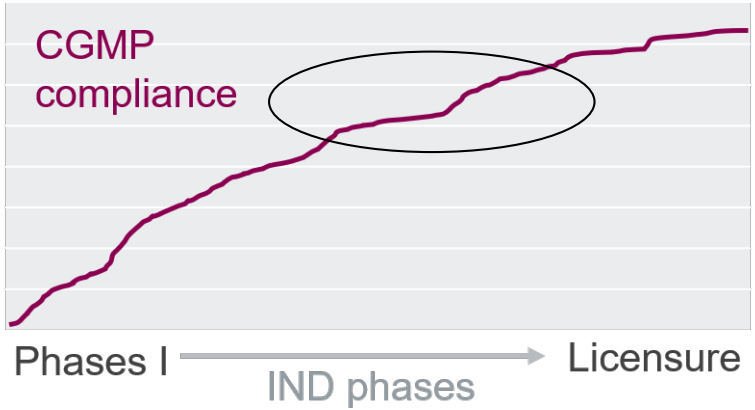
- **Media Fill** = Process simulation
- Most products **except for vector, viral and plasmid gene** products **cannot be sterile filtered**
- Therefore quality has to be established by demonstrating state of control (APV)
  - **Prevention of contamination from environment and operators**

Regulatory and Compliance Convergence

- In **cell and gene therapy** space transition from **academic to cGMP** like product manufacturing is challenging (Phase1/II to Pivotal/Phase III)
- **Commercial scale** manufacturing is usually targeted for entry into **pivotal studies**.
- **Virtual companies** consider **commercial manufacturing** as critical part of their **due diligence**
  - Selection of **in-house versus CMO**
  - **Criteria** for selection of CMO
  - Criteria for selection of facilities that **collect starting biological materials**
- **Selection** of **CMO** or **Procurement Facility** (Manufacturing and Material Collection)
  - **Quality Oversight (Quality System)**
  - **Material Supply Management**
  - **Donor Eligibility**
  - **GTP versus GMPs**
- **Technology Transfer**
- **Facility Audit** for determining Manufacturing **Controls and Compliance**
- **Inspectional readiness** for Prelicensure Inspection

Regulatory and Compliance Requirements for Licensure

- Compliance with full **cGMP** is verified at time of licensure
- Planning for full cGMP compliance must **start ideally before licensing trials** and **continue thereafter**
  - BLA review considerations
  - Inspectional considerations



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QUESTIONS

Thank you

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- Long term follow up After Administration of Human Gene Therapy Products
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- ICH Q2(R1) – Includes Validation of Analytical Procedures
- ICH Q5E – Includes concepts of comparability and how to establish comparability
- ICH Q6 – Includes concepts of quality standards, acceptance criteria and specifications
- ICH Q8 – Pharmaceutical Development:
- Includes concepts of critical quality attributes and critical process parameters
- Includes concepts of Quality by Design and examples of design space
- ICH Q9 – Quality Risk Management
- Describes a systematic process for the assessment, control, communication and review of quality risks
- ICH Q10 – Pharmaceutical Quality Systems
- Describes systems that facilitate establishment and maintenance of a state of control for process performance and product quality