Carl Bermingham

nibrt
National Institute for Bioprocessing Research and Training

Lecture 2: Product Characterisation, Clinical Trials, and Initial Process Development

Written Assessment

Answer BOTH of the below:

- **Part 1 (70%).** Elaborate, in detail, on a typical sequence of process validation activities (from product development to validated process) for a biopharmaceutical product. Give reference to modern best practices, guidances, industry advancements, etc.

- **Part 2 (30%).** Compare and contrast the process validation requirements for a traditional, stainless-steel bioprocess versus a single-use/disposable technologies bioprocess.

Notes:

- You must provide references to support your writing. **Lecture notes cannot be used as references. You will need to research papers/articles/regulatory guidelines to use as references.**

Written Assessment

- 3,000 - 3,500 words - **references/bibliography not included in word count.**
- **You must reference the information in your work. Use Harvard referencing. You will be marked on referencing.**
- If you are not familiar with referencing make sure to look it up online.
- **You cannot use the lecture notes as reference and you must use multiple reference sources to support your work.** References must be reputable sources (don't use Wikipedia).
- If you use ChatGPT/AI to write your work, you'll receive a fail
- Due April 25th 2025. 10-15 minute recorded presentation also due at this time (10%)

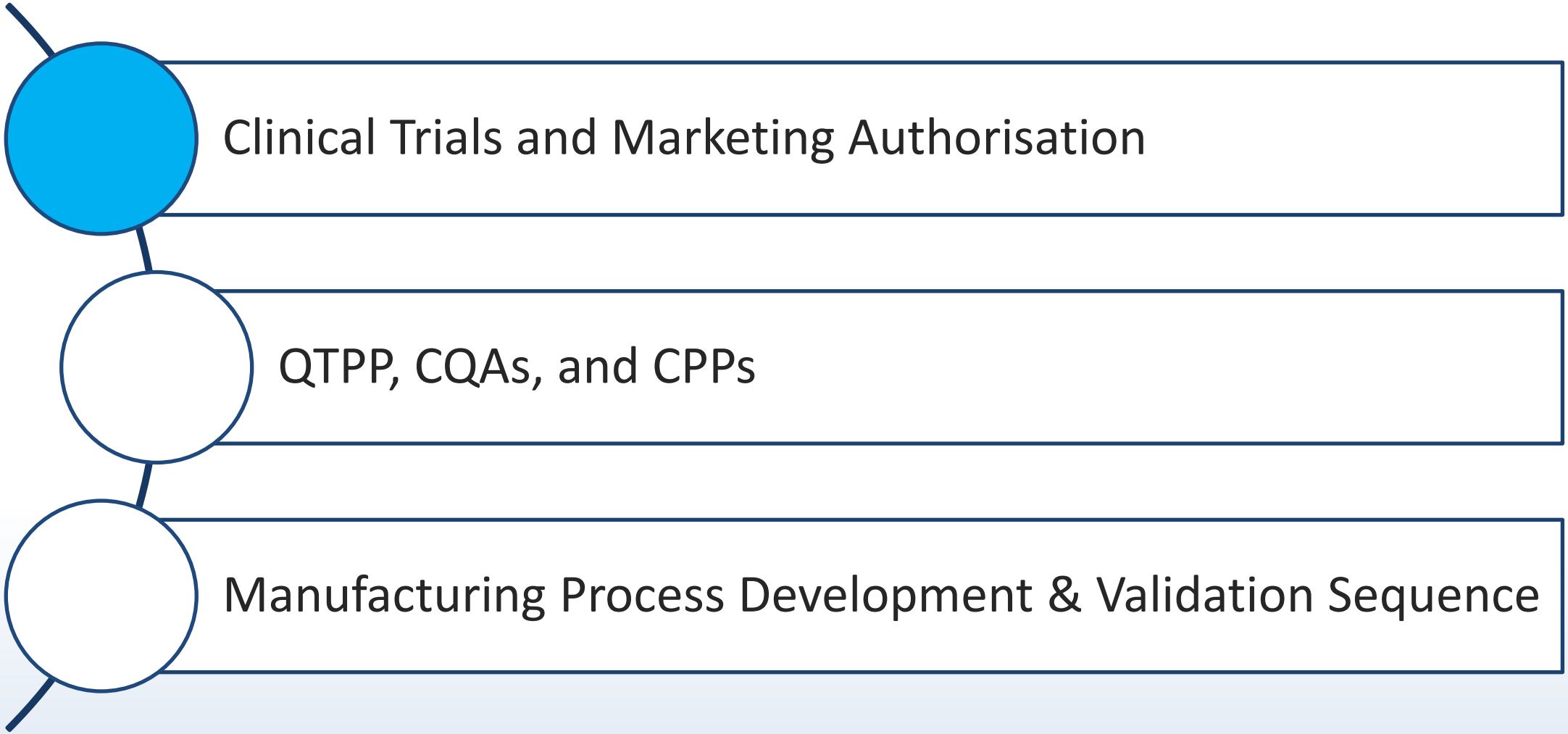
Written Assessment

- To be submitted via Turnitin – **plagiarism will be penalised.** If you are not familiar with plagiarism make sure to look it up online before beginning your assignment.
- A test link will be available where you will have **one attempt to check your work for plagiarism before submitting**. **If you use a test link from one of your other modules to get an extra attempt at checking for plagiarism this will be picked up by Trunitin. If you have already submitted the same work to Turnitin for another module this will appear as self-plagiarism and will be penalised.**

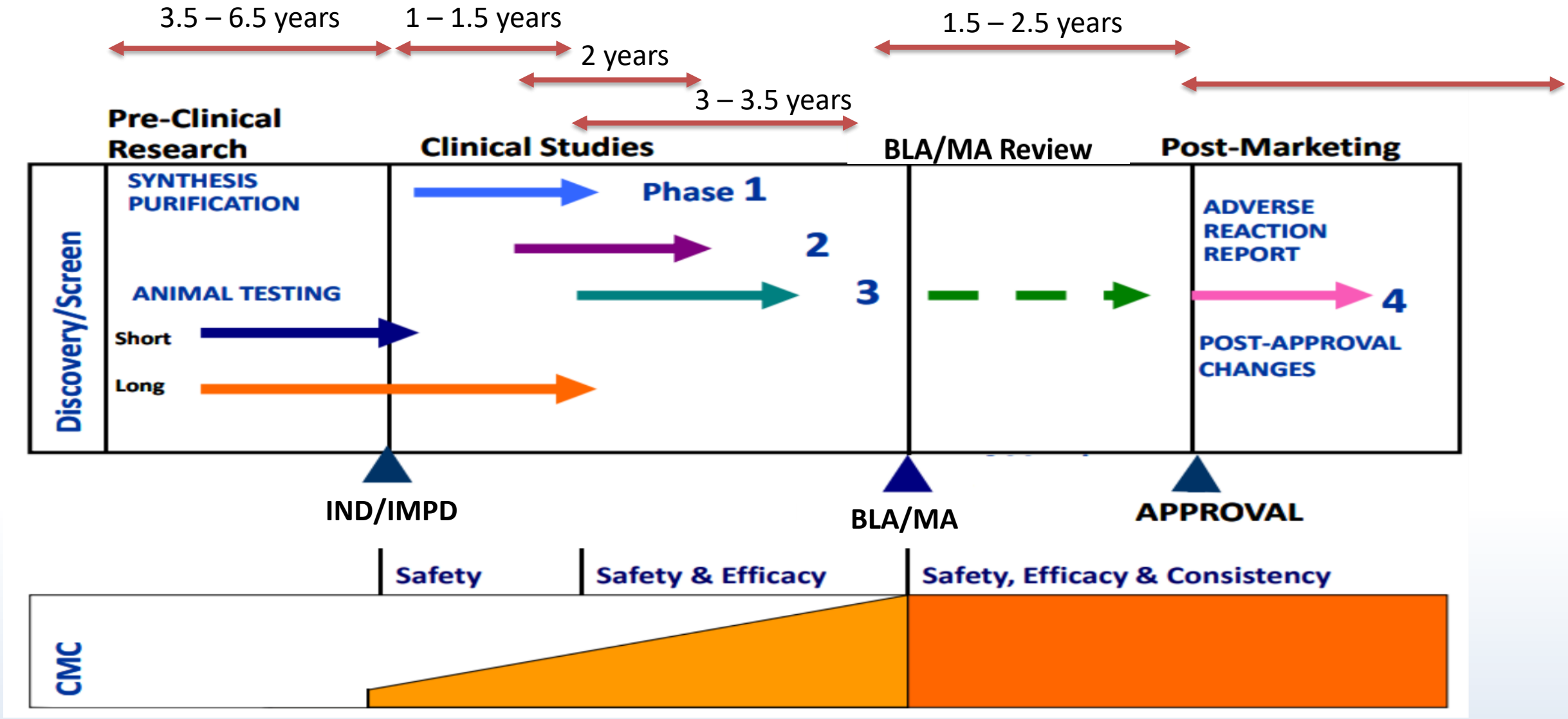
- Use diagrams/images as required. Focus on delivering an appropriately high-level of information within the given word-count

- **Due dates are final and it is your responsibility to plan for these.**

Topics


Clinical Trials and Marketing Authorisation
QTPP, CQAs, and CPPs
Manufacturing Process Development & Validation Sequence

Research to Market



Preclinical Trials

- Laboratory and Animal Studies used to determine the Liberation, Absorption, Distribution, Metabolism, and Excretion (LADME) properties of the drug.
- Assesses safety, biological activity, and drug formulation before testing in humans.
- On average, only one in every 5,000 compounds that enters drug discovery at the stage of preclinical development becomes an approved drug.
- Typically 3.5 – 6.5 years.

Clinical Trials

- Clinical Trials are a systemic investigation in human subjects for evaluating the safety and efficacy of any new drugs.

- Clinical trials are conducted only when:
  1. Satisfactory information has been gathered on the quality of the nonclinical safety studies.
  2. Health authority/ethics committee approval is granted in the country where approval of the drug is sought.

- There are four phases in the Clinical Trials process:
  1. Phase 1 – Safety
  2. Phase 2 – Proof of Concept
  3. Phase 3 – Regulatory Proof
  4. Phase 4 – Post-Marketing Safety Monitoring

Clinical Trials – Phase 1

- The first time a drug is tested in humans happens in Phase I Clinical Trials
- Healthy volunteers, or patients with the specific condition relevant to the new drug
- Typically, 20 – 80 participants, several months duration.
- Aims:
  - Evaluate the new drug's safety, alone and when given with another drug
  - Determine a safe dose range
  - Identify any side-effects
  - Detect early proof of the drug's efficacy if used in patients with the disease.

Clinical Trials – Phase 2

- Test the efficacy of the drug in patients with the disease or condition that the new drug is supposed to target.
  - 100–300 participants, approximately 2-year duration.

- Aims:
  - Identify the correct effective dose
  - Identify any typical short-term side effects
  - Identify the best experimental protocol/dosing regime that should be used in larger Clinical Trials.
  - Initial POC : the drug does what it is supposed to do (i.e. correct & effective molecular target interaction)

- Additional info:
  - commercial formulation development – initial manufacturing development – stability studies performed

Clinical Trials – Phase 3

- Confirm & verify that the new drug is beneficial and safe in a large, targeted patient population (with the disease)
  - 1000-3000 participants, 3 to 3.5-year duration

- Aims:
  - Confirm safety, efficacy, dosing, & look for any additional side effects
  - Compare the new drug to any commonly used treatments or placebo
  - Risk-benefit ratio of the drug
  - Good basis for labelling after approval
  - Manufacturing process, analytical methods, and commercial formulation are validated

- Success leads to marketing/licensure application/approval

Licensure/Marketing Authorisation

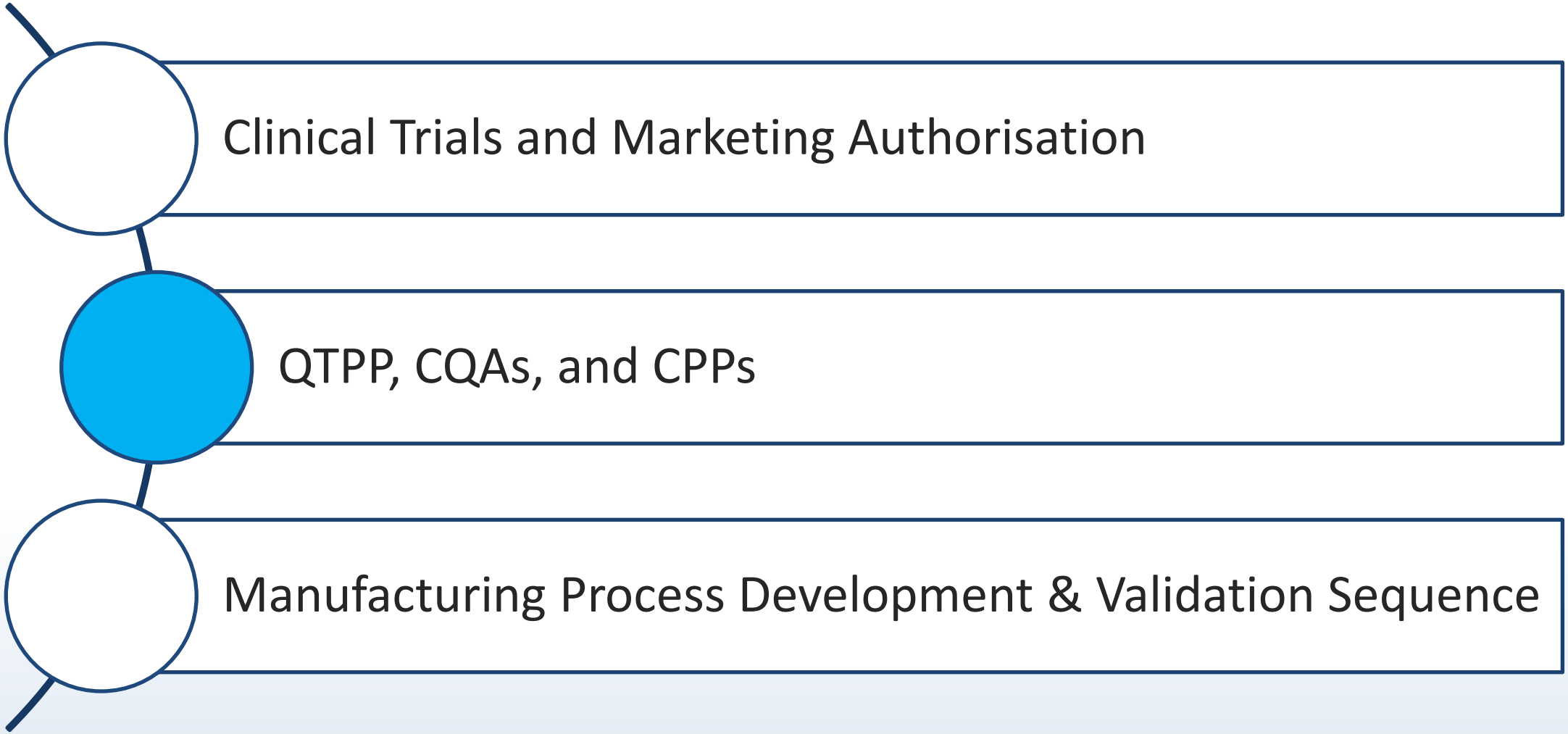
US Submission

- Before clinical trails:
  - IND – Investigational New Drug application
- For Marketing approval (after Phase 3):
  - BLA – Biologics Licence Application
  - NDA – New Drug Application (for chemical drugs)
- Approval
  - Marketing Authorisation and post-marketing monitoring/review

EU Submission

- Before clinical trails:
  - IMPD – Investigational Medicinal Product Dossier
- For Marketing approval (after Phase 3):
  - MAA – Marketing Authorization Approval
- Approval
  - Marketing Authorisation and post-marketing monitoring/review

Topics



Protein Characterisation

- Prior to commencing clinical trials, preliminary protein characterization studies are conducted, establishing and evaluating the drug's quality attributes and determining the initial quality target product profile.
- Initial reference standards for final product and intermediate materials are established.
- Evaluating the quality attributes and determination of the quality target product profile is a continuously evolving process throughout the entire product lifecycle
- Early process design experiments are conducted in accordance with sound scientific methods and principles, including good documentation practices.

Understand Your Product & Process

Identify the criteria and specifications that must be met to deem your product safe, effective, and of acceptable quality.

This determines your product's Quality Target Product Profile (QTPP)

- The labeling concepts are specified by the QTPP. The ideal version of what the manufacturer would like to claim in labeling guides the design, conduct, and analysis of clinical trials to maximize the efficiency of the development program.
- Ideally, the final version of the QTPP will be similar to the annotated draft labeling submitted with a Biologics License Application (BLA)/Marketing Approval Authorisation.

TPP Resource - FDA

Guidance for Industry and Review Staff

Target Product Profile — A Strategic Development Process Tool

Understand Your Product

- An important component of the QTPP are Critical Quality Attributes (CQAs):
  - *“chemical, physical, biological and microbiological attributes that can be defined, measured, and continually monitored to ensure final product outputs remain within acceptable quality limits”.*

- In simpler terms…
  - Which attributes/characteristics of your product are critical to its quality, safety, and efficacy?

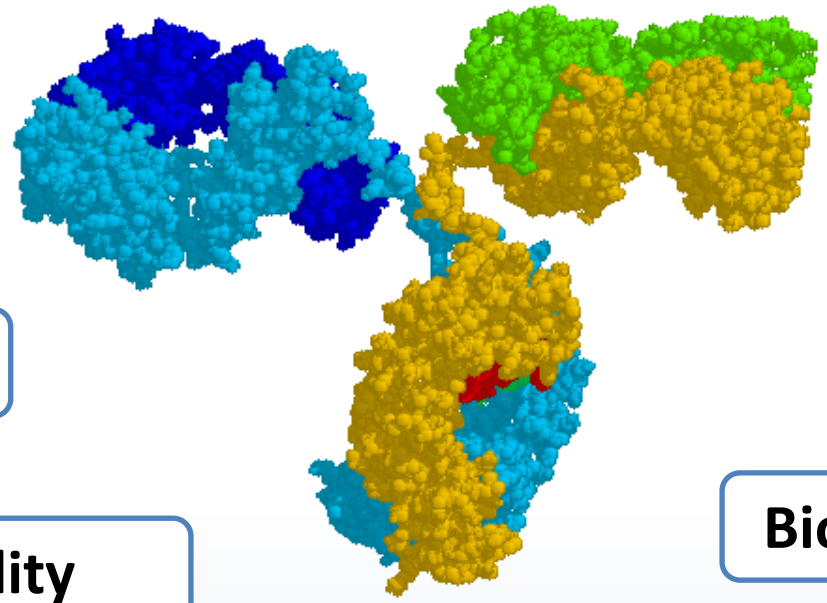
CQAs – Some Examples

Size and Shape (3D Structure)

Aggregation

Charge & Isoelectric Point

Glycosylation



Efficacy

Purity

Biological Activity

Sterility

Which **parameters** throughout the process could impact these critical quality attributes?

Parameter Definitions

- **Performance Parameter:** An output variable or outcome that cannot be directly controlled but is an indicator that the process performed as expected.
  - Example: Yield

- **Operational/Process Parameter:** An input variable or condition of the manufacturing process that can be directly controlled in the process.
  - Typically, these parameters are physical or chemical (e.g., temperature, process time, column flow rate, pH, mixing rate).

- **Critical Process Parameter (CPP):** An input process parameter that should be controlled within a meaningful, narrow operating range to ensure that drug substance quality attributes meet their specifications.

Parameter Definitions

- **Non-Critical Process/Operational Parameter:** All input process parameters that fall outside the definition for critical process parameter are non-critical. Non-critical process parameters are divided into key and non-key process parameters.

1. **Key Process Parameter:** An input process parameter that should be carefully controlled within a narrow range and is essential for process performance. A key process parameter does not affect critical product quality attributes. If the acceptable range is exceeded it may affect the process (e.g., yield, duration) but not necessarily product quality.
2. **Non-key Process Parameter:** An input process parameter that has been demonstrated to be easily controlled or has a wide acceptable limit. Non-key operational parameters may still have an impact on drug substance quality or process performance if acceptable limits are exceeded.

Understand Your Process

- **Risk Assessments** must be carried out to determine which aspects of your process can impact the CQAs of your product. These are known as **Critical Process Parameters (CPPs).**

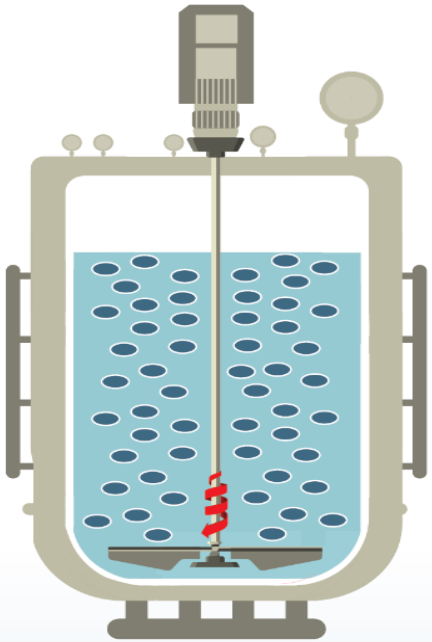
- CPPs must be **monitored and controlled** throughout the manufacturing process to ensure that their values remain within **predetermined specifications.**

- An understanding of the impact of CPP value **variation,** and the impact of CPP-CPP **interactions,** must also be demonstrated.

- There must be **documented evidence** to support this!

Process Parameters – Upstream Processing Examples

- Agitation Rate
- Medium Osmolality
- Dissolved Oxygen
- Cell Density
- Temperature
- Pressure
- pH
- Nutrients & Metabolites



The Critical Process Parameters must be determined. Acceptable operating ranges for each of these parameters must be determined to ensure that CQAs are not negatively impacted!

Process Parameters - Downstream Processing Examples

Flowrate

Conductivity

Temperature

Pressure

pH

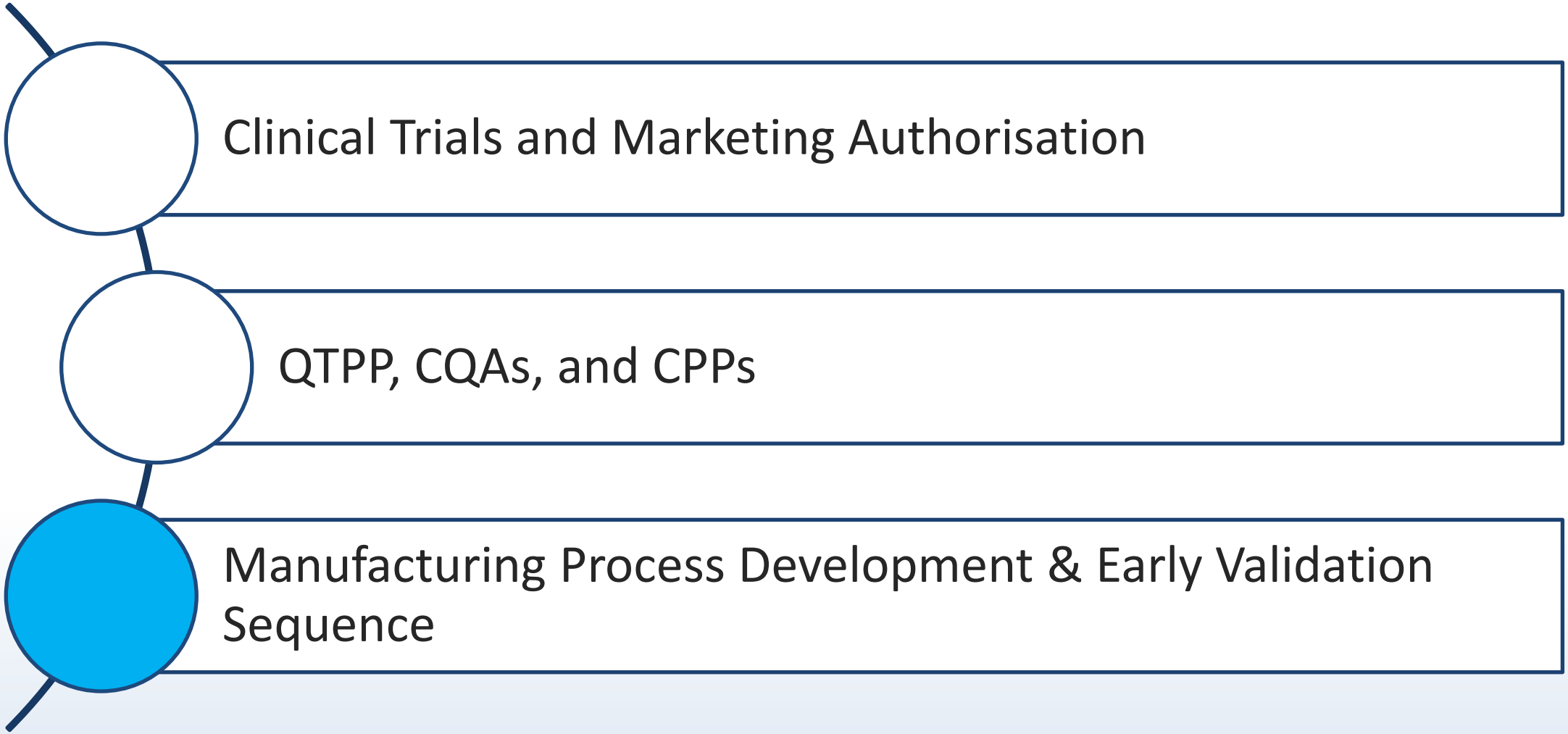
Column Load

The Critical Process Parameters must be determined. Acceptable operating ranges for each of these CPPs must be determined to ensure that CQAs are not negatively impacted!

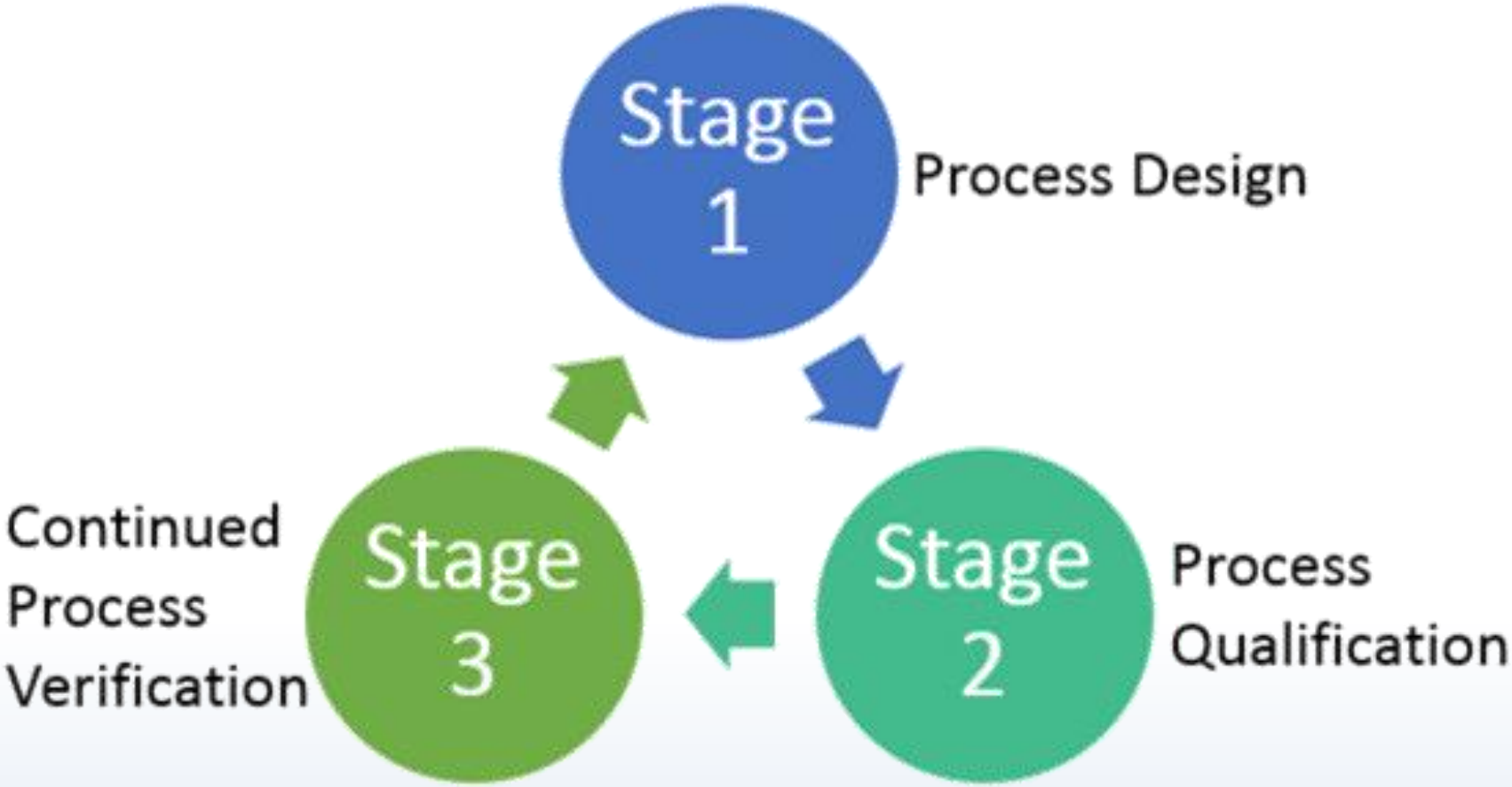
Hypothetical Parameter Summary Table

Unit Operation	Process Parameter	Unit	Parameter Type	Set Point	Operating Range	Acceptable Limits
Inoculation	Cell Density	Cells/mL	Key		0.2 – 2.0 x 10^6	0.2 – 2.0 x 10^6
	Cell Viability	%	Key			≥ 80%
Production	Temperature	^oC	Critical	37	36 - 38	35.5 – 38.5
	Agitation	RPM	Critical	30	25 - 40	≤ 45
	pH		Critical	7.00	6.9 – 7.1	6.8 – 7.2
	DO	%	Key	20	15 - 30	≤ 15
Chromatography	Column Load	g/L	Non-key	15		≤ 20
	Flow Rate	L/hr	Key	12	11.6 – 12.4	10 - 14
	pH		Critical	7.00	6.9 – 7.1	6.8 – 7.2

Topics



Process Validation Lifecycle



https://www.emersonprocessxperts.com

Preliminary Clearance of Process Contaminants

- Before Phase 1 Clinical Trials begin, studies to establish preliminary clearance of process contaminants must be performed.
- These contaminants consist of process-related impurities and product-related impurities.
- Examples of process-related impurities include host cell proteins, DNA, serum components, media components, leachables, and chromatography ligands.
- Product-related impurities include truncated forms, modified forms, and aggregates.
- Removal of adventitious agents also needs to be evaluated such as viruses, endotoxin and bioburden.

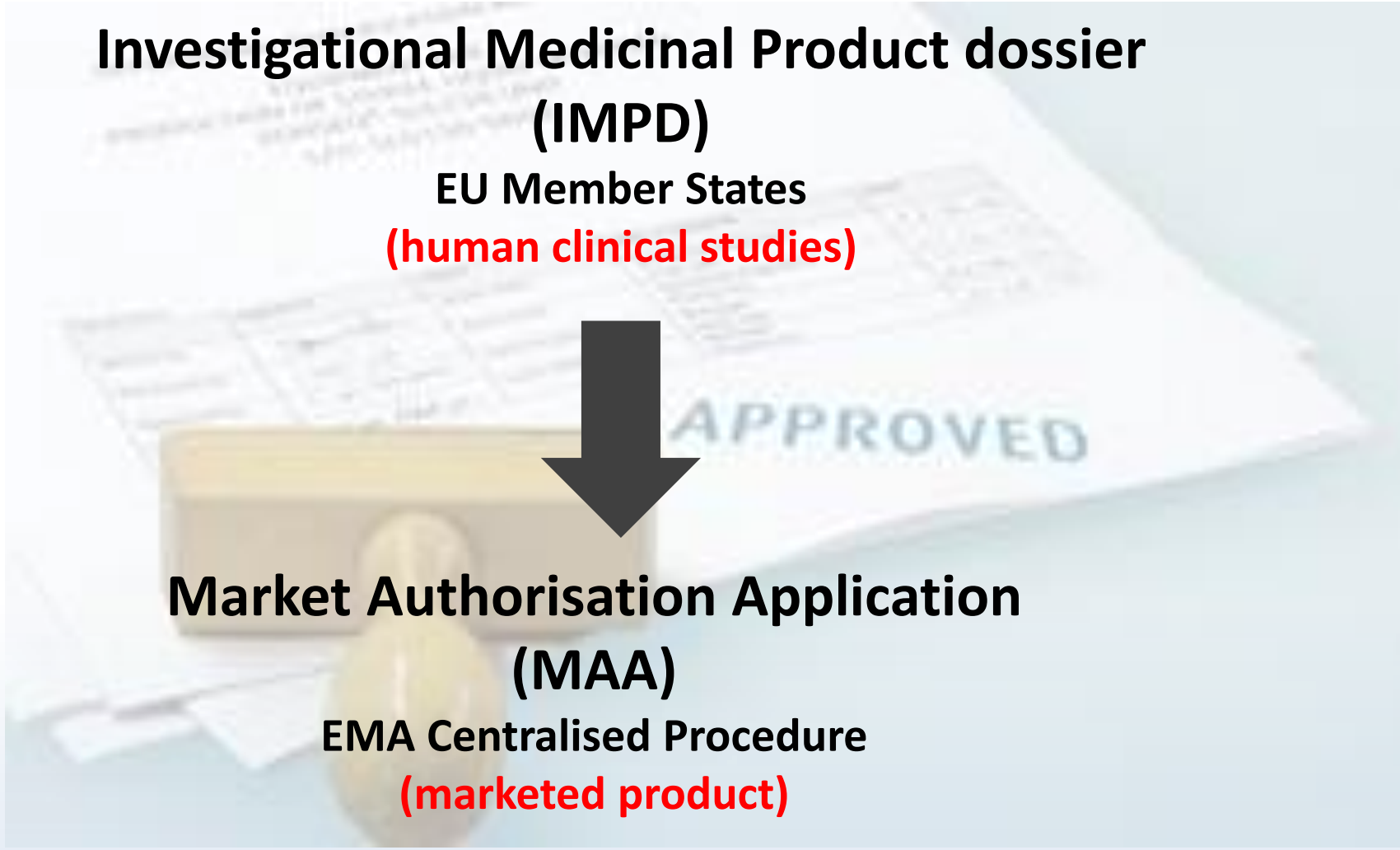
Viral and Impurity Clearance Studies

- Viral and impurity clearance studies should be performed under good manufacturing practice (GMP) conditions, in conjunction with good scientific methods and principles.
- The quality unit should be involved in impurity clearance studies from the outset.
- Studies on the clearance of process contaminants are generally conducted on scaled-down model process systems
- Studies are updated and ongoing throughout the entire development and clinical phases.
- The studies are generally completed prior to, and independent from, the manufacture of conformance lots on the full-scale commercial manufacturing system.

Clinical Trial Batch Manufacture

- Following initial Clearance Studies and pre-clinical activities, batch manufacturing for clinical trials use (not for commercial distribution!) is initiated.
- A clinical process description is generated, followed by the associated production batch records.
- Appropriate GMP concepts need to be applied, with a suitable mechanism of approval for each batch.
- Formal stability studies are also typically carried out at this stage.
- Appropriate regulatory documentation must also be submitted and approved before clinical trials can begin in humans

EU Regulatory Drug Development Pathway



Investigational Medicinal Product dossier (IMPD)

EU Member States

(human clinical studies)

Market Authorisation Application (MAA)

EMA Centralised Procedure

(marketed product)

US Regulatory Drug Development Pathway

Investigational New Drug (IND)
21 CFR 312
(human clinical studies)

FD&C Act

New Drug Application (NDA)
21 CFR 314
(marketed product)

Investigational New Drug (IND)
21 CFR 312
(human clinical studies)

PHS Act

Biologics License Application (BLA)
21 CFR 600 - 680
(marketed product)

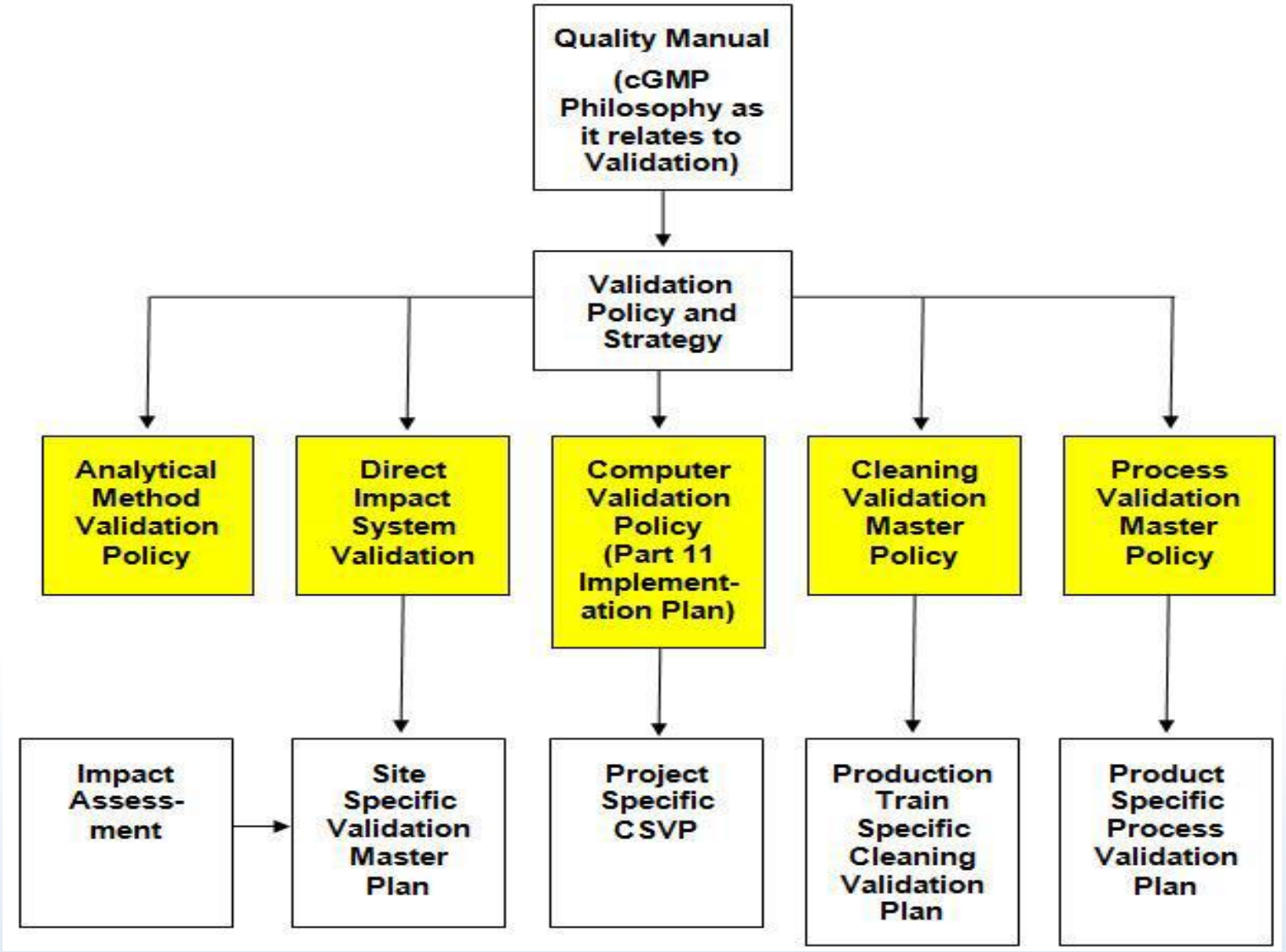
IND and/or IMP

- By this stage, the manufacturer should have submitted an Investigational New Drug (IND) application to the United States regulatory authorities, and/or submitted an Investigational Medicinal Product (IMP) Dossier for approval of clinical trials to the competent authorities in the European Union.
- Once approved, Phase 1 Clinical Trials can proceed.
- Equipment/process validation studies can begin (at small scale) in tandem with Clinical Trials activities.
- It is important that you identify which validation/development activities are necessary at each stage, and which activities it would be beneficial to begin in order to save time down the line and make process development more efficient.
- If you invest too much time and effort into validation activities in the early stages and the product fails, then this will have a significant financial impact. If you don't do enough validation activities at the early stages, then significant time may be wasted down the line to finalise process development.

Validation Master Plan

- It is recommended to commence the development of the overall process Validation Master Plan as early as possible in the drug lifecycle.
- The plan needs to be approved prior to any formal qualification studies being undertaken (midway through phase 2 clinical trials, at the latest).
- A VMP is a document that details the way a company will operate, who has control over the various aspects of the validation activities, and how production, quality control, and personnel management will be directed.
- The VMP allows companies to agree upon and document an overall validation strategy, which can be provided to regulators to serve as clear justification for the validation effort. The VMP allows manufacturers to show they are in control of their quality system and focused on quality.

Types of Validation



1. Equipment
2. Process validation
3. Cleaning validation
4. Analytical methods validation
5. Software Validation

When Should Validation Activities Begin?

PDA Technical Report #42 makes the following specific recommendations:

- *"Successful process validation begins early in the development phase of a product with acquisition of preliminary process data and knowledge".*

- *"Although formal process validation is not generally required in Phase-1 [Clinical Trials Phase-One], some exceptions are made for product safety issues (e.g., viral clearance validation for mammalian cell products)".*

Small Scale Process Studies

- From a risk and financial perspective, it makes sense to initiate process validation studies on small-scale equipment early in the drug development process, rather than invest in large-scale equipment before marketing approval is more likely to be achieved.
- On smaller-scale equipment systems, the projected full-scale commercial process can be accurately reproduced where the data generated can be compared to the full-scale commercial manufacturing equipment.
- Scaled-down models are typically used to demonstrate the clearance of contaminants.
- All significant process parameters should be maintained at constant levels.
- Chromatography example: column bed height; linear flow rate; flow rate to bed volume ratio; contact time; buffer and gel types; pH; temperature; and the concentration of protein, salt, and product should all be shown to be representative of full-scale commercial manufacturing.

Qualification Studies

- Qualification studies will also be conducted, in accordance with pre-approved protocols, on the following:
  - Process intermediate stability
  - Process solution stability
  - Drug substance fill, freeze, thaw, and storage
  - Mixing studies (product and process solutions)
  - Chromatography resin and reusable filter membrane lifetime validation

- Similar to the contaminant clearance studies, these are also completed prior to, and independent from, the manufacture of the full-scale conformance lot.

Operational Parameters and Ranges

- At this stage the operational parameters and ranges (e.g., inoculum cell density, number of generations from the working cell bank, temperature range, etc.), should have been set and the Design Space established.

- Once a process definition has been established, the commercial process description can be developed and process control strategy defined.

- From here, the commercial production master batch records can be developed.

Assay Development and Characterization

- In parallel, analytical assay development and protein characterisation studies continue. By the end of Phase 2 Clinical Trials it would be desirable to have all assays and analytical methods completely validated.

- For example
  - Validate SDS PAGE for identity and purity analysis
  - Validate carbohydrate analysis for identity analysis
  - Validate biological activity assay (or potency assay) for activity analysis
  - Qualify process impurities for process clearance analysis of cell culture components, column leachables, etc.
  - Qualify host cell protein for process clearance
  - Qualify host cell DNA for process clearance

Phase 3 Clinical Trials

- As Phase 3 Clinical Trials progress, the focus of process development can be shifted towards qualifying the full-scale commercial manufacturing plant/process that will ultimately manufacture the conformance lots.

- The remainder of the process validation protocols are developed and pre-approved as per the list of deliverables in the Validation Master Plan.

- By the end of Phase 3 Clinical Trials the protocols for small-scale contaminant clearance studies (especially viral), and the protocols for all the other independent studies should be completed and post-approved.

Phase 3 Clinical Trials & Facility/Process Validation

- It is likely that throughout Phase 3 Clinical Trials, the commercial manufacturing facility is being commissioned and qualified. In this scenario the design was probably frozen around the time of Phase 1 Clinical Trials, and construction commenced, at risk, sometime during the Phase 2 Clinical Trials.

- Ensure all qualification activities are complete prior to the manufacturing of the conformance lots.

- Confirm the real-world equivalence of the actual, installed, full-scale commercial process to the experimental and theoretical scaled-down models used during the various qualification studies, and satisfactorily explain any observed anomalies associated with natural phenomena.

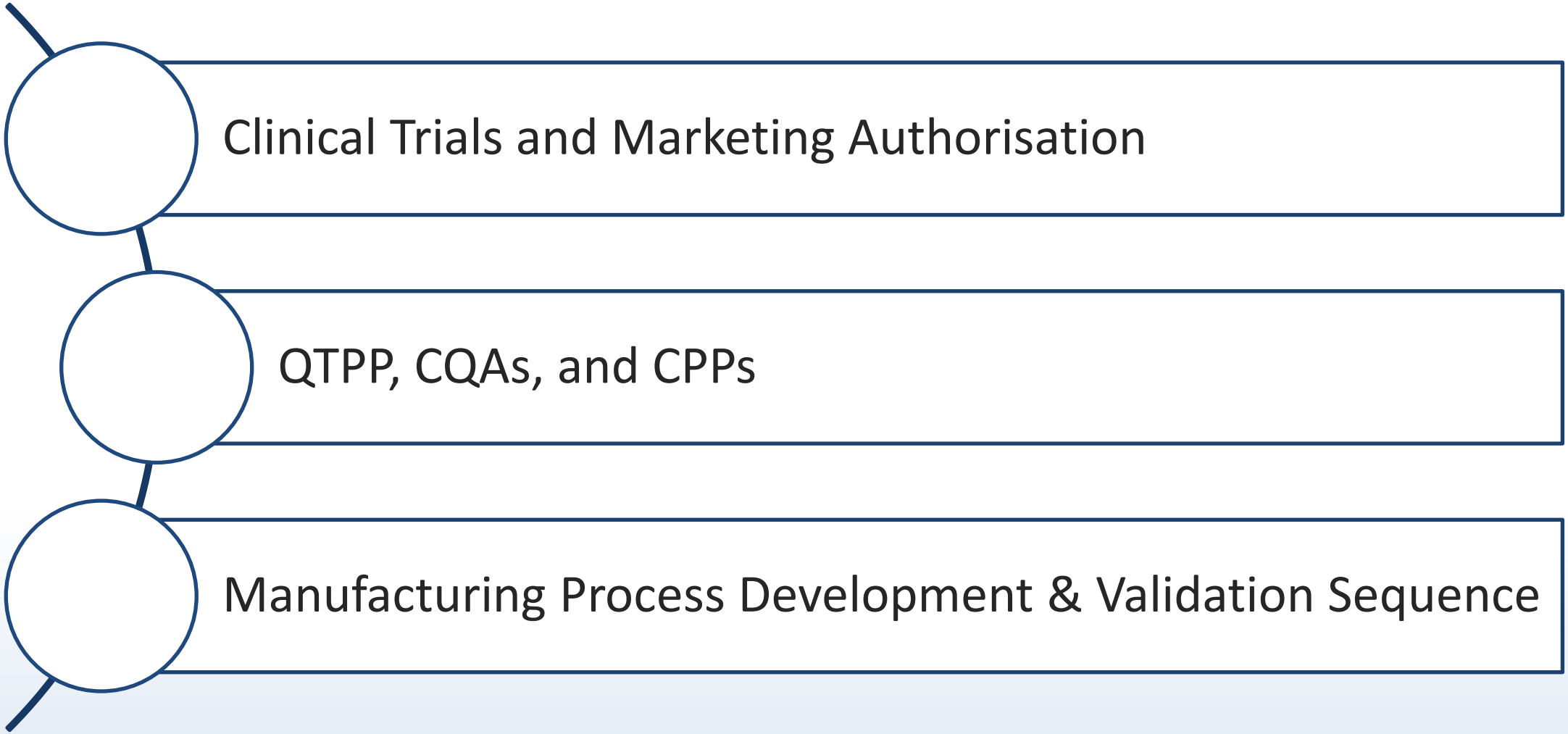
Conformance Lots

- In parallel with ongoing Phase 3 Clinical Trials, full-scale validation studies can be executed, culminating with the manufacture of the all-important conformance lots.
- These conformance lots are strictly monitored and evaluated to demonstrate processing consistency.
- By now many of the small-scale studies (and confirmatory studies at full-scale), have adequately demonstrated the clearance of contaminants.
- All Validation activities combined should now demonstrate the ability to consistently produce product (at full-scale) to meet predetermined acceptance criteria.

Licensure

- The regulatory license application should now be submitted in the form of a BLA (Biological Licence Application) in the United States, or as a MAA (Marketing Authorization Application) in the European Union, and should have passed a pre-approval inspection.
- All process validation reports should also be completed, approved, and archived.
- Once regulatory approval has been obtained (Marketing Authorisation) commercial manufacturing and distribution can begin.
- An ongoing, continued verification program consisting of process monitoring reviews and associated generation of periodic reports should be implemented.

Topics



Thank You