Staying on the Critical Path

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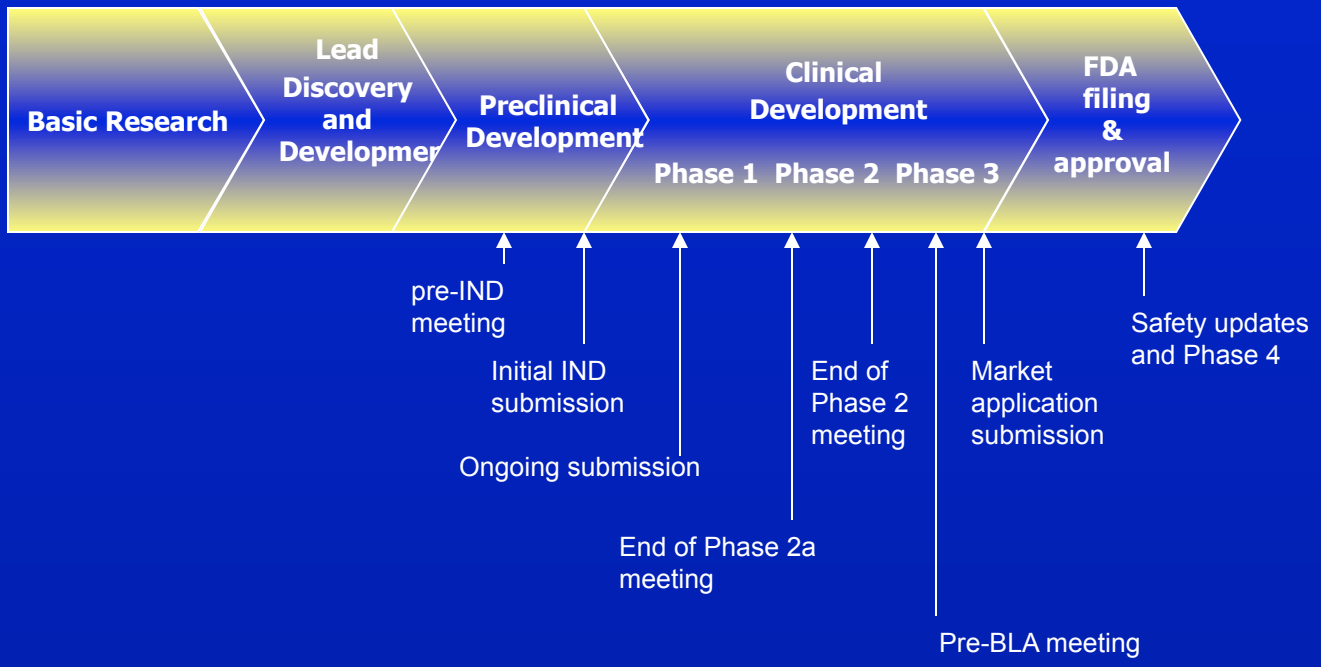
Drug Development Pathway



Pre-IND Meeting

- Pre-IND meeting
  - Discuss preliminary findings
  - Review plans for development
    - Input on preclinical safety testing plans
    - Input on manufacturing and testing plans
    - Input on proposed experimental design for clinical trials
    - Input on dose ranges to be attempted during clinical trials
- Type B
- 60 days
- Provide briefing package 30 days in advance

Investigational New Drug Application – IND

- Animal pharmacology and toxicology
  - Sufficient information for FDA to assess safety of product and proposed dose for initial testing
- Clinical Protocols and Investigator information
  - Information provided varies with Phase of study
  - Information on the qualifications of the investigators

Investigational New Drug Application – IND

- CMC (Chemistry, Manufacturing Controls)
  - Drug composition
    - » Monoclonal antibody
    - » Viral vector
      - Gene map, vector diagram, sequence analysis
    - » Cells
      - Substrate (monoclonal antibody, viral substrate)
      - Autologous (no donor screening, pathogen propagation, adventitious)
      - Allogeneic (donor screening, adventitious agents
      - Feeders (xenotransplantation guidance)
  - Manufacturing methods (DS, DP, cell banks, viral banks)
    - » Exposure
  - Quality Control procedures
    - » Release testing, characterization, stability profile, facility information

IND Submission and Clinical Hold

- Submit IND
- Wait 30 days to begin trial
- FDA reviews information provided for safety and compliance
- If trial cannot proceed safely, FDA can issue clinical hold

Clinical Testing

- Investigational New Drug application (IND)
- Phase 1
- Phase 2
- Phase 3
- GCP

Market Application, Review, and Approval

- **Pre-NDA or Pre-BLA meeting**
  - Discuss FDA expectations for NDA/BLA
  - Address any concerns raised during clinical testing
  - Format
  - Discuss any potential Phase 4 studies or post-approval surveillance
- **Provide sufficient information to determine:**
  - Drug has been shown to be effective for its proposed use
  - Safety has been assessed by all reasonably applicable methods
  - Drug is safe for its intended use (benefits outweigh the risks)
  - Drug's proposed labeling provides adequate directions for use
  - Methods for manufacturing drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, purity, and potency
- **Submit New Drug Application (NDA) or Biologics License Application (BLA)**
  - 60 days to determine if the application is complete
  - Can issue an RTF (missing information) or recommend withdrawal of application

Market Application, Review, and Approval – continued

- FDA review
  - 10 months standard, 6 months priority
- FDA review team evaluate the submission
  - Pre-approval inspection
  - Chemists, Pharmacologists, Toxicologists, Physicians, Clinical Pharmacologists, Statisticians, Microbiologists
- Evaluations considered by team leaders, division directors, office directors
- Advisory committee
- First Action
  - Approved, approvable, not approvable
- License

Market Application, Review, and Approval – continued

- On-going surveillance and risk management
- Phase 4 studies

The GXPs

- GLP: Good Laboratory Practice
- cGMP: Current Good Manufacturing Practice
- GCP: Good Clinical Practice
- GAMP: Good Automated Manufacturing Practice
- GEP: Good Engineering Practice
- GDP: Good Development Practice
- GDP: Good Documentation Practice

Where is it written?

- Code of Federal Regulation (CFR)

  U.S. FDA quality practices approved by Congress and enforceable by law *("thou shalt…").*

- Guidance for Industry (GFI)

  Information from FDA on recommended activities to satisfy specific CFR requirements *("how to….")*

- Compliance Policy Guidance (CPG)

  Guidance to FDA reviewers/inspectors on what to look for in product submissions and manufacturing operations *("did they…")*

Good Laboratory Practice – What they are

- A set of federal regulations describing how to conduct a nonclinical safety study
  - 21 CFR 58
- The purpose of the GLPs is to assure the quality and integrity of safety data generated for each study
- Applies to non-clinical laboratory studies
  - In vivo or in vitro experiments in which test articles are studied prospectively in test systems…to determine their safety.
- Does not apply to studies utilizing human subjects…does not include basic exploratory studies…to determine whether the test article has potential utility

Good Laboratory Practices – What they are not

- Pre-GMP
- Spirit of GMP
- GMP-ish
- GMP Lite
- R&D with a little R and a big D
- Any non-GMP lab activity during development
- QC laboratory quality practices for clinical trials

- Not manufacturing

The word "LABORATORY" confuses many people about the actual focus of GLP

GLP vs GMP: Different Objectives

GLP = Practices to assure a GOOD STUDY

GMP = Practices to assure a GOOD PRODUCT

While there are many similar *quality practices* that support the conduct of good studies and the manufacturing of a good product, there are significant differences in some key elements.

cGMPs During Product Development

Elements of cGMP

- Quality Management
- Facility design to control operations
- Equipment calibrated/qualified
- Environmental monitoring
- Production and process controls
- Validation
- Personnel training & certification
- Quality control/assurance
- Adequate documentation/records
  - *Scripta manent* (Whatever is written remains)

cGMPs During Product Development

Elements of cGMP, Continued

- Starting Materials
- Packaging Instructions
- Labeling Instructions
- Release of Batches
- Returns/Complaints/Recalls

cGMPs During Product Development

- "The Commissioner finds that, as stated in 211.1, these CGMP regulations apply to the preparation of any drug product for administration to humans or animals, including those still in investigational stages…The Commissioner is considering proposing additional CGMP regulations specifically designed to cover drugs in research stages."

- Code of Federal Regulations, Title 21, Subchapter C, "Current Good Manufacturing Practices in Manufacturing, Processing, Packing, or Holding," (U.S. Government Printing Office, Washington, DC), revised 28 March 1979

cGMPs During Product Development

Guideline on the Preparation of Investigational New Drug Products (Human and Animal), March 1991.

- At Phase 1, only limited process validation is possible
- Product quality is established through the use of qualified equipment and extensive in-process and finished product tests
- Degree of cGMP control needed increases as the investigational trials near completion

cGMPs During Product Development

Guidance for Industry: Content and Format of INDs for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-derived Products (Nov 1995)

"validation data and established specifications ordinarily need not be submitted at the initial stage of drug development"

cGMPs During Product Development

Draft Guidance for Industry: INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Chemistry, Manufacturing, and Controls Content and Format (Feb 1999)

- **cell bank characterization and adventitious agent testing should have been described in phase 1**
- **update phase 1 composition and process info from safety perspective, implement tentative in process controls and specs during phase 2**
- **updates, more complete info during phase 3**

cGMPs During Product Development

Guidance for Industry. CGMP for Phase I Investigational Drugs (July 2008)

- **Foster CGMP activities that are more appropriate for Phase I clinical trials**
- **Improve the quality of Phase I investigational drugs**
- **Facilitate the initiation of investigational clinical trials in humans while continuing to protect trials subjects**
- **Replaces 1991 guidance**

cGMPs During Product Development

EC GMP Annex 13, *Manufacture of investigational medicinal products* 1997;

"Manufacture of investigational medicinal products should comply with the basic Good Manufacturing Practice for medicinal products"

cGMPs During Product Development

ICH Q7A, *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* 2001

"Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism for approval of each batch"

"Process validation for the production of APIs for use in clinical trials is normally inappropriate"

cGMPs During Product Development

The CGMP Continuum: 'Sliding Scale"

- CGMPs that develop with clinical studies; examples:
  - process validation
    - » e.g. manufacturing, cleaning and sterilization
  - methods validation
  - process controls: in-process testing, specifications
  - SOP development

cGMPs During Product Development

Common Issues During the IND Phase

- Changes in manufacturing facilities or shared facilities
- Changes in manufacturing process
- use of research facility as “GMP” facility
- lack of process validation
- keeping up with current issues/regulations

cGMPs During Product Development

Analytical Method Qualification for Phase I

- Focus on methods that demonstrate safety, purity, identity, and stability
- Qualify the analytical equipment
- Full validation not required or expected
  - Specificity (assess analyte in presence of other components)
  - Accuracy (closeness to "true" value)
  - Precision (closeness of agreement between multiple measurements of same sample)
  - Linearity
  - Limit of Quantitation
  - System suitability

Points to Consider
Quality practices during development

- Many scientists have been trained by good mentors in sound experimental design and R&D study documentation
- Some will continue with these habits; others will not ('unnecessary burden of paperwork') or cannot, due to 'time constraints'
- Most R&D scientists make unsubstantiated assumptions about:
  - the nature of the reagents and materials they use
  - the processes and test methods they perform
  - the instruments and equipment they have
- Most R&D scientists think anyone who wants to know what they did will just come and ask them (forever?)
- Most R&D Directors do not review the primary documentation generated by their groups to verify if all information is being captured by every analyst with adequate detail and traceability for use in product development reports

Points to Consider
Quality practices during Development

- Principles of GP and Management Responsibilities
- Content, format and traceability of laboratory notebooks
- Use of reagents, materials, reference standards
- Maintenance and use of instrumentation and equipment
- Content, format, and change control of protocols and SOPS
- Content and management of training records
- Technology transfer practices
- Establishing product and test method specifications

How do Good Development Practices Affect Product Development and Support activities?

It is vital to have complete, traceable, accurate, retrievable development documentation for the following audiences:

Quality Assurance/Compliance:

- ***FDA 21st Century Initiatives for cGMP***
- ***FDA Quality Systems for cGMP***
- ***Q8 Pharmaceutical Development,***
- ***Q9 Quality Risk Management, Q10 Pharmaceutical Quality System***

Regulatory Affairs:

- ***ICH Common Technical Document CMC Sections***

Legal Affairs:

- ***Investors, Acquisitions, Partnerships***
- ***Patent Applications***

Research Phase

- Official Requirements: Essentially None
- Recommendations
  - Adopt in-house good practices
  - Use basic framework of GLP regulations
    - » Data are accurate and verifiable
    - » Documents are traceable
  - Calibration of instruments
  - Basic documentation system (SOPs)
  - Qualification/Validation of test methods under consideration
  - Definition of data requirements before handing over to development
- Emphasis on sound data (good documentation practice)
- Future patent position can be as important than GMP

Development Phase, Pre-clinical

- Official Requirements: Essentially None
- Recommendations
  - Limited testing of raw materials
  - Basic Documentation (SOPs, Manufacturing Documentation)
    - » Data are accurate and verifiable
    - » Documents are traceable
  - Data are accurate and verifiable
  - Basic change control procedures
  - Use of “Good Practices” for manufacture of stability and tox materials
- GMP still not a requirement.
- First preparations and considerations taking place

Development Phase Toxicological Testing

- **Official Requirements**
  - All testing carried out to GLP standards
  - No requirements for the manufacture of test samples
- **Recommendations**
  - Samples manufactured to GMP appropriate for early phase product
  - Batch records (not necessarily officially approved)
    - » What was done, By whom, When, With What?
  - Raw materials tested and released
  - Testing and release of test articles
  - Stability testing progresses
- **GMP still not a requirement.**
- **Toxicology material should be equivalent of that in Phase I**

Development
Phase I and II

- **Official Requirements**
  - GMP is applied
  - Some flexibility
- **Recommendations**
  - Quality System well underway with QA established
  - Specifications for starting materials and products
  - Environmental monitoring in place
  - Facility and equipment qualified
  - Cleaning issues addressed
  - Operators trained in GMP
  - Analytical methods qualified
- **Product must be safe and of acceptable quality.**
- **Process Validation not required**
- **Emphasis on testing to demonstrate batch quality**
- **Not all GMP regulations applied in full**

Development Phase III

- **Official Requirements**
  - Full GMPs apply
- **Recommendations**
  - All of Phase I and II
  - Full commercial scale and at commercial facility
  - Full manufacturing control and documentation
  - All prospective process validations performed (except consistency batches)
  - Analytical methods fully validated
  - Operators fully trained in GMP
- **Facilities and Quality Systems used for preparation of Phase III batches should be fully prepared for a PAI**

cGMPs During Product Development

Conclusions

- Compliance with CGMPs is required from phase 1 onward
  - adequate documentation (traceability) and facilities
  - sterility assurance
  - QC/QA oversight
- Certain CGMPs develop with product
  - defined in-process controls
  - full process and assay validation

Key Process Development and Formulation Activities

GLP	"Early" GMP	"More" GMP	"Late" GMP	Full GMP
Pre-Clinical	**Phase 1**	**Phase 2**	**Phase 3**	**Post-Approval**
CHOOSE API PURIFICATION PROCESS	OPTIMIZE API PURIFICATION PROCESS	QUALIFY API PURIFICATION PROCESS	VALIDATE API PURIFICATION PROCESS	RE-VALIDATE API PURIFICATION PROCESS (CHANGES)
CHOOSE VIRAL CLEARANCE PROCESS(ES)	VALIDATE VIRAL CLEARANCE PROCESS(ES)	RE-VALIDATE VIRAL CLEARANCE PROCESS(ES)	RE-VALIDATE. VIRAL CLEARANCE PROCESS (CHANGES)	RE-VALIDATE VIRAL CLEARANCE PROCESS (CHANGES)
CHOOSE IN-PROCESS TEST METHODS	OPTIMIZE IN-PROCESS TEST METHODS	QUALIFY IN-PROCESS TEST METHODS	VALIDATE IN-PROCESS TEST METHODS	RE-VALIDATE IN-PROCESS TEST METHODS (CHANGES)
CHOOSE INITIAL DRUG PRODUCT FORMULATION	SCREEN DRUG PRODUCT FORMULATIONS	SELECT FINAL DRUG PRODUCT FORMULATION	VALIDATE FINAL DRUG PRODUCT FORMULATION	RE-VALIDATE DP FORMULATION (CHANGES)
CHOOSE INITIAL PRODUCT PRIMARY PACKAGING	EVALUATE MATERIAL COMPATIBILITY	SELECT PRIMARY PRODUCT PACKAGING	CONFIRM PRIMARY PACKAGING	RE-VALIDATE PRIMARY PACKAGING (CHANGES)
PRODUCTION OF TOXICOLOGY API AND DP LOTS	PRODUCTION OF PHASE 1 API AND DP CLIN LOTS	PRODUCTION OF PHASE 2 API AND DP CLIN LOTS	PRODUCTION OF PHASE 3 API AND DP CLIN LOTS	PRODUCTION COMMERCIAL API AND DP LOTS
RETAIN TOX BATCH SAMPLES	RETAIN CLINICAL BATCH SAMPLES	RETAIN CLINICAL BATCH SAMPLES	RETAIN CLINICAL BATCH SAMPLES	RETAIN COMMERCIAL BATCH SAMPLES
ESTABLISH INTERIM API & DP SPECS AND ACCEPTANCE CRITERIA*	REVIEW INTERIM API & DP SPECS AND ACCEPTANCE CRITERIA*	REVIEW INTERIM API & DP SPECS AND ACCEPTANCE CRITERIA*	VALIDATE FINAL API & DP SPECS AND ACCEPTANCE CRITERIA*	MONITOR FINAL API & DP SPECS AND ACCEPTANCE CRITERIA*

**in conjunction with Analytical Development*

Key Analytical R&D and QC CMC Activities

GLP	"Early" GMP	"More" GMP	"Late" GMP	Full GMP
Pre-Clinical	**Phase 1**	**Phase 2**	**Phase 3**	**Post-Approval**
CHOOSE API & DP RELEASE TEST METHODS	OPTIMZE API & DP RELEASE TEST METHODS	QUALIFY API & DP RELEASE TEST METHODS	VALIDATE API & DP RELEASE TEST METHODS	RE-VALIDATE API & DP RELEASE METHODS (CHANGES)
CHOOSE API & DP STABILITY TEST METHODS	OPTIMIZE API & DP STABILITY – INDICATING TEST METHODS	QUALIFY API & DP STABILITY-INDICATING TEST METHODS	VALIDATE API & DP STABILITY-INDICATING TEST METHODS	RE-VALIDATE API & DP STABILITY METHODS (CHANGES)
PRELIMINARY HOLDING-HANDLING CONDITIONS	EVALUATE HOLDING-HANDLING STABILITY	FORCED DEGRADATION ASSESSMENT	FORCED DEGRADATION ASSESSMENT (CHANGES)	FORCED DEGRADATION ASSESSMENT (CHANGES)
STABILITY OF API & DP TOXICOLOGY LOTS (INC. SHIPPING STABILITY)	STABILITY API & DP PHASE 1 CLINICAL LOTS	STABILITY API & DP PHASE 2 CLINICAL LOTS	STABILITY API & DP PHASE 3 CLINICAL LOTS	STABILITY API & DP 1 ANNUAL LOT
TEST API & DP TOXICOLOGY LOTS	QC RELEASE TEST PHASE 1 API & DP CLIN LOTS	QC RELEASE TEST PHASE 2 API & DP CLIN LOTS	QC RELEASE TEST PHASE 3 API & DP CLIN LOTS	QC RELEASE TEST COMMERCIAL API & DP LOTS
INITIAL PRODUCT CHARACTERIZATION	CLIN LOT & REF STD CHARACTERIZATION	CLIN LOT & REF STD CHARACTERIZATION	CLIN LOT & REF STD CHARACTERIZATION	CERTIFICATION OF NEW REF STD LOTS
	TOX - PHASE 1 LOT COMPARABILITY	TOX -1-2 LOT COMPARABILITY	TOX-1-2-3 LOT COMPARABILITY	PROCESS CHANGE COMPARABILITY
ESTABLISH INTERIM API & DP SPECS AND ACCEPTANCE CRITERIA*	REVIEW INTERIM API & DP SPECS AND ACCEPTANCE CRITERIA*	REVIEW INTERIM API & DP SPECS AND ACCEPTANCE CRITERIA*	VALIDATE FINAL API & DP SPECS AND ACCEPTANCE CRITERIA*	MONITOR FINAL API & DP SPECS AND ACCEPTANCE CRITERIA*

**in conjunction with Process and Formulation Development*

"But Most of This Doesn't Actually Apply to *Us*, Does It?"

- "Our product is different …"
- "Our product is too complex …"
- "We already know everything about our product …"
- "We already know this process is sound …"
- "We are confident these methods will work …"
- "It isn't technically possible …"
- "I didn't know we were going to submit this…"
- "It will be too difficult …"
- "Trust us, we're scientists …"
- "Why do we need to audit the data? It's been published…"
- "Management won't allow us …"
- "We just want to get through Phase II …"
- "The reviewer didn't ask about this before …"
- "The FDA really wants this product …"

Risks of Non-compliance - GLP

- **Problem:** Improper handling of samples (frozen for 2 – 4 weeks vs. industry standard of immediate testing or overnight at 2 – 8 C)
- **Result:** Results of toxicology test uninterpretable
- **Impact:** 9 month study had to be repeated. A second 9 month study with a second species was required.

Program was delayed for 18 months and nearly cancelled

Risks of Non-compliance – GMP

- **Problem:** Failed to do container closure studies at specified storage temperature (< -20C)
- **Result:** Placed on clinical hold until container closure studies performed and batches re-made
- **Impact:** 9 month delay in clinical program

Risks of Non-compliance – GMP

- **Problem:** Insufficient sample taken to allow for complete viral safety testing profile
- **Result:** New low volume assay needed to be developed, qualified and approved
- **Impact:** 8 month delay in clinical program

Staying on the Critical Path Questions to Ask Along the Way

- Where are you in development?
- Are you ready for the next big milestone?
  - Preclinical studies (proof of concept)
  - Pre-IND meeting
  - IND
- Conduct an honest assessment
  - Assay methods, materials, specifications appropriate to phase of development?
  - Control over process
  - Paperwork in order (chain of custody, traceable)
  - Decisions early can have big implications later
    - » Pre-Master, Master, Working Cell Banks and Virus Seeds
  - When to accelerate or slow down
- What next?
  - Remember to keep the end goal in mind

Staying on the Critical Path
Where to get help

- FDA (www.fda.gov)
  - Guidances, Small Business Guide (Division of Small Business, International and Consumer Assistance)
- ICH (www.ICH.org)
  - Q2 Analytical Validation
  - Q5A – Q5E Biotechnology Products
  - Q6A - Q6B Specifications
  - Q7 Good Manufacturing Practice
  - Q8 Pharmaceutical Development
- WHO
- USP/NF
- CIRM
- Colleagues
- Consultants
- Vendors