



*The Use of Exploratory INDs
and
Other Regulatory Initiatives to Expedite Drugs to
Market*

*Linda Storbeck, MS
Director, Technical Regulatory Affairs
July 11, 2006*

Outline of Presentation



- The Current State and Challenges of Drug Development
- The “Tool Kit”
 - FDA Critical Path Initiative
 - FDA “A Risk Based Approach – cGMP” Initiative
 - ICH – Global Regulatory Harmonization
- The “Tools”
 - Exploratory INDs
 - INDs
 - NDA/ANDA
 - Post Approval
- Using the “Tools” to Align CMC throughout Drug Development
- Summary/Questions

MDS Pharma Services



- Headquarters – King of Prussia, PA
- Global Infrastructure -US, Canada, Europe and Asia
- Early Stage – Phase 0/Phase 1
 - Drug Discovery/ Pre-clinical
 - Pharmaceutical and Biopharmaceutical Development
 - Early Clinical Research
 - Bioanalysis
- Late Stage – Phase 2 – NDA/ANDA
 - Global Clinical Development
- Drug Development Program Planning
- Global Regulatory Affairs

Current State and Challenges of Drug Development



FDA Report “Innovation or Stagnation ? Challenge and Opportunity on the Critical Path to New Medical Products” March 2004

- Analysis of the “pipeline problem”
- New drug applications have decreased
- Cost of product development has increased
- Rising health care costs
- Innovators efforts are on high market return
- “If costs and difficulties with product development continue to grow, innovation will continue to stagnate and will not be able to deliver new products intended for the prevention, treatment and cure of serious illness.”

What is the problem?

FDA Report “Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products” March 2004



- Product development not kept pace with scientific innovation
- New science is not guiding development of biomarkers and analytical technology
- State-of-art technology not applied to manufacturing process
- Need new tools to get better answers about:
 - “How the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs”

Result

FDA Report “Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products” March 2004



Clinical Development

- Majority of products that enter clinical trials fail
- Development programs halted after investment of time and resources

Result - High failure rate drives up costs

Product Development

- High in-process inventories and low factory utilization
- High costs of formulation and process development
- Compliance issues

Result - High cost + decrease productivity

FDA Conclusion:

FDA Report “Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products” March 2004

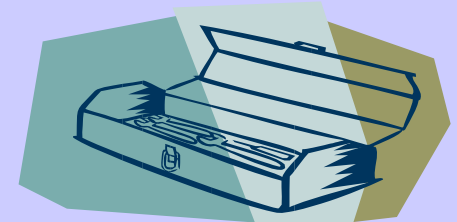


“Path to market is long, costly and inefficient due in part to the current reliance on cumbersome assessment methods.”

“We need to make the effort required to create better tools for developing medical technologies.”

Resolution: A New Product Development “Toolkit”

FDA Report “Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products” March 2004



Critical Path Initiatives

- Assessing Safety – Preclinical/Clinical Safety
- Demonstrating Medical Utility – Preclinical/Clinical Effectiveness
- Industrialization – Compound from lab to commercial production

FDA Critical Path Initiatives

FDA Report “Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products” March 2004



- State-of-art manufacturing processes
- Science into regulations = “Tools”
- Regulation - slowed innovative science
- Bridge “in vitro” and “in vivo” data
- Early “proof of concept” trials before commitment to full-scale development

A New Quality Approach to cGMPs “Toolkit”

FDA Report “Pharmaceutical cGMPs for 21st century – A Risk Based Approach”

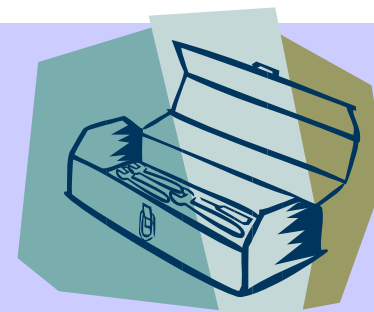
September 2004



cGMP Initiative

A “Desired State” for Pharmaceutical Quality

- Effective and efficient manufacturing processes
- Product specifications – based on formulation and process
- Continuous improvement / “real time” assurance of quality
- Regulatory procedures – scientific knowledge
- Risk based regulatory scrutiny:
 - Scientific understanding of formulation
 - Manufacturing process factors = product quality
 - Capability of process control strategies

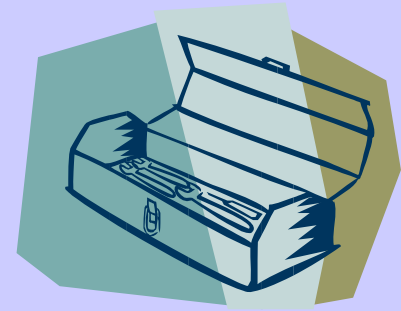


International Conference on Harmonization – “Toolkit”



The Need to Harmonize

- Rising costs of health care
- Escalation of cost of R&D
- Different regulatory systems =delay to market



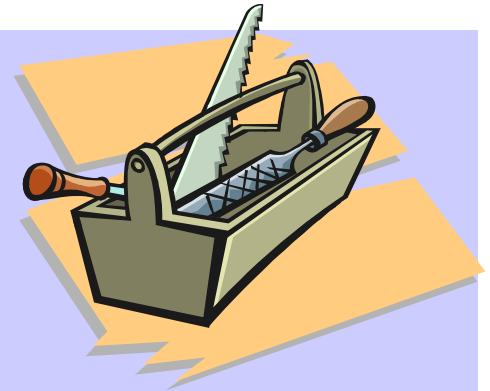
ICH Initiative

- Harmonize Regulatory Requirements
Safety, Quality, Efficacy, Multidisciplinary
Europe, Japan, US
- Harmonize Compendial Requirements

The “Tools” – Chemistry, Manufacturing and Controls

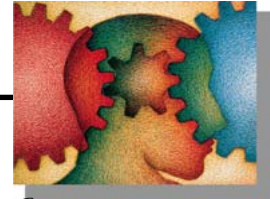


- FDA Guidance to Industry
 - IND
 - Exploratory IND – Phase 0
 - NDA
 - PAT
 - Comparability Protocols
 - Quality Systems - cGMP
 - ANDA
 - CMC - Question Based Review

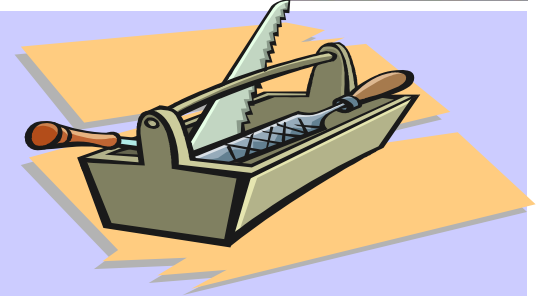


The “Tools” – (Cont’d)

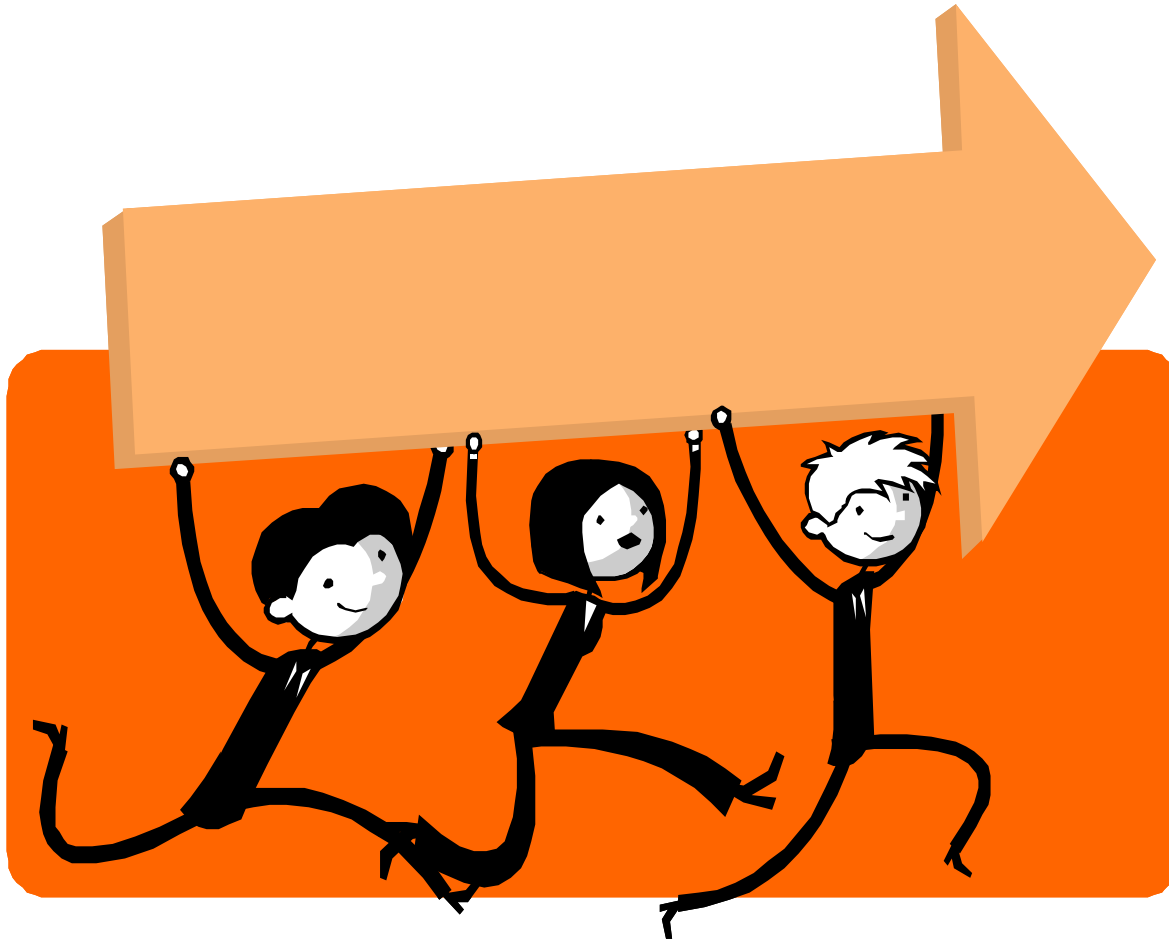
Chemistry, Manufacturing and Controls



- FDA Guidance
 - Procedural
 - Continuous Marketing Application
 - Fast Track Drug Development Programs
 - Post Approval
 - BACPAC/SUPAC
 - PAC-ALTS
 - BE Waiver
- ICH – Global Regulatory Guidelines
 - Common Technical Document



CMC – Who? What? Why?



CMC is Critical to the Success of Drug Development



Who we are?

Regulatory Scientists – Apply the “Tools” through Drug Development to Engineer and Build Quality Regulatory Submission

What we do?

- CMC strategy alignment to drug development timelines
- CMC documentation required for CTD submission
- Regulatory liaison with regulatory agencies
- CMC consultation-documentation requirements
- Post approval filings – annual reports, CBE, PAS
- CMC sections to support ANDA filings



Why we do what we do?

- Maintain compliance to global regulatory and quality requirements
- Product quality, safety and efficacy

Active Pharmaceutical Ingredient Development

Phase 0 to Phase 2



Phase 1 Development

Establish API synthetic process

Analytical Characterization/ specifications/ analytical methods

Impurity profile/ stability

Phase 2 Development

Minimize number of process steps/ maximize yield/ scale-up

Validation of analytical methods

IND Submission

Lab scale synthesis

Establish Solubility profile

Stress stability studies

Evaluation of Thermal properties of API

Synthesis of C14 Labeled API

Development of analytical methods / acceptance criteria

Physical, chemical characterization

Pre-Clinical Development

Phase 0 Development

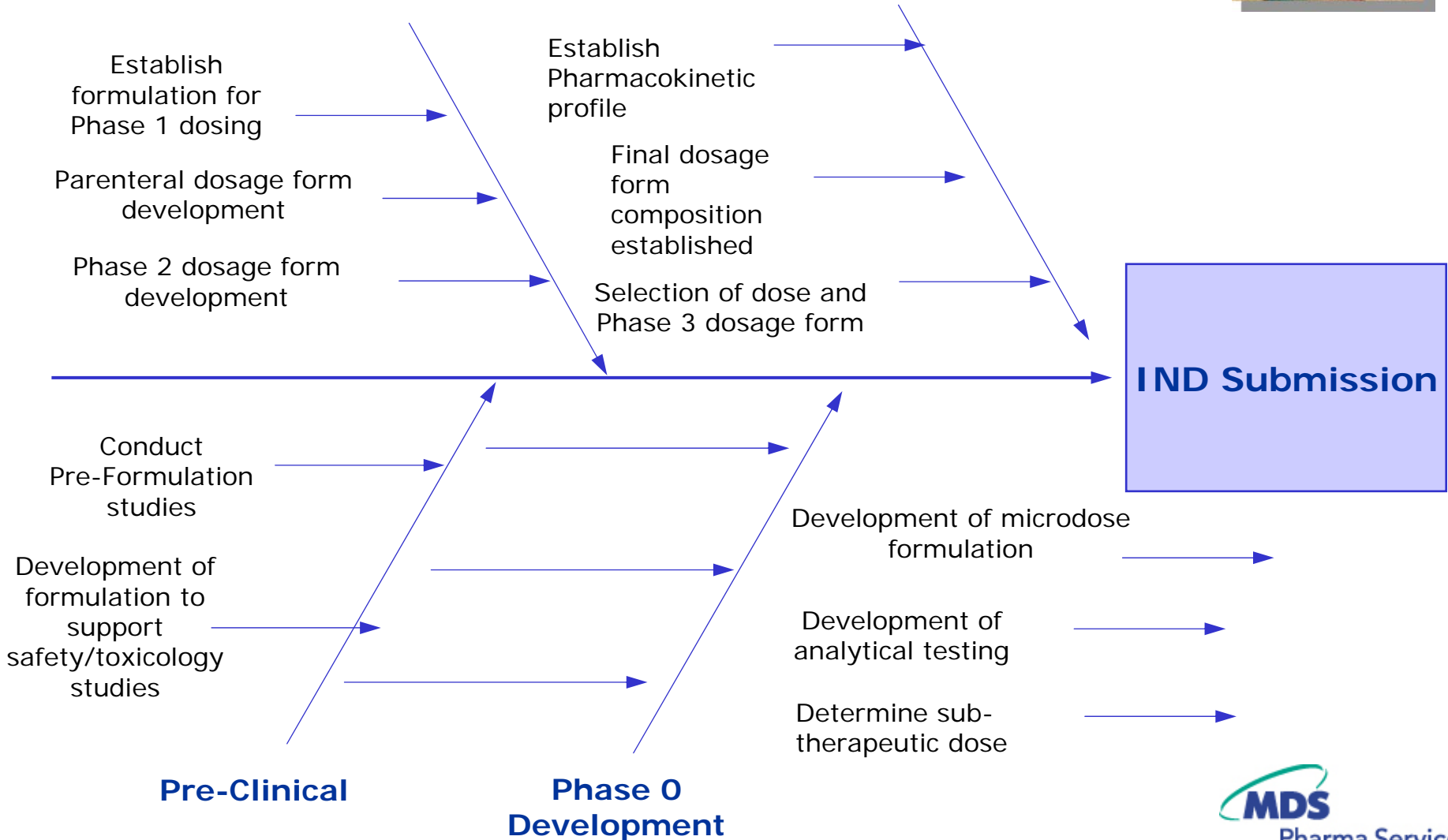
Pharmaceutical Formulation Development

Phase 0 to Phase 2



Phase 1 Development

Phase 2 Development



Using the “Tool” – Exploratory INDs



- Clinical trial - phase 0
- Limited human exposure
- Sub-therapeutic doses of a product - less than 1/100th of dose
- Conducted prior to dose escalation, safety or tolerance studies
- Limited duration of dosing (e.g. 7 days)
- PK screening of multiple compounds

Developing a CMC Strategy for Drug Development Preclinical to Phase 0 - Exploratory IND Filing



OBJECTIVE – Expedite selection of New Chemical Entities –
Phase 0 clinical studies-Submission of an Exploratory IND.

STRATEGY – CMC Regulatory Involvement - critical review of the
following to support requirements for Exploratory IND:

- C14 labeled API and microdose formulation
- Solubility Profile
- Stability - Forced degradation studies
- Thermal properties
- Analytical methods – quantitate ug/C14
- Physical, chemical characterization
- Preliminary specifications established
- Composition - Drug-excipient compatibility
- Selection of sub-therapeutic dose

CMC Requirements for Exploratory IND Filing CMC Summary Report



DRUG SUBSTANCE

- Physical, chemical and/or biological characteristics
- Source and therapeutic class
- Synthetic process
- Specifications and test methods

DRUG PRODUCT

- Quantitation composition of the product
- Name and address of manufacturer
- List of excipients (GRAS)
- Specifications and test methods
- Certificate of analysis
- Method of manufacture
- Container/closure system
- Stability – data from material used in Toxicology studies/plans for evaluation during clinical trial

Developing a CMC Strategy for Drug Development Phase 1 to Phase 2 - IND Filing



OBJECTIVE – Early pharmaceutical development initiatives - optimization of process and establishing bioequivalence of Phase 1 and Phase 2 formulations.

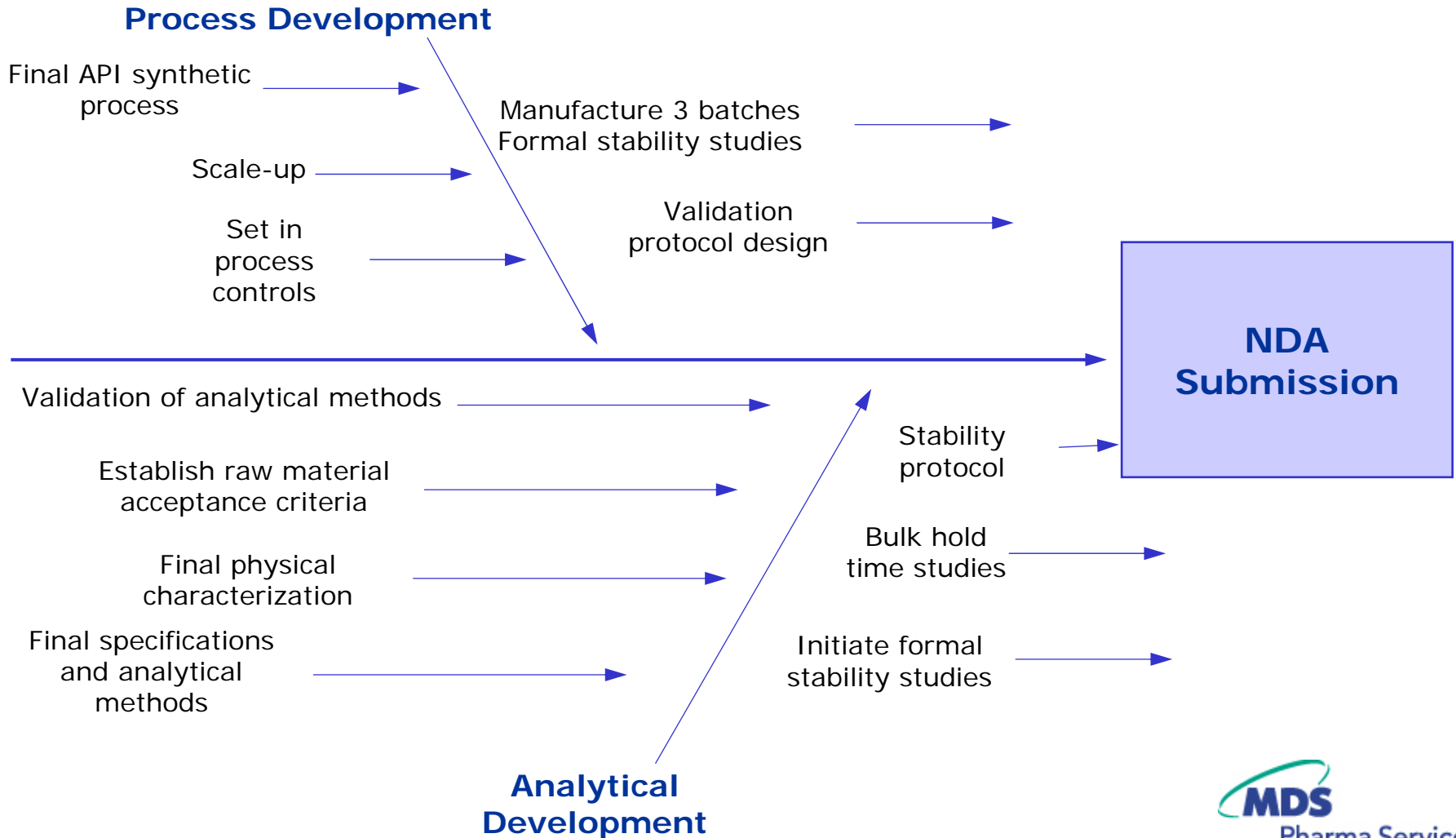
STRATEGY – CMC Regulatory Involvement - critical review of the following to support requirements for IND filing:

- Composition of formulation (assess any changes made)
- Stability – ICH standards
- Analytical Methods – ICH standards
- Manufacturing Process – (assess any changes made)
- Specifications – ICH Standards
- Acceptance criteria for excipients
- Assessment of polymorphism, isomerism (establish controls)

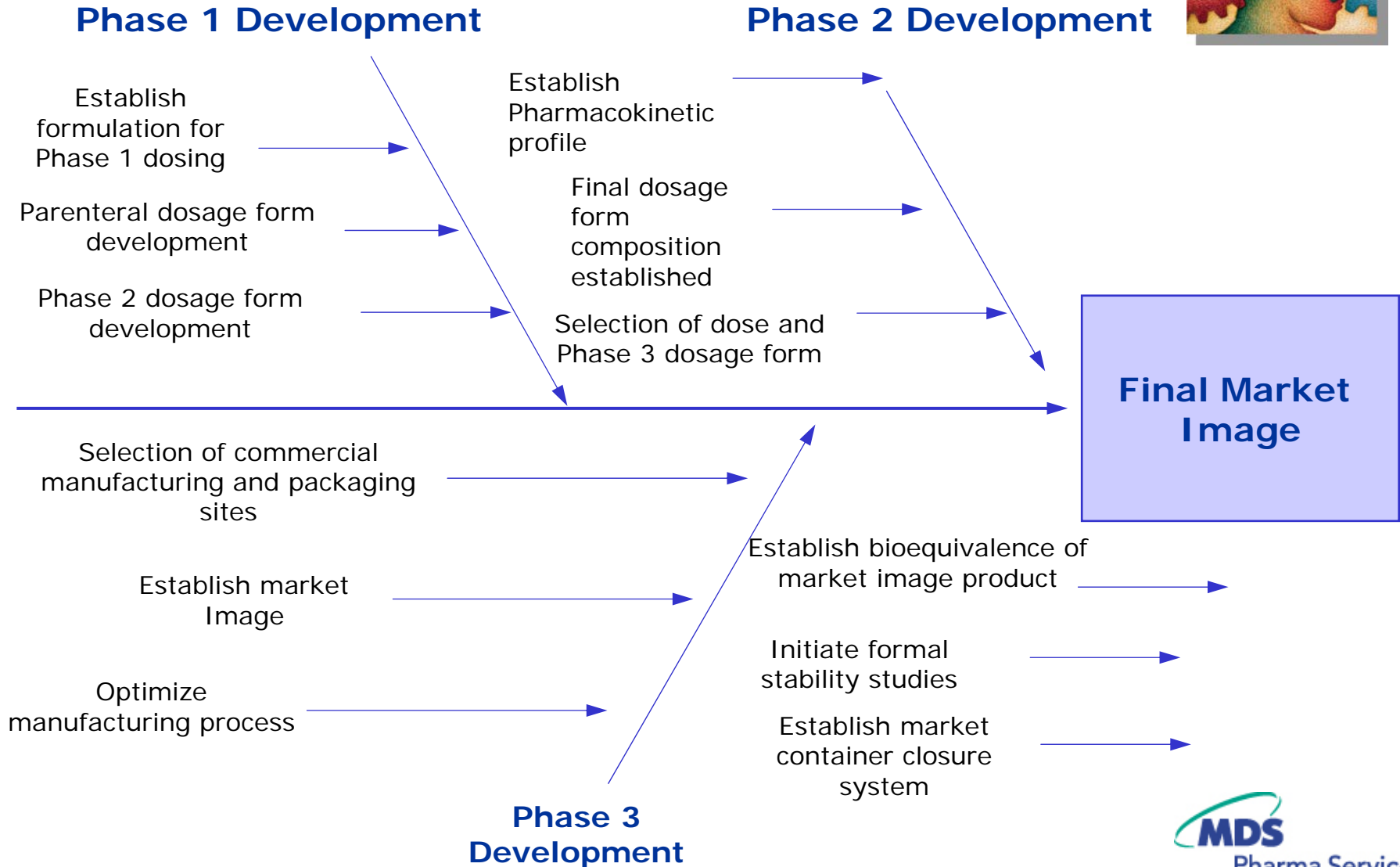
Active Pharmaceutical Ingredient – Phase 3



Clinical Development -Phase 3 Clinical Trials



Pharmaceutical Formulation Development – Phase 3



Using the “Tools” - NDA



NDA

- PAT – “Real Time Release”
- Comparability Protocols
- Quality by Design
- Procedural
 - Continuous Marketing Application
 - Fast Track Drug Development Programs
- Common Technical Document

Using the “Tool” - ANDA



CMC - Question Based Review for Generic Drugs

- Ensure Quality - Quality by design and performance-based specifications
- Reduce supplements – Risk-based assessment facilitates continuous improvement
- Enhance Quality of CMC Evaluation – Standardized review questions
- Reduce Review Time – QbR-based Quality Overall Summary (QOS) assists with CMC review

Developing a CMC Strategy for Drug Development Phase 3 to NDA Filing



OBJECTIVE – Expedite NDA filing timeline and ensure quality assessment by preparing the CMC section simultaneously in alignment with development timeline

STRATEGY – CMC Regulatory involvement throughout development - critical review of the following :

- Process and analytical documentation
- Process development plans
- Formal stability study protocol
- Proposed market image
- Market container closure system
- Regional market regulatory requirements
- Development of comparability protocols
- Ensure “Quality by Design” approach

NDA Submission → Market Launch



NDA submission →

API / Drug Product Manufacturing Site

Pre-approval inspection – site readiness →

Validate process →

Manufacture launch quantities →

Package launch quantities/assess risk based on label review →

Market Launch

Pre-approval site inspection by FDA →

NDA review comments/responses →

Expiration Dating established →

Labeling – review/revisions →

NDA approval →

Regulatory

CMC Strategy

NDA Submission to Market Launch



OBJECTIVE – NDA approval, successful Pre-Approval Inspection and launch to markets worldwide

STRATEGY – CMC Regulatory involvement throughout regulatory review process and pre-approval site inspection

- Responses to agency review comments
- Amendments for submission to NDA
- Expiry extension
- Post approval commitments
- Review validation protocol/report
- Risk management of production and packaging of launch quantities
- CMC regulatory documentation during pre-approval inspection
- Address 483 observations that require regulatory submissions

Using the “Tools” – Post Approval



Post Approval

- BACPAC/SUPAC
- PAC-ALTS
- BE Waiver – Establish in vitro/in vivo correlation/BCS

Summary



- A New Product Development “Toolkit”
- Proactive steps - science to guide the development process
- Development of guidance documents - “Tools”
- Streamline Product Development Timelines
 - Exploratory INDs
 - Quality by design and real time testing
 - Common Technical Document
 - Continuous Marketing Application
 - Fast Track Development Programs
- CMC Regulatory Collaboration is critical throughout development

Questions???



Thank You!

*Linda Storbeck, MS
Director, Technical Regulatory Affairs
MDS Pharma Services
The Triad
2200 Renaissance Blvd.; Suite 400
King of Prussia, PA 19406
Tel: 800-554-0502 ext. 234
e-mail: linda.storbeck@mdsps.com*