Optimizing Pharmaceutical Manufacturing: FDA’s Critical Path Initiative

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Agenda

- Update on FDA’s Critical Path Initiative
- “Pharmaceutical Quality for the 21st Century” Initiative as part of Critical Path
- Progress regarding pharmaceutical manufacturing and PAT
- Linking critical product attributes to clinical outcomes
Investment and progress in basic biomedical science has far surpassed investment and progress in the medical product development process.

The development process – the critical path to patients – becoming a serious bottleneck to delivery of new products.

We are using the evaluation tools, technologies, and infrastructure of the last century to develop and manufacture this century’s advances.
Rising Public Expectations About the Prospects for New Therapies Based on New Biomedical Discoveries

- Sequencing of the human genome
- Genomic and proteomic technologies
- Systems biology
- Advances in medical imaging
- Nanotechnology advances
- Tissue engineering
- Drug discovery: combinatorial chemistry and automated microscale screening
- Robotics
Novel Drug Submissions Remain Flat through 2006

NMEs Filed by Fiscal Year

* for NMEs submitted prior to 1992, type A and type B applications are counted as Priority review and type C applications are counted as Standard review.
The Pharmaceutical Pipeline

- There is clearly a dip or plateau in the pipeline
- Cause is multifactual

- Genomics & other new science not at full potential (10-15 yrs)
- Mergers and other business arrangements have decreased the number of candidates
- Easy targets taken/chronic disease harder to study
- Failure rate has not improved
- Rapidly escalating costs & complexity decrease willingness/ability to bring many candidates forward into the clinic
Greater Challenges; Lower Chance of Success

- Public calling for larger, longer development programs to increase certainty about product performance before marketing

- Despite advances in science, success rate of product development has NOT improved
  - New compounds entering Phase I development today have 8% chance of reaching market, vs. 14% chance 15 years ago

- Phase III failure rate now reported to be 50% vs. 20% in Phase III, 10 years ago
Central “Critical Path” Thesis

- Societal investment in R&D to improve the pharmaceutical development process - that is inextricably intertwined with FDA standards - has been lacking
- Huge private & public basic research & specific product development investment
- Minor investment in development tools & public standards
  - Academia not funded
  - Not conceptualized as FDA’s role
  - Efforts in private sector not generalizable or are proprietary
The Critical Path for Medical Product Development
Science to evaluate safety & efficacy of new products, and enable manufacture, is different from basic discovery science.
What is on "Critical Path" to Medical Product Development?

Applied science to address 3 key dimensions:

- **Assessment of Safety** – how to predict if a potential product will be harmful?

- **Proof of Efficacy** – how to determine if a potential product will have medical benefit?

- **Industrialization** – how to manufacture a product at commercial scale with consistently high quality?
Recent Expansion of Critical Path Concept

- Foods and veterinary drugs
- Generic drug whitepaper published
- Broadening to postmarket surveillance, since robust safety net needed if development program cannot answer all questions
Guiding Principles of FDA Initiative

- Collaborative efforts among government, academia, industry and patient groups
- Infrastructure and “toolkit” development, not product development
- Build support for academic science bases in relevant disciplines
- Build opportunities to share existing knowledge & database
- Develop enabling standards
Progress to Date

- Published Initial Report 5/04; ongoing projects 11/06 (see CP web page)

- FDA Amendments Act (9/07) established Reagan Udall Foundation for FDA
  - Critical path research
  - Education and training

- FDA ’08 budget: additional $7.5 M in appropriations for Critical Path work

- Establishment of Critical Path Office at FDA: Rachel Behrman, M.D., Director

- FDA Science Board subcommittee reviewed scientific capacity at FDA—strongly endorsed Critical Path
Major Opportunities for Modernization per “Critical Path Report and List”

- Biomarker Qualification
  - In-vitro diagnostics
  - Imaging
  - Preclinical toxicogenomics

- Clinical Trial Modernization
- Bioinformatics
- Modernizing Manufacturing
- Pediatric Treatments
- Public Health Emergencies
Ongoing Projects

- C-Path Institute, Tucson, AZ
  - Predictive Safety Testing Consortium
    - 15 member industry consortium
    - Cross-validation of animal toxicology markers
    - First set of markers—drug induced nephrotoxicity, under review by FDA
  - Cardiac Safety Markers, others

- SAE consortium
  - Industry consortium
  - Evaluating genetic basis of rare AEs
Ongoing Projects

- “The Biomarker Consortium”: NIH/FDA/PhRMA/BIO and others
  - Discovery and development of new biomarkers
  - Multiple markers under discussion
- Cardiac safety consortium
  - Duke University/FDA/others
  - Digital ECG warehouse; research
Consortia in Formative Stages

- Clinical Trials Consortium: Duke University/FDA/many others: modernization of clinical trial procedures
- Nanotechnology
- FDA’s “Sentinel Network” for postmarketing surveillance
- Many others
Regulations/Guidances

- Exploratory IND and Regulation on Phase 1 GMPs
- Expect 2 stages of modifications to GMP regulations
- Several clinical trial guidances
- Data standards through HL-7
Modernizing Manufacturing

- FDA’s “Product Quality for the 21st Century” Initiative began in 2003
- Goal: Incorporate up-to-date manufacturing and quality science into regulation of pharmaceutical manufacturing
- Prototype for larger critical path initiative
- Modernizing manufacturing theme subsequently incorporated into Critical Path
What does This Have to Do with PAT?

- Critical Path about accelerating pace of introduction of new science/technology into regulation and regulated industry
- PAT emblematic of new way of thinking about pharmaceutical manufacturing
- Move from empirically-derived trial-and-error methods to rigorous, mechanistically-based and statistically controlled processes
Changes in Multiple Sectors Required: Product Quality

- Manufacturers will need to change approach, invest in new technology, break down silos between R&D and production, be less conservative.
- Internationally, regulators will need to accept and encourage new ways of doing business and harmonize regulatory approaches.
Changes Required: PAT

- Manufacturers will need to invest in developing this technology for their processes.
- Equipment vendors will need to focus on pharmaceutical market.
- International regulators need to signal acceptance (maybe encouragement) and modify processes to accommodate PAT.
- Standard-setting organizations/professional societies engage in standards and training.
- Academic research to advance the field.
Towards International Regulatory Acceptance

- Develop regulatory standards within ICH
- Develop technical standards within standards organizations
- FDA and EU having ongoing discussions about approaches to variations and about modernizing regulation of manufacturing
- FDA evaluating best strategies to bring in other nation’s regulators who are outside ICH
Barriers: PAT

- Regulated industry: highly conservative, risk averse, not eager (especially currently) to invest in manufacturing
- Perceived regulatory barriers
- Need for appropriate technology and standards specific to pharmaceuticals
- These are addressable
Linking Critical Product Attributes to Clinical Performance: Is it Possible?

- Currently not known: regulatory standards often highly conservative based on uncertainty

- “Gross excursions” used as examples
  - Failure to inactive virus vaccine (polio)
  - Contamination/substitution (e.g., ethylene glycol)
  - Total in vivo dissolution failure
Question: “What are the Clinical Effects of Minor Variations in Content Uniformity (OOS)"

- Clinical reviewer: “I don’t know, but I’m worried”
- Reviewing chemist: “significant”
- Investigator: “very large”
- Today’s presentor: “clinically undetectable in vast majority of cases”
Why?

- Example: solid oral dosage form
- Patient exposure may vary 1.5X based on liver & renal status, weight, size, drug-drug interactions and individual absorption differences
- Exposure may vary 4X with polymorphic metabolism
- Nevertheless, these variations are rarely adjusted for in the clinic
- Does not therefore imply that content should be highly variable, only that contribution to overall variability usually negligible
- Exceptions exist: thyroxine
Moving Forward

- Major future opportunity will be better linkage between clinical performance and quality parameters
- This will inform what to measure (and what not to measure)
- Important concept for “Quality by Design”—have to understand parameters of quality
Future of Critical Path Initiatives

- FDA and Commissioner are committed to moving these forward
- Manufacturing is a significant component
- Mature and dedicated FDA group working on this initiative
- You can expect continued progress in this area in FY 08; CDER funding and staffing will be considerably improved this year