Engineering A Pharmaceutical Product Using Drug Development Knowledge

Russ Somma, Ph.D.
November 2006

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Objectives

- To understand the process for developing a commercial pharmaceutical product and obtaining regulatory approval.
- To outline activities which should be done before entering manufacturing and attempting market entry.
- To identify the data needed to address regulatory concerns as well as providing a pragmatic baseline for facility requirements.
- To provide an introduction to new technologies for manufacture and development.

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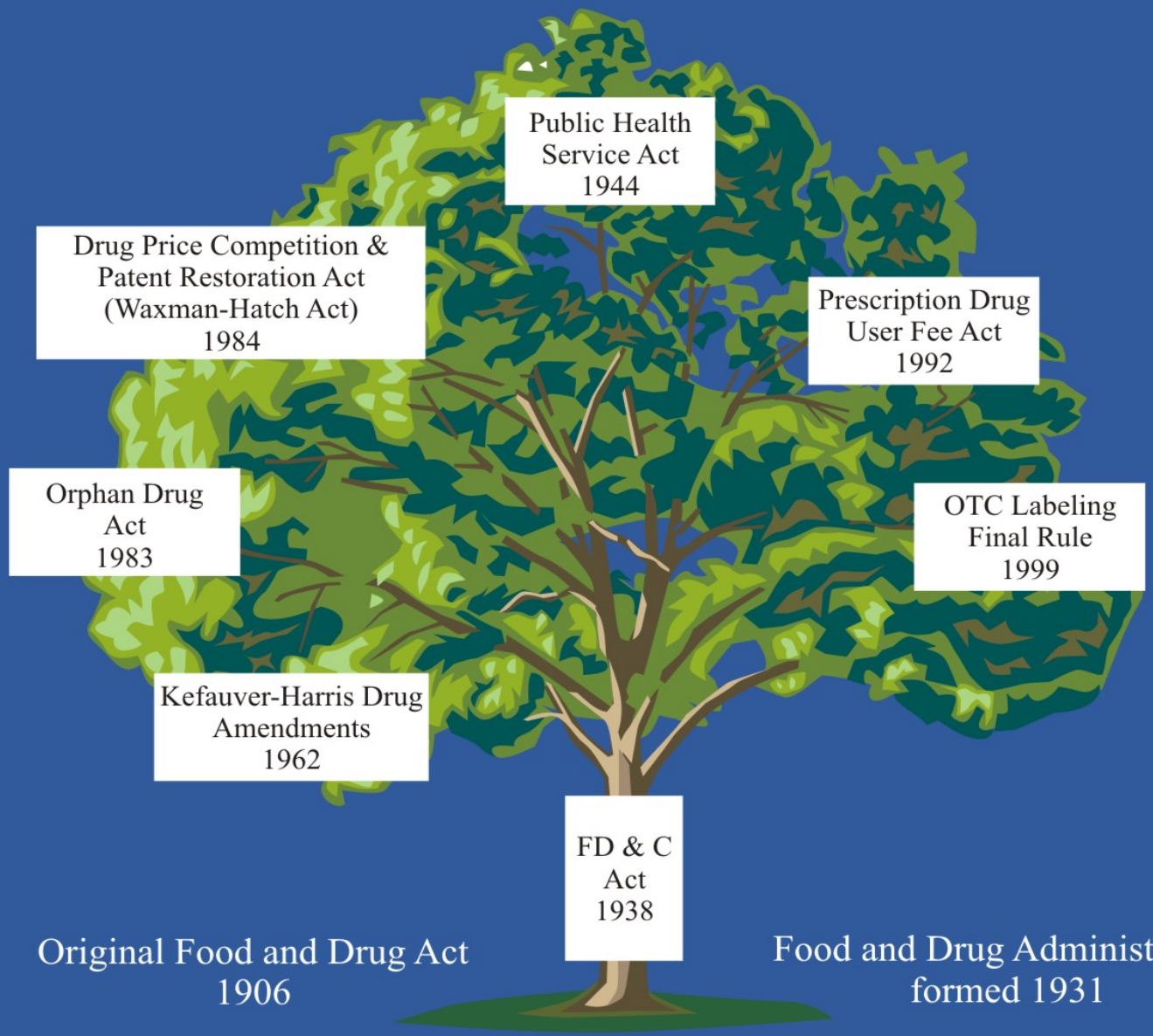
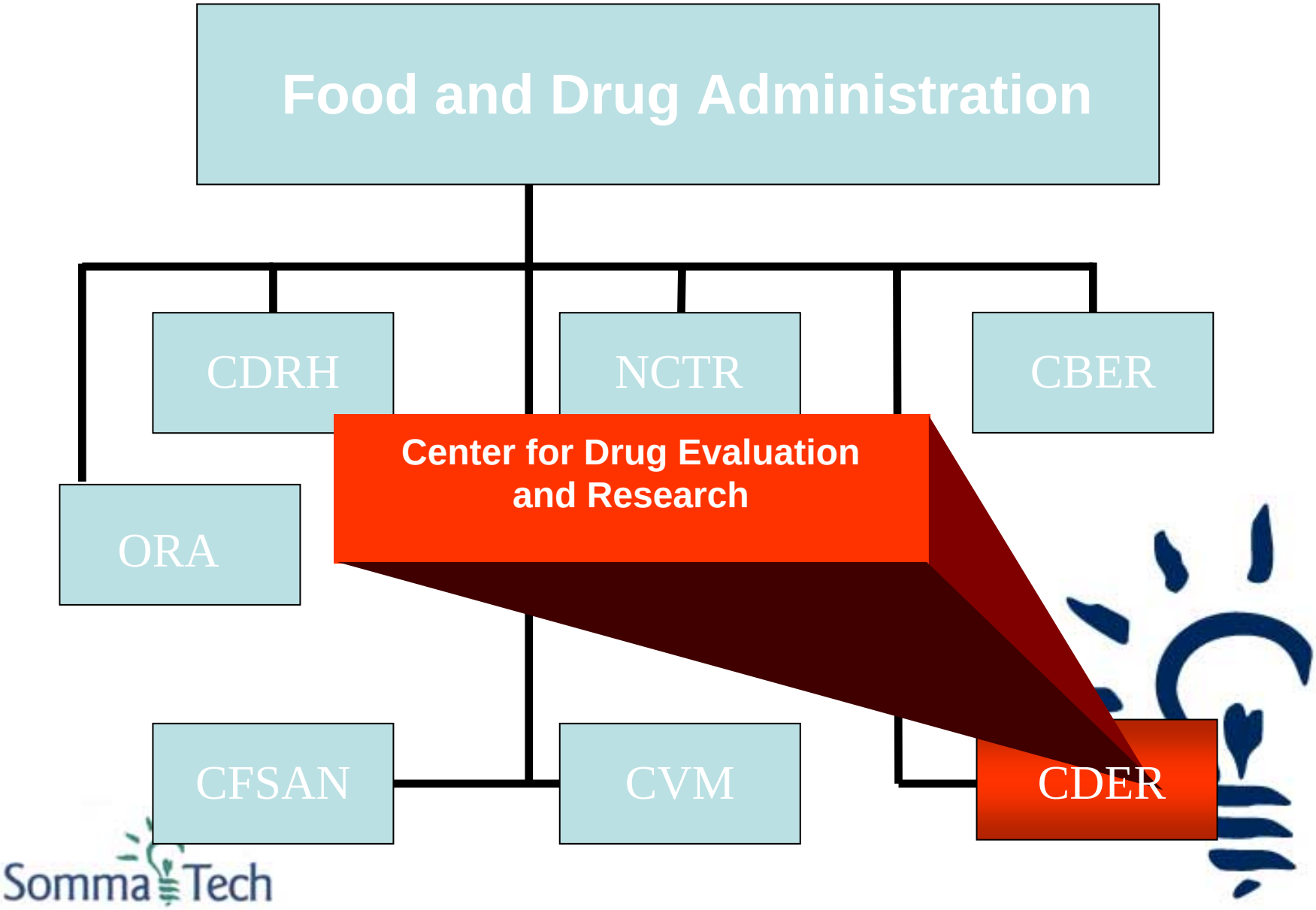

Public Health Service Act 1944
Drug Price Competition & Patent Restoration Act (Waxman-Hatch Act) 1984
Prescription Drug User Fee Act 1992
Orphan Drug Act 1983
OTC Labeling Final Rule 1999
Kefauver-Harris Drug Amendments 1962
FD & C Act 1938
Original Food and Drug Act 1906
Food and Drug Administration formed 1931


Food and Drug Administration
CDRH
NCTR
CBER
Center for Drug Evaluation and Research
ORA
CFSAN
CVM
CDER
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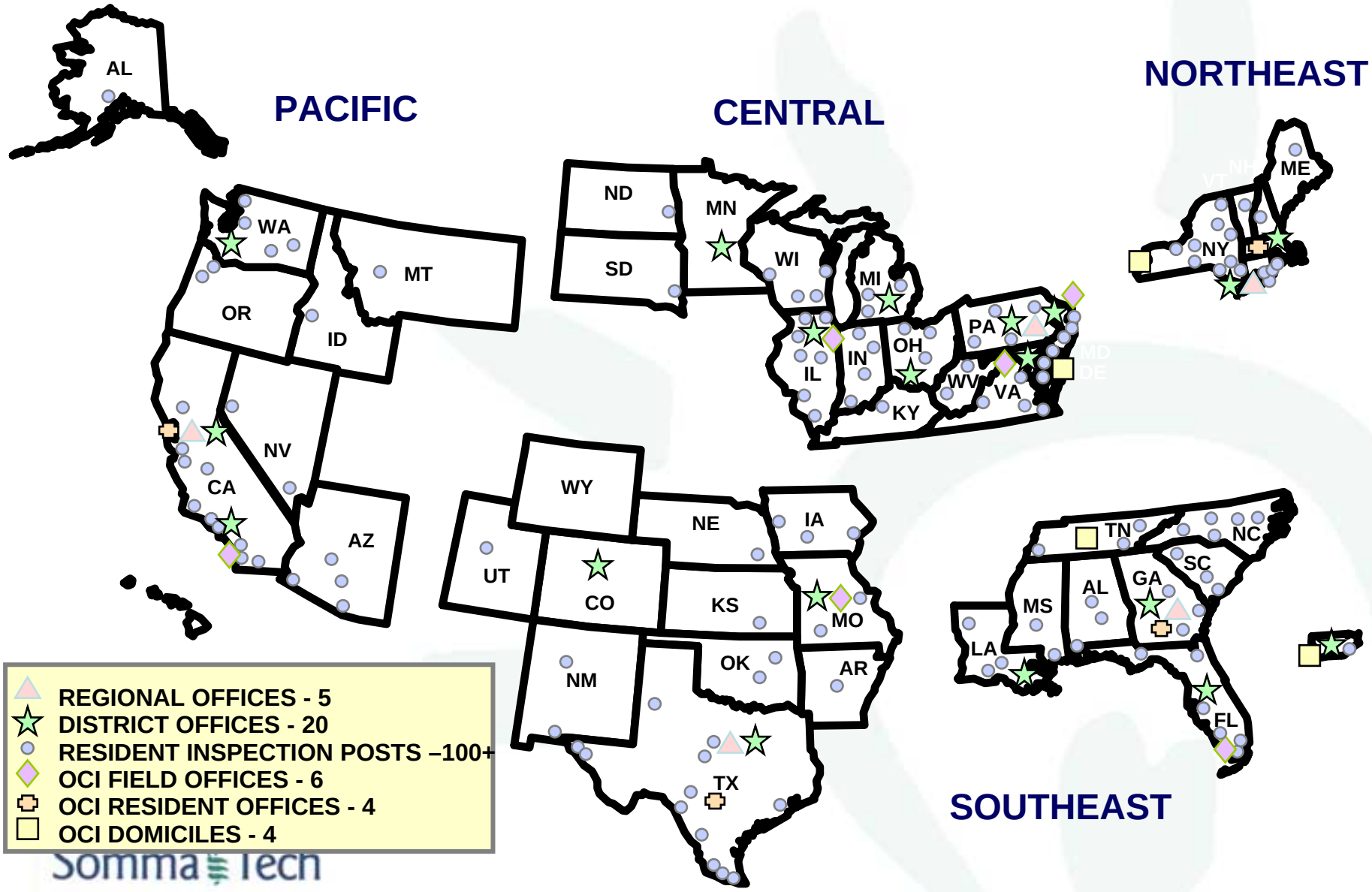
OFFICE OF REGULATORY AFFAIRS
175 OFFICES IN FY 2001



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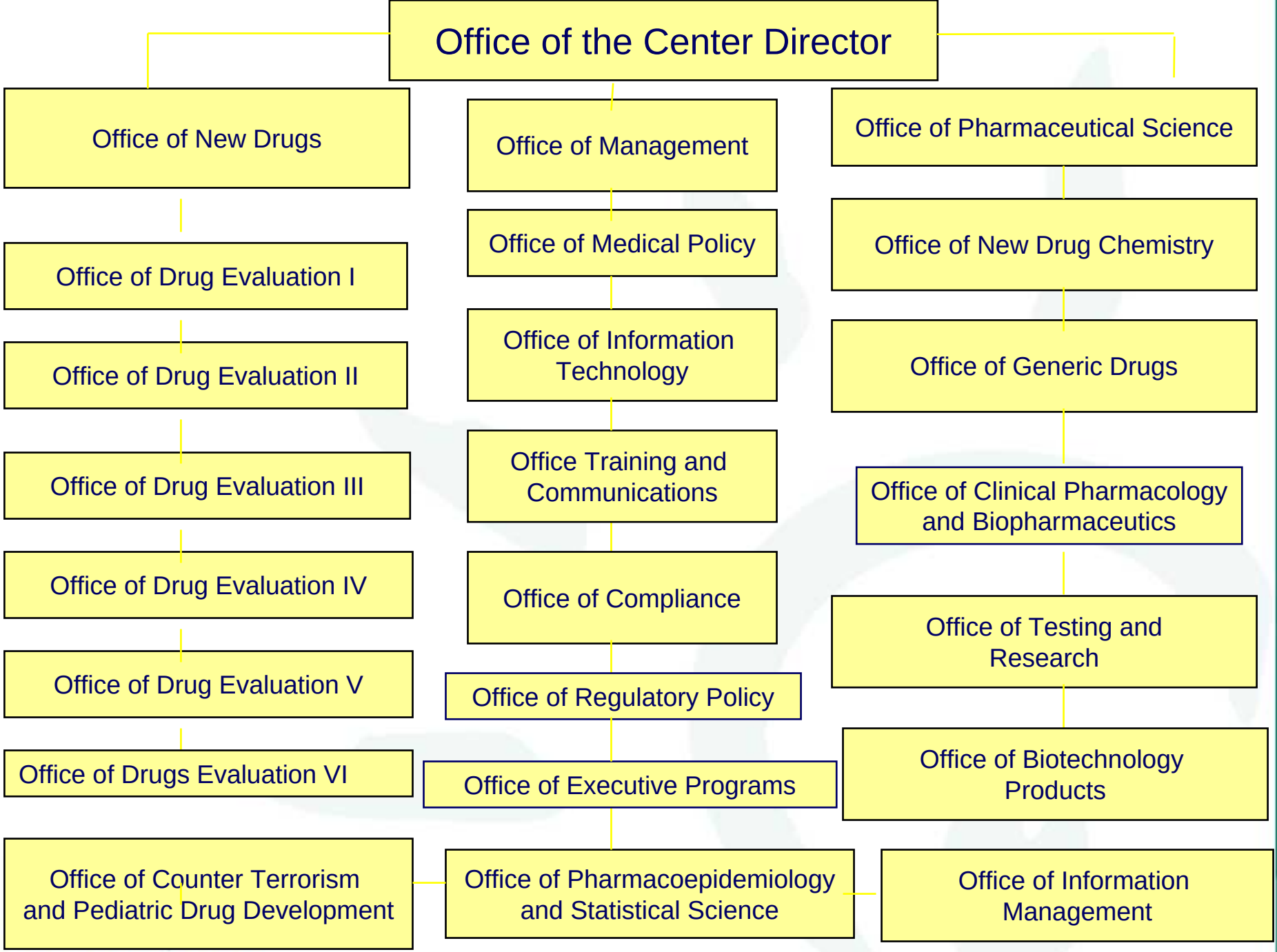
Office of the Center Director
Office of New Drugs
Office of Drug Evaluation I
Office of Drug Evaluation II
Office of Drug Evaluation III
Office of Drug Evaluation IV
Office of Drug Evaluation V
Office of Drugs Evaluation VI
Office of Counter Terrorism and Pediatric Drug Development
Office of Management
Office of Medical Policy
Office of Information Technology
Office Training and Communications
Office of Compliance
Office of Regulatory Policy
Office of Executive Programs
Office of Pharmacoepidemiology and Statistical Science
Office of Pharmaceutical Science
Office of New Drug Chemistry
Office of Generic Drugs
Office of Clinical Pharmacology and Biopharmaceutics
Office of Testing and Research
Office of Biotechnology Products
Office of Information Management

A Drug is Defined as:

a) articles recognized in the official USP, HPUS or NF or any supplement to any of them,

b) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals,

c) articles (other than food) intended to affect the structure or any function of the body of man or other function of the body of man or other animals…..

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What is a Biologic?

Any virus, therapeutic serum, toxic, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives, applicable to the prevention treatment or cure of diseases or injuries of man.

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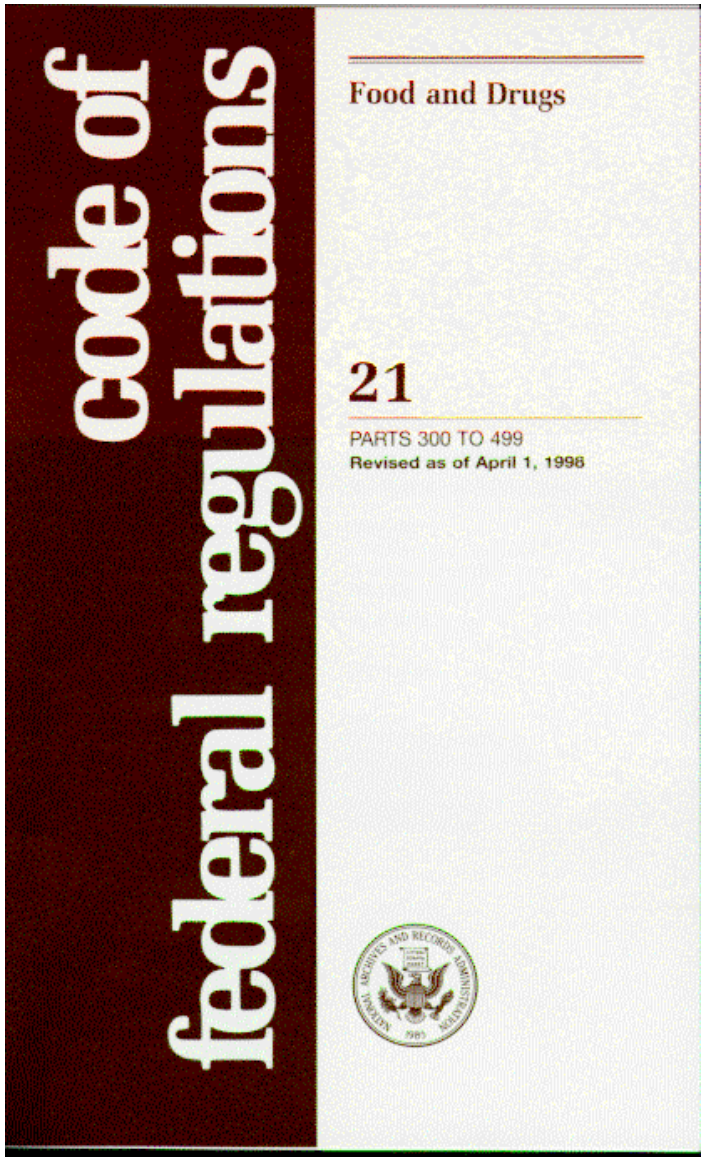

Industry Guidance

http://www.access.gpo.gov/nara/cfr/

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Drug Development Components

- **Discovery and Formulation**
- **Preclinical Evaluation**
- **Clinical Evaluation**
  - **Phases I – IV**
- **Post-Marketing or Life Cycle Management**

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Discovery

Where Do We Get The Chemical Entity?

- Luck or Serendipity
- Historical Search
- High Throughput Screening
- Customized Drug Design
  - Targeted Screening
  - Molecular Modeling
  - Physiological Models
  - Biotechnology

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PRE-CLINICAL RESEARCH

DISCOVERY/SCREENING

SYNTHESIS AND PURIFICATION

INDUSTRY

FDA TIME

FDA & INDUSTRY TIME

SPONSOR/FDA MEETINGS

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Preclinical Evaluation

What Works And What Is Safe?

- **Assess Primary Safety, Biological Activity, and Therapeutic Level**
- ***In vivo* Physiological Models**
- ***In vitro* Physiological Models**
- **1 In 10,000 Compounds Make It Through**
- **3-4 Years to Develop a Candidate**

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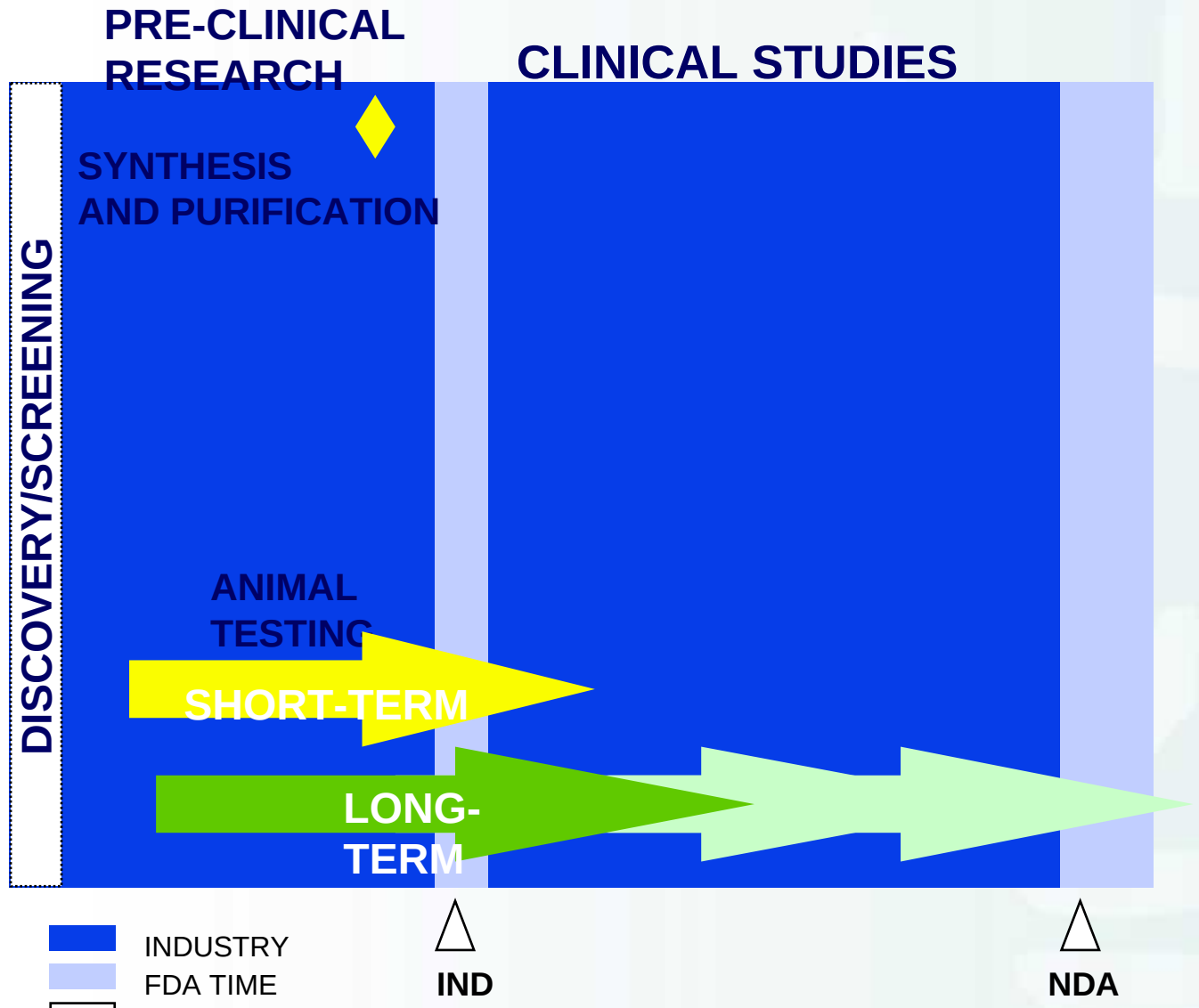
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CLINICAL STUDIES
SYNTHESIS AND PURIFICATION
DISCOVERY/SCREENING
ANIMAL TESTING
SHORT-TERM
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FDA TIME
FDA & INDUSTRY TIME
SPONSOR/FDA MEETINGS

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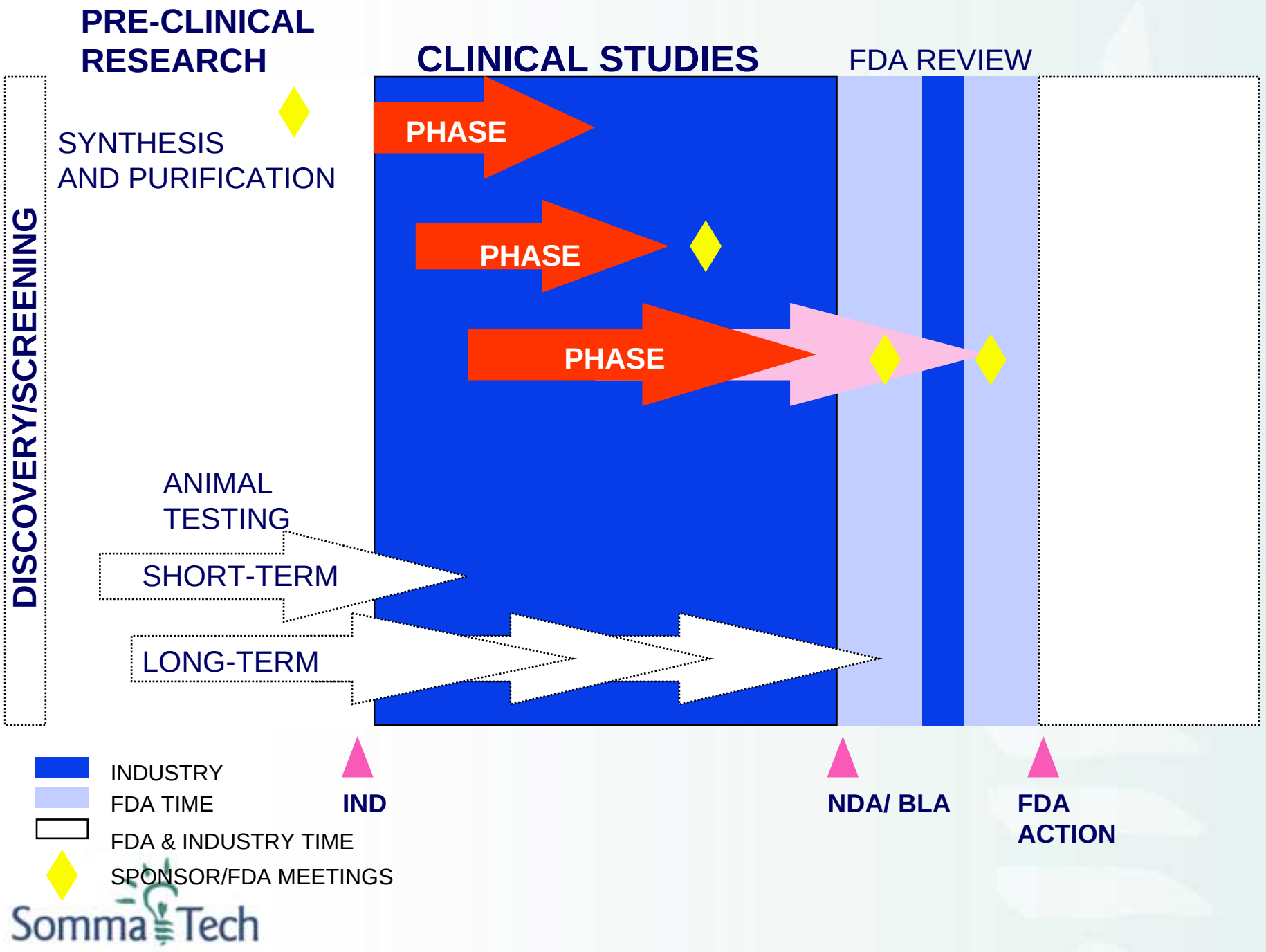
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SYNTHESIS AND PURIFICATION
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FDA & INDUSTRY TIME
SPONSOR/FDA MEETINGS
IND
NDA/ BLA
FDA ACTION
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Phase I	Phase II	Phase III
First in Man	Proof of Concept	Large Multicentered
Safety and Tolerability	Dose Ranging	Usually Placebo-Controlled
Pharmacokinetics	Safety/PK in Special Populations and Risk Factors	Usually Replicated
		Primary Data to Support Marketing Approval in NDA

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Phase I Clinical Trials

What is the Delivery Route?

Is it Safe and Effective?

- Determine Primary Safety, Dose Range as well as a Route of Administration in Humans.
- Normal, Healthy Volunteers (20 – 100)
- 2 of 3 drugs make it this far.
- Normally, 1 year in Phase I trials.

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Phase II Clinical Trials

What is the Effect on the Disease State?
Is it Safe?

- **Evaluate Effectiveness, Determine Adverse Events, and Select Target Dose or Range.**
- **Volunteer Patients (100 – 500)**
- **1 in 3 drugs go this distance.**
- **2 – 3 years in Phase II trials**

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Phase III Clinical Trials

What is the Final Dose?

What is the Market Form?

What Will Be Brought into the Facility?

- **This is also termed the Pivotal Study Phase**
- **Verify Effectiveness, Long-term Safety, and establish Optimal Dose / Range**
- **Volunteer Patients (1000 – 3000)**
- **4 of 5 Drugs Pass**
- **3 years in Phase III Trials**
- **Submit the New Drug Application (NDA)**

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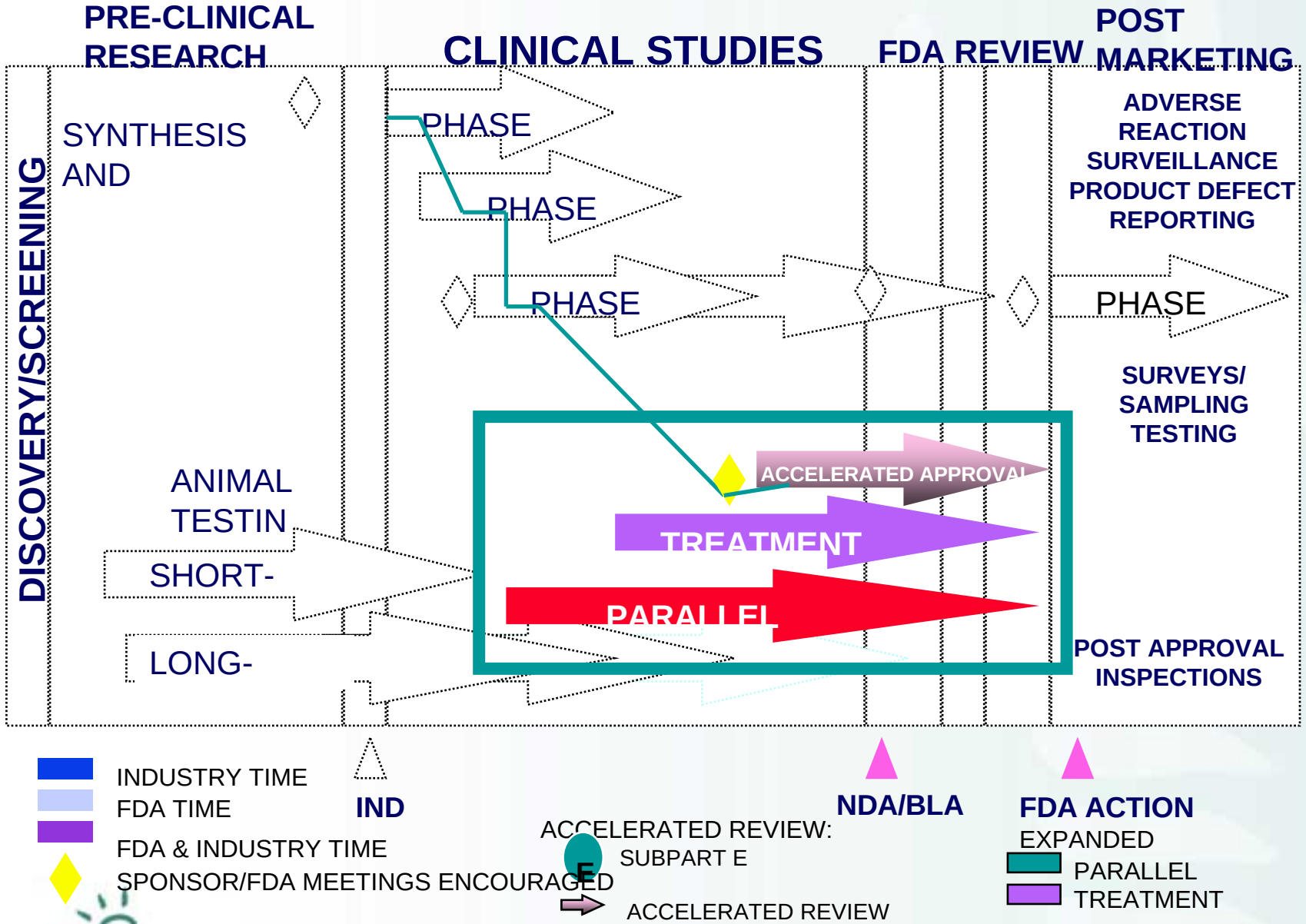
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ADVERSE REACTION SURVEILLANCE PRODUCT DEFECT REPORTING
SURVEYS/ SAMPLING TESTING
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ACCELERATED REVIEW
EXPANDED
PARALLEL
TREATMENT

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New Drug Application (NDA) or Biologic License Application

(BLA) contains the following:

- **Pre-clinical studies**
- **Human clinical studies**
- **Manufacturing details**
- **Labeling**
- **Additional information**

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A Better Way

The equivalent of 50,000 paper pages of data..

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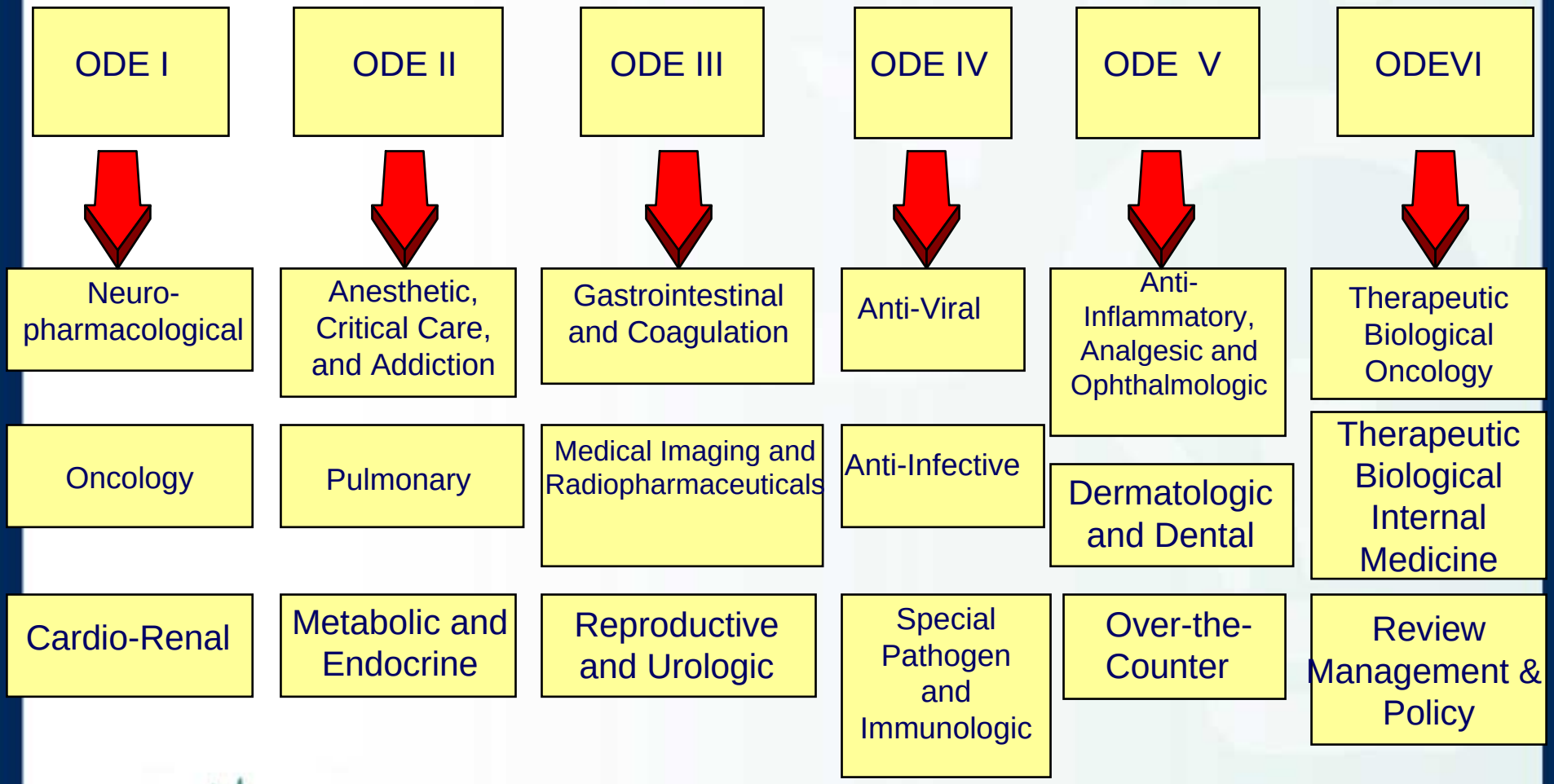
DRUG PRODUCT DIVISIONS



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Review Team

- Project Manager
- Medical Officer
- Chemist
- Microbiologist
- Statistician
- Pharmacologist
- Establishment/Facility Reviewer
- Support Personnel

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Advisory Committee

http://www.fda.gov/oc/advisory/default

- **Panel of OUTSIDE Experts**
- **Provide advice and opinions to the FDA drug review team**
- **FDA advisory committee information**
  - 1-800-741-8138 or 301-443-0572

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Prescription Drug User Fee Act (PDUFA)

http://www.fda.gov/oc/pdufa/default.htm

- **Permits CDER/CBER to charge pharmaceutical manufacturers a fee to review drug applications**
- **These fees provide appropriate resources to accelerate the review of applications**
- **Not the only source of funds for CDER/CBER**
- **Funds go directly to CDER/CBER, not individuals**

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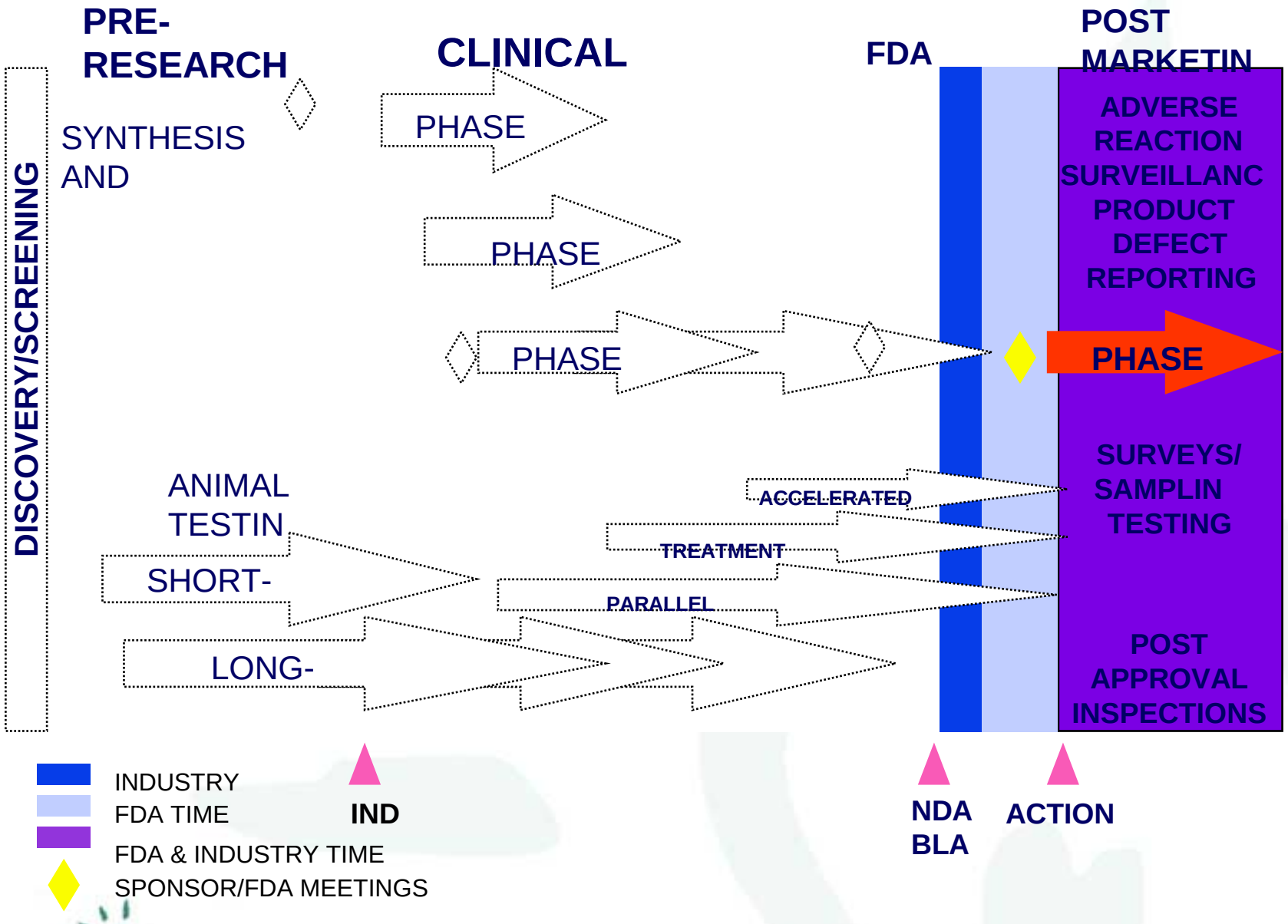
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FDA TIME
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IND
NDA
BLA
ACTION

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FDA Ruling on NDA

- **Approved, Not Approved or Approvable**
- **First two are evident**
- **Approvable:**
  - **Applications that are Approvable means that the basics for approval are evident (safety and efficacy). However, there are some minor aspects that still need correction or modification and when the necessary changes are complete we can grant approval status.**

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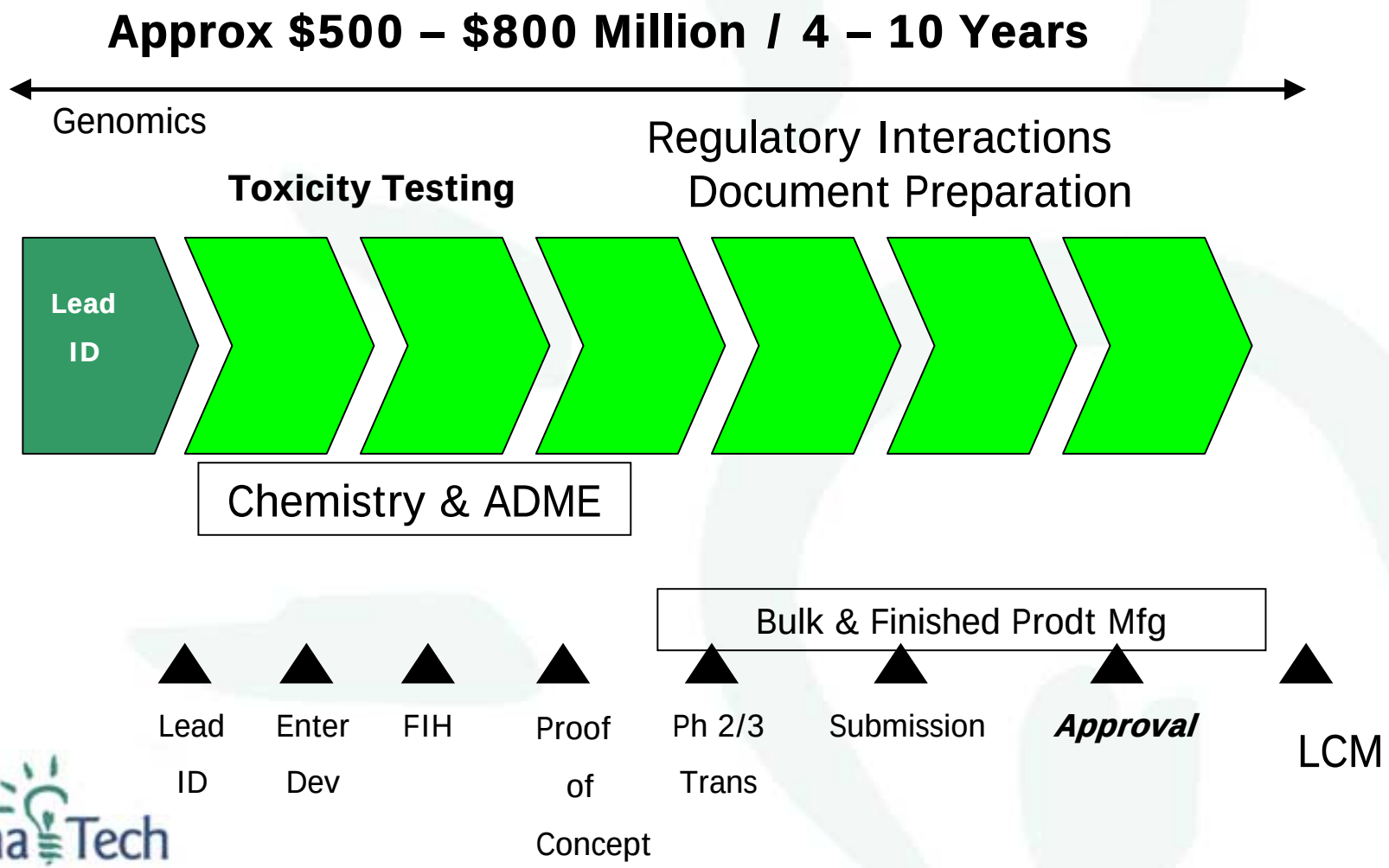
Approx $500 – $800 Million / 4 – 10 Years
Genomics
Regulatory Interactions
Document Preparation
Toxicity Testing
Lead
ID
Chemistry & ADME
Bulk & Finished Prodt Mfg
Lead
ID
Enter
Dev
FIH
Proof
of
Concept
Ph 2/3
Trans
Submission
Approval
LCM

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What Do We Know?

In the normal course of development we create a knowledge store. We need to understand where it is.

- ***Components which are needed to address a review dialogue are fundamentally those needed for determining facility needs.***
- **In conducting the clinical trails, a significant amount of product and process knowledge is gathered.**
- **The data must provide an understanding of the product and process in terms of fundamental, mechanistic properties as opposed to empirical.**
- **Utilization of prior knowledge in defining the product and process.**

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What Do We Know?

What Tools Do We Have to Better Manage Knowledge for Process Introduction and Facility Design?

- Tablet development is time consuming and still retains some iterative functions.
- The least understood being the transfer from lab scale to pilot / commercial scale.
- New techniques in the area of compression simulation as well as hybrid continuous process systems exist.
- These technologies reduce the tacit knowledge of scale-up with the explicit knowledge gained using a measurable and reproducible data base.

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dissolution rate
mechanical strength
porosity
compression
consolidation
compaction

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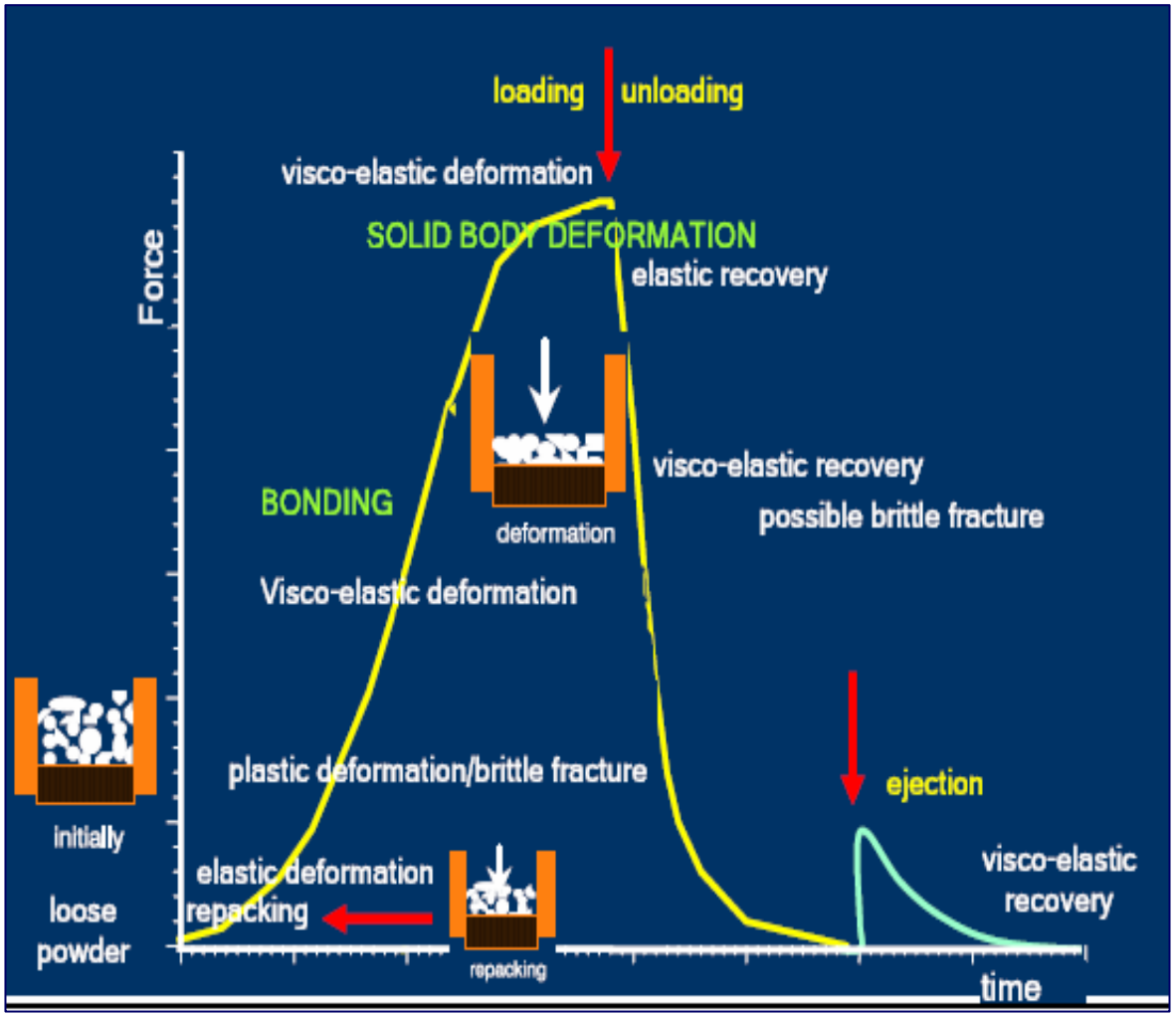
loading
unloading
visco-elastic deformation
SOLID BODY DEFORMATION
elastic recovery
Force
visco-elastic recovery
possible brittle fracture
BONDING
deformation
Visco-elastic deformation
plastic deformation/brittle fracture
ejection
initially
loose powder
elastic deformation repacking
repacking
visco-elastic recovery
time

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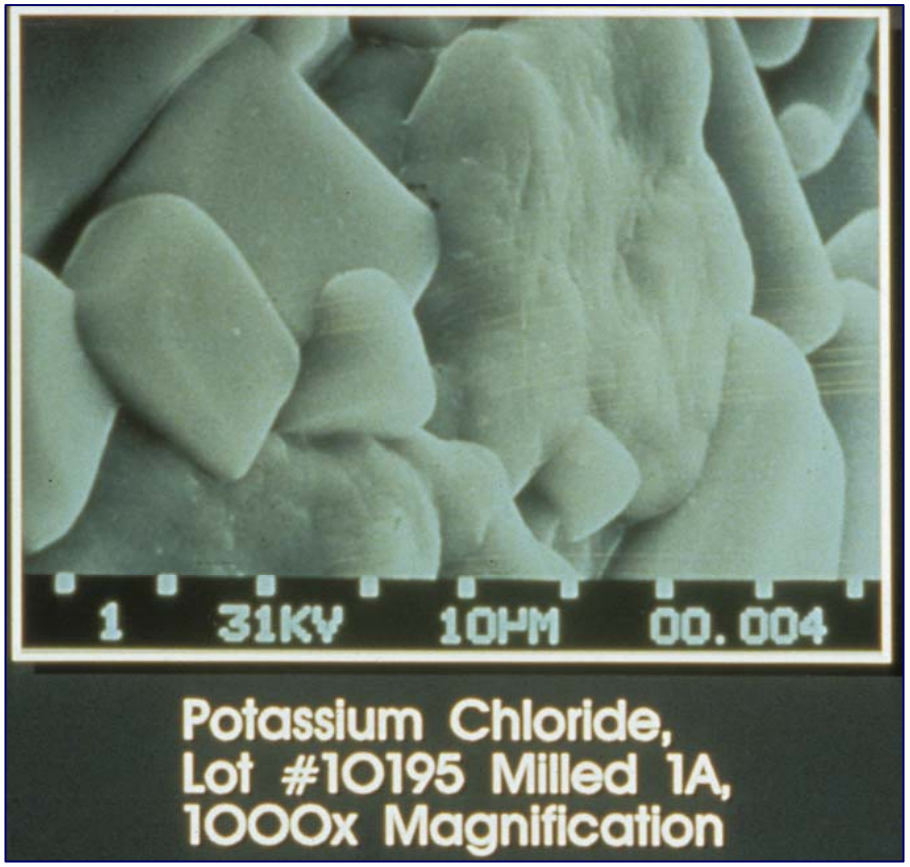
1 31KV 10MM 00.004
Potassium Chloride,
Lot #10195 Milled 1A,
1000x Magnification

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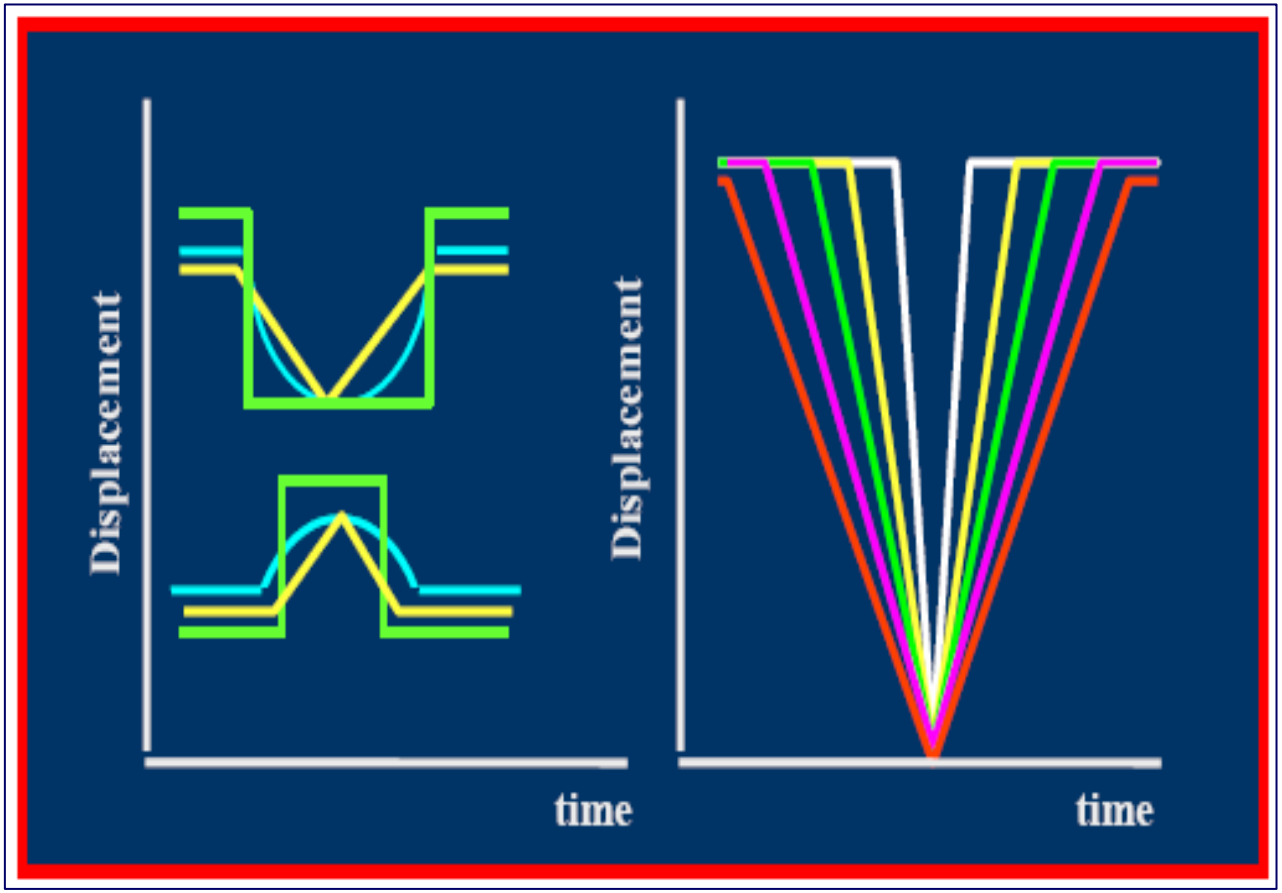
Compaction Profiles and their importance



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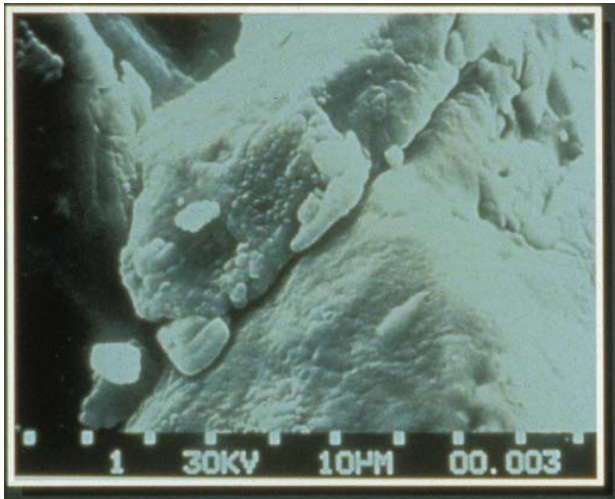
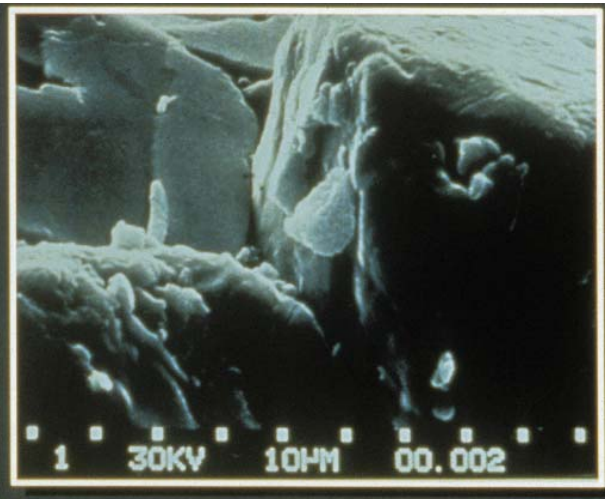


Potassium Chloride
Lot #L7490 140-160 μm
Undried, 1000x Magnification



Potassium Chloride
Lot #L7490 140-160 μm
Dried, 1000x Magnification

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Stylcam
A New Generation Compaction Simulator

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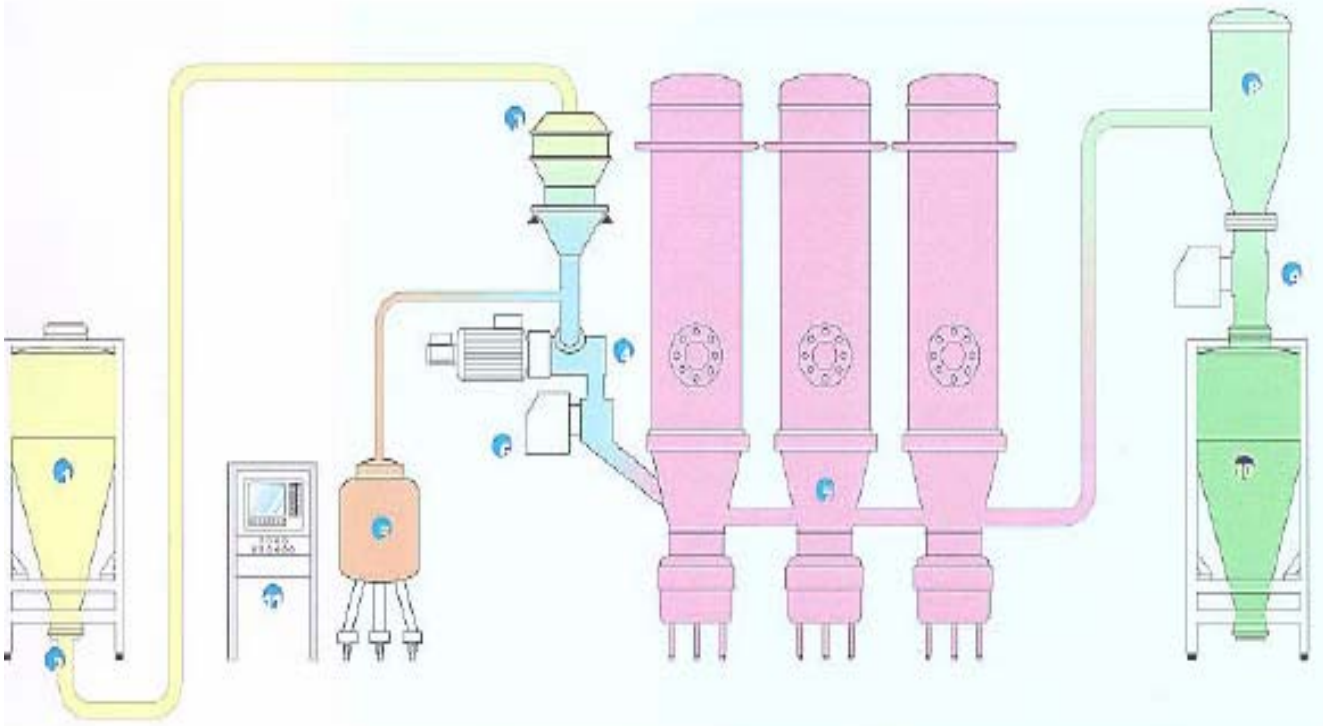
Glatt Multicell GMC 30



Courtesy of Prof. H. Leuenberger

Technology	Lödige 900/WSG 300	Multicell	
Process	Batch process	Continuous process	
Batch size	Fixed to equipment capacity	Flexible depending on process time	
Mode of operation	Manual-driven and monitored	Almost lights-out-operated	
Floor space	130 m²	100 m²	-23%
Investment	1,6 Mio. US$	2 Mio. US$	+25%
Volume of equipment	900 l (270 +/- 50 kg)	30 l (8 +/- 2 kg)	
Output	55 kg/h	96 kg/h	+75%
Overall output	10 kg/24 h/m²	20 kg/24 h/m²	+100%

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So ask yourself:

”When we begin to define facility needs and required capacity, did we have all these aspects covered?”

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What Should We Adopt for Plant Introduction?

- **Clear roadmap for product development leading to technology transfer.**
- **Data maintained in meaningful summaries with narratives (not a thesis!).**
- **Plans must include post approval or life cycle changes, such as increased demand.**
- **The data must be used to adequately define our product and process or design space.**

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What Do We Have to Define Our Quality Analysis and Design Space?

- Drug substance specifications, which include physicochemical properties.
- Drug product specifications as well as basic knowledge of excipient interactions and process understanding.
- Raw material characteristics and variability.
- Target product profile, “desired state”.
- Stability of clinical forms / prototypes as well as drug substance.

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Consider these questions. If answered upfront, they have a significant effect on the facility and position us for success.

- What properties of the drug substance effect product performance?
- What is the formulation intended to do given drug substance properties?
- What are the special requirements of the drug substance and drug product?
- How do we define the critical process steps?
- What are the process parameters for each step and how are they monitored and controlled?

How do we effectively answer these questions and prepare for a rapid plant introduction and submission in support of the NDA?

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Process development should be used as a platform to establish proven acceptable ranges starting early in the development cycle.

Proven Acceptable Ranges:

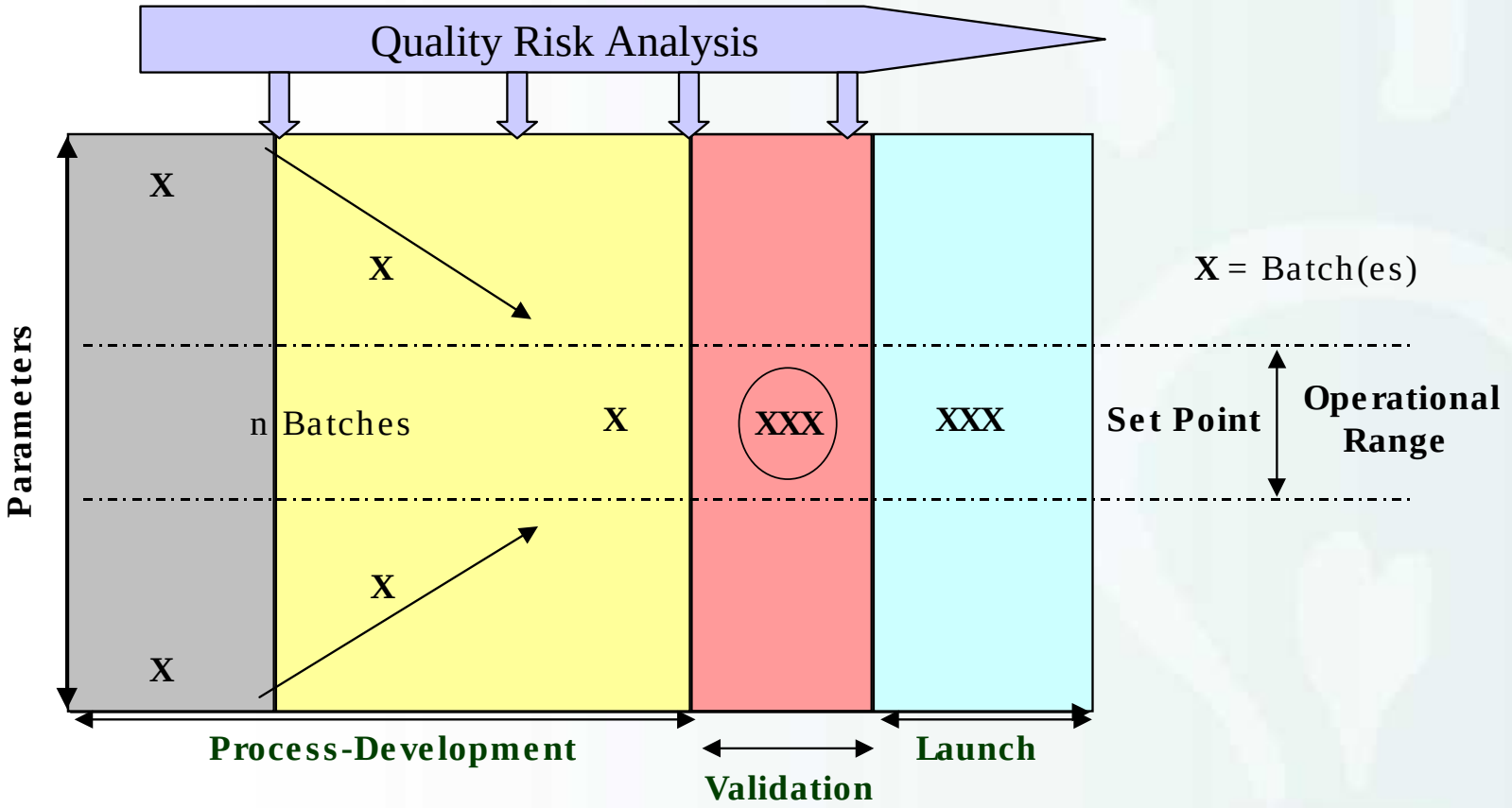
- **Provide a historical database for the product.**
- **May start at a broad range during the early stages which are subsequently tightened.**
- **Require a systematic reporting method which is referenced during clinical batches, pilot scale, scale-up and validation.**
- **Become a part of the knowledge store for the product and basis for statistical process control,facility design and maintenance.**

Proven Acceptable Ranges (continued):

- Establish a chart for all process steps and controllable parameters.
- Brief description of the process step and controlled parameter.
- The engineering units which are recorded.
- The anticipated result for exceeding the proven acceptable range.
- Risk evaluation of exceeding the range is it major or minor.

Proven Acceptable Ranges (continued):

- Establish the operating range to be utilized in the plant for process control.
- The proven acceptable range is documented. It may be referenced in the development report, batch records, validation reports and protocols.
- Acceptable ranges which are dependent on scale changes may be listed as to be determined (number of spray guns, FBD air volumes).



Validation: specified parameters at operational range if required (by operations).

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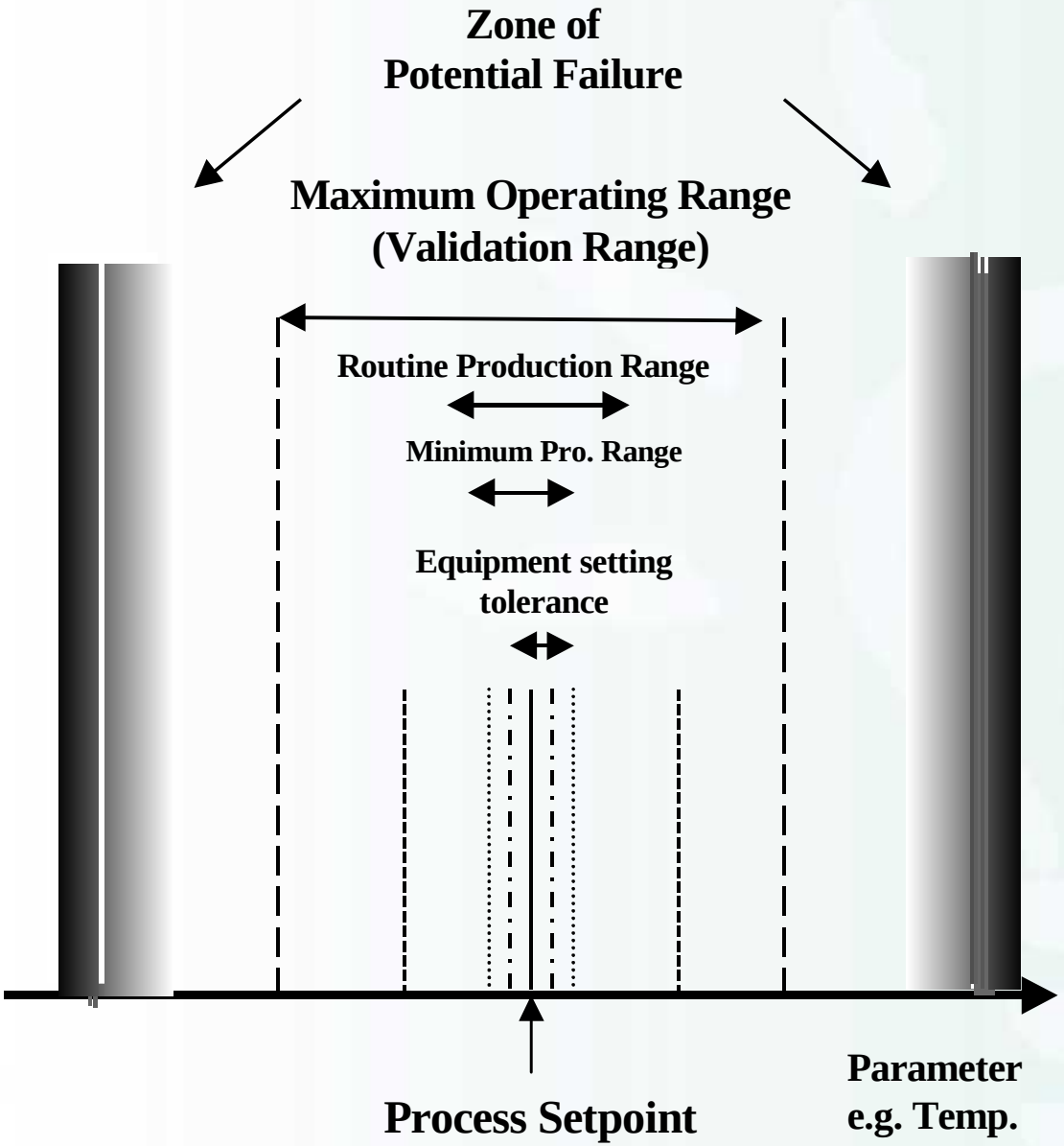
Zone of
Potential Failure
Maximum Operating Range
(Validation Range)
Routine Production Range
Minimum Pro. Range
Equipment setting
tolerance
Process Setpoint
Parameter
e.g. Temp.

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Establish both a *good scientific* and *common sense* approach to rate each process step as having high, low or no impact on product quality.

This will aid in minimizing the subsequent validation effort (SUPAC equipment terms add clarity).

Critical Area Checklist:

- **Weighing / addition of raw materials (vendors, personnel)**
- **Pre-blending of materials (volume, bulk density)**
- **Granulation (speed, rate of addition, time)**
- **Drying (LOD, time, temperature)**

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Critical Area Checklist (continued):

- **Particle size reduction (screen, feed rate, speed)**
- **Blending / lubrication (time, bulk density, assay)**
- **Compression (speed, feed rate, force)**
- **Coating (suspension prep., endpoint, air flow, temperature, spray rate)**

This provides for subsequent data review for traits, atypical behavior and suspected facility excursions.

Data may be shown graphically to identify process variability within established specifications (process comparability).

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In the context of PAT we now have the required framework to begin to define:

- ***Process Critical Control Parameter (PCCP)*** **– Process variable that can be controlled to maintain critical product quality attributes.**
- ***Parametric Release*** **– The release of product based on all process parameters being within pre-validated tolerances instead of on the results of final product testing.**
- ***Sensitivity Analysis*** **– Systematically analyzing the impact of process deviation(s) on the quality attributes of a product.**

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If we have established this framework, our next steps would be to define:

- PAT Tools:
  - Process and endpoint monitoring and control tools.
    - Identify and measure critical material and process attributes.
    - Design a process measurement system to allow real time monitoring.
    - Design process controls.
    - Develop mathematical relationships.
  - Continuous improvement and knowledge management tools.

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PAT Tools

- Multivariate data acquisition and analysis tools
- Modern process analyzers or process analytical chemistry tools
    - Off-line in a laboratory
    - At-line in the production area
    - On-line via a process slipstream
    - In-line
    - Non-invasive at-line

PAT Test Technologies Examples:

- Near Infrared Spectroscopy
- Raman Spectroscopy
- Laser Induced Fluorescence
- Thermal Effusivity
- Magnetic Resonance
- Conductivity/TOC
- pH
- Refractive Index

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In any case, PAT based or not, we have established a means to facilitate:

- **Process Understanding**
  - Critical sources of variability known
  - Variability is managed
  - Product quality attributes can be predicted
  - Rationale for changes in output (e.g.,batch size)
- **Facility Requirements and Monitoring**
- **Risk Based Approach – level of process knowledge commensurate with amount of risk to product**
- **Integrated System Approach**
- **Real Time Release**

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Many firms apply PAT and use add on technologies and try to retrofit existing processes.

- The problem here is the process understanding along with the attempt to pattern acceptable results is usually somewhat anecdotal.
- By application of the aspects of knowledge management new technologies which use neural networks and artificial intelligence are more effective.
- By taking the explicit knowledge gained during development experiments a data set is established which may be applied for process control in real time with responses based on the defined design space.

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What is the take away message?

Knowledge may be categorized into several areas which we need to manage during development.

- **Incremental knowledge** is a result of ongoing activities and grows with each development project.
- **Tacit knowledge or "sticky knowledge"** cannot be communicated in a formal, systematic or codified language. "Commonly referred to as a feel for the process."
- **Explicit knowledge** may be set down in procedures and easily codified.

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What is the take away message?

Explicit knowledge is cost effective and transferable.

- **It produces a well defined set of core technologies.**
- **It speeds development and process introduction.**
- **We deal with explicit knowledge daily. It is the basis of our work (robust formulations, meaningful specifications, facility design).**

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What is the take away message?

Incremental knowledge is the impetus for rethinking business processes and is intrinsic to continuous improvement. We learn as we go and share the experience.

- **It improves the quality of "handbooks."**
- **It moves the collective knowledge base forward.**
- **It provides information which reduces uncertainty.**
- **Reducing uncertainty accelerates process transfer.**
- **Eliminates "over designing" the facility.**

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What is the take away message?

Technology=Knowledge=Continuous Improvement

So what is at the heart of continuous improvement and what aspect links this to our process and facility?

- **Learning is more accurately organizational learning.**
- **Knowledge transfer is the basis for this effort.**
- **Learning occurs during transfer within teams, across teams and from the market.**
- **Market learning is gained from what we gather from our competitors (industry news, vendors,regulatory citations).**

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The following case study contrasts taking an old product and developing a “new” or novel form.

Background:

Develop a modified release product which will match clinical requirements and address an unmet medical need.

Objectives:

- **Provide up to 12 hours of activity.**
- **Maintain dosage form size.**
- **Use available conventional technology.**
- **Match current in-vivo profile as established by clinical practice.**
- **Leverage process and site changes.**

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Outcome

- A “fast and slow” study was selected as the best approach to establish a range.
- Clinical materials were prepared based on simulations and the anticipated need for release rate specifications.
- These specifications were balanced against process capability and envisioned variability.
- Move forward with a study to confirm the in-vitro results.

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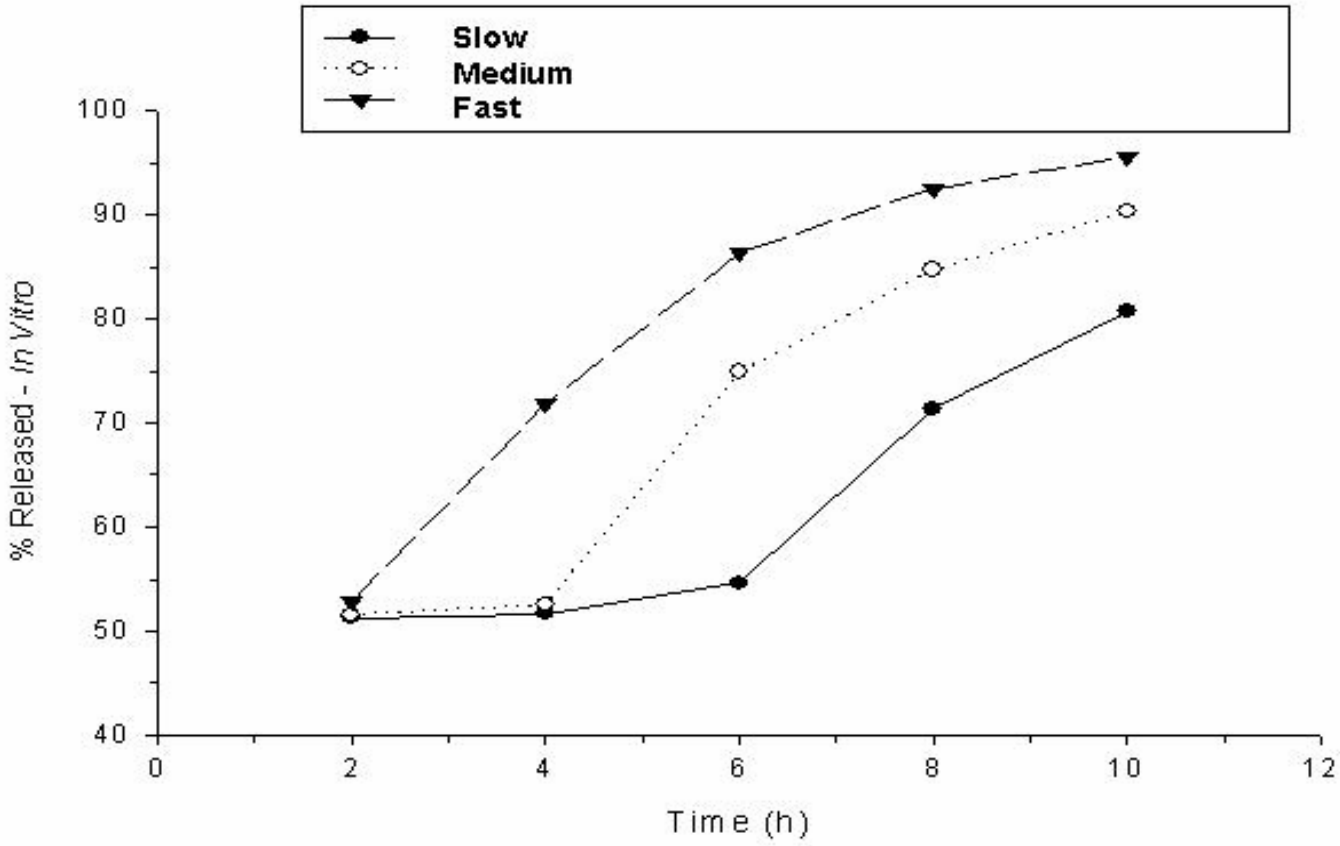
Slow
Medium
Fast
100
90
80
70
60
50
40
% Released - In Vitro
0
2
4
6
8
10
12
Time (h)

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Study Results

- **The study was conducted comparing the fast and slow samples to the target as well as a reference.**
- **This provided the establishment of a BE baseline for the extremes studied in this product.**

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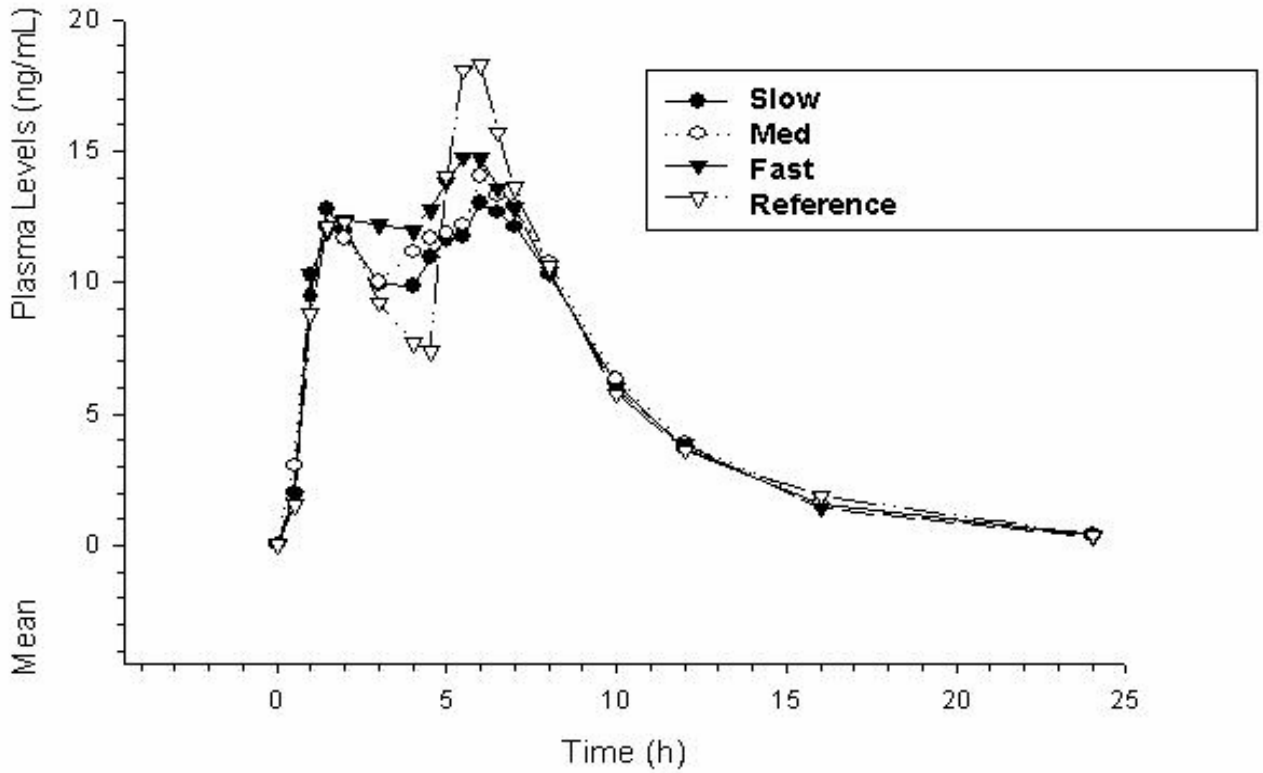
Plasma Levels (ng/mL)
Mean
20
15
10
5
0
0
5
10
15
20
25
Time (h)
Slow
Med
Fast
Reference

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Process Comparison

Current Product

- **Standard non-coated tablet.**
- **Wet granulation.**
- **High shear mixer, fluid bed dryer, milled, blended, compressed.**

Novel Product

- **Hard shell capsule.**
- **Coated beads using several coating processes.**
- **Column coater, encapsulation, check weighing.**

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Process Comparison

Process Time and Facility Requirements:

- **For a million units, the time needed is 24 hours for the tablets, 32 hours for the capsules.**
- **Facility space was the same as the check weighing system took the place of the granulation process.**

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3DP™ Process
Aprecia (Langhorne, PA)

- **Process Overview**
  - Computer Aided Design and Manufacturing (CAD/CAM)
  - Adaptation of ink-jet printing technology
  - Layer-by-layer build process
  - Drying and Retrieval
- **Main Attributes**
  - Control over internal and external geometry
  - Compositional gradient
  - Accuracy and precision of deposition
  - Microdosing and Multi-drug loading
  - Less dependency on batch size: less scale up issues
  - Rapid prototyping

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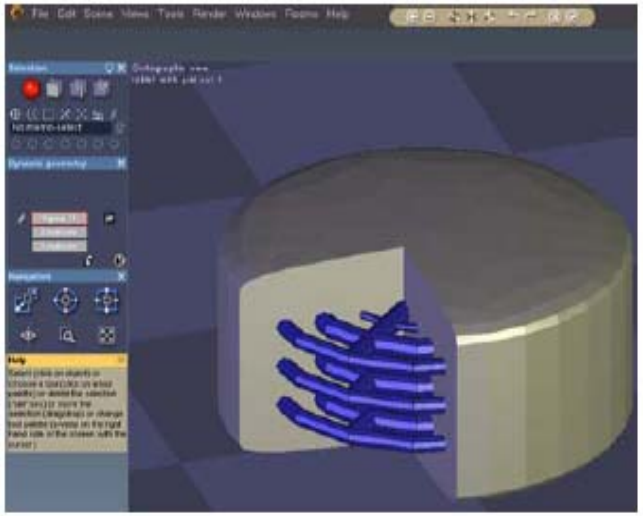
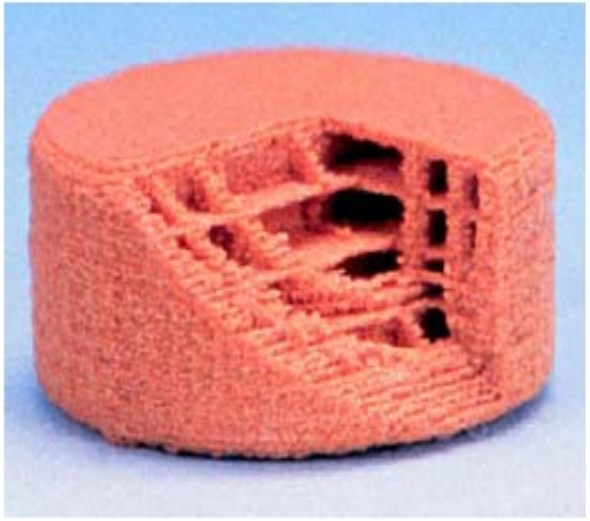
3DP™ Process
Aprecia (Langhorne, PA)





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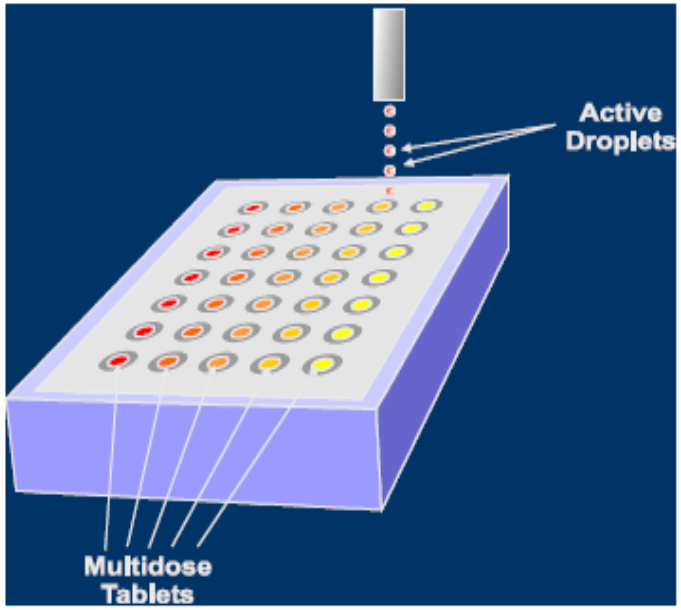
3DP™ Process
Aprecia (Langhorne, PA)



Hagia Sophia

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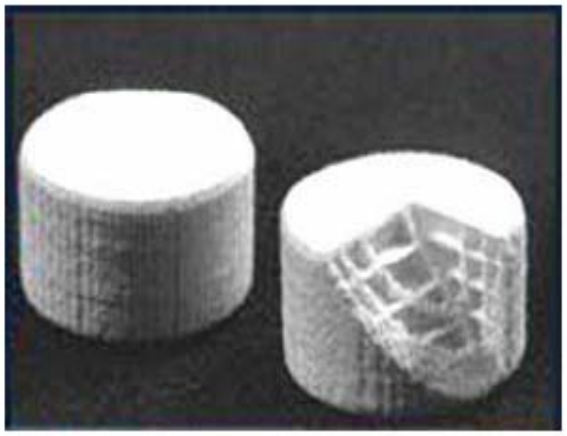
3DP™ Process
Aprecia (Langhorne, PA)



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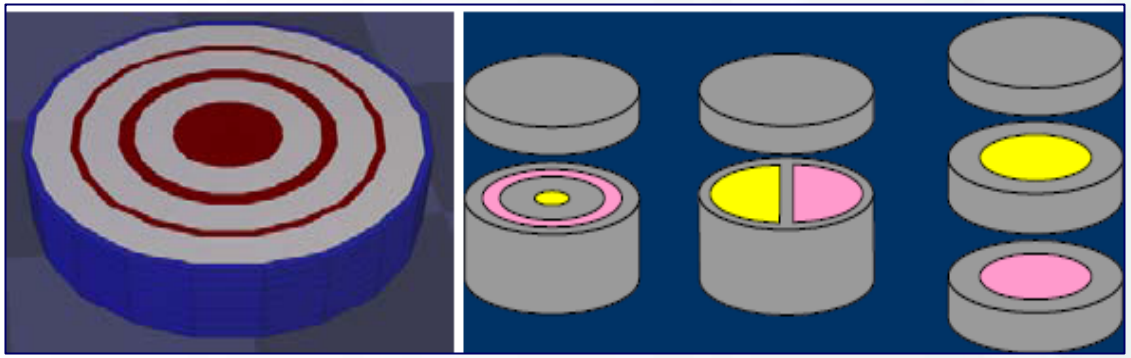
3DP™ Process
Aprecia (Langhorne, PA)



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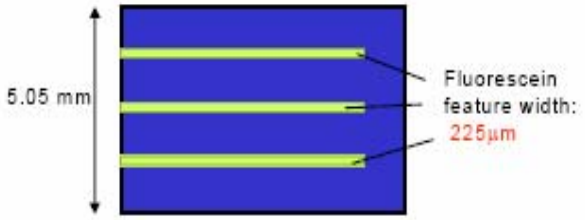
3DP™ Process
Aprecia (Langhorne, PA)

- Exploit the ability to place designed markers within dosage forms
- Location, amount, and shape of the marker can be precisely controlled
- Invisible markers increase the level of difficulty for counterfeiting
- Markers can be designed specifically for product or customized for each batch



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Summary

- The systems to achieve this are simple and may be applied to existing business models.
- In any case with product knowledge we are positioned for success and to deal with plant design and process introduction.
- New technologies exist which remove the sticky knowledge elements for process control.
- There are technologies which allow the lab experience to be transferred directly into manufacture eliminating the scale-up issue and permitting the lower risk based scale-out scenario.
- Based on the drug substance properties entire trains of unit operations may be replaced by one highly advanced system.
- Know what you do not know.

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Summary

- The development aspects needed to support a submission are very similar to those which are key to design of a cost effective facility and process.
- Systematic updates provide a means to leverage key CMC aspects of our submission.
- Answering questions along the way prevents the “fishing expedition” and delay.
- Clear path to where we see the product in its life cycle allow proactive rather than reactive post approval submissions strategies.
- We have the majority of the data available but need to configure it to defend our product,facility, and process.

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