RET 2012

Industrial Perspective: Basic Elements of Pharmaceutical Research & Development

Department of Chemical, Biological & Pharmaceutical Engineering, NJIT, Newark, NJ, July 05, 2012

Ecevit Bilgili (with contributions from Boris Khusid and Raj Dave)
Department of Chemical, Biological, and Pharmaceutical Engineering
NJIT, Newark, NJ

NJIT New Jersey's Science & Technology University

Outline of the Presentation

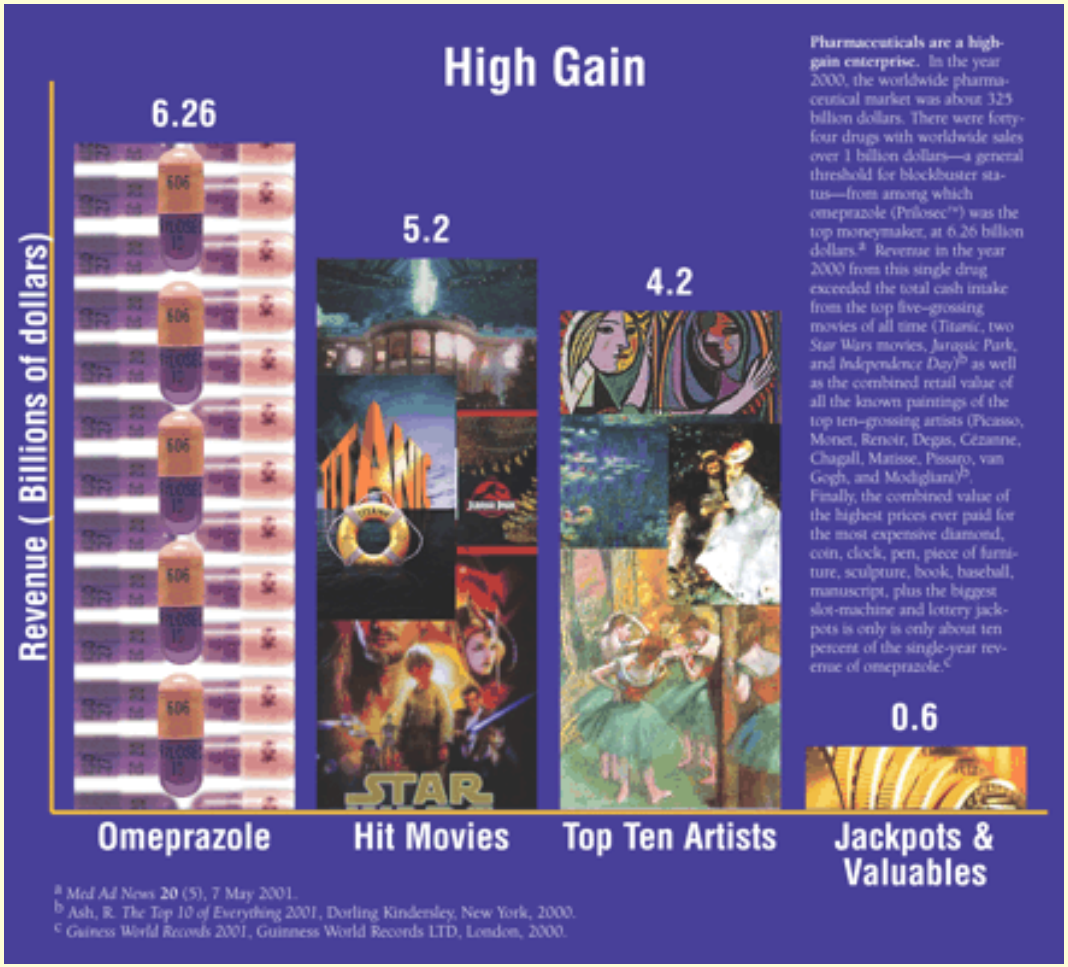
- Pharmaceutical business
- Drug development cycle
- Dosage form attributes
- A review of common process trains

Pharmaceutical Business & Drug Development Cycle

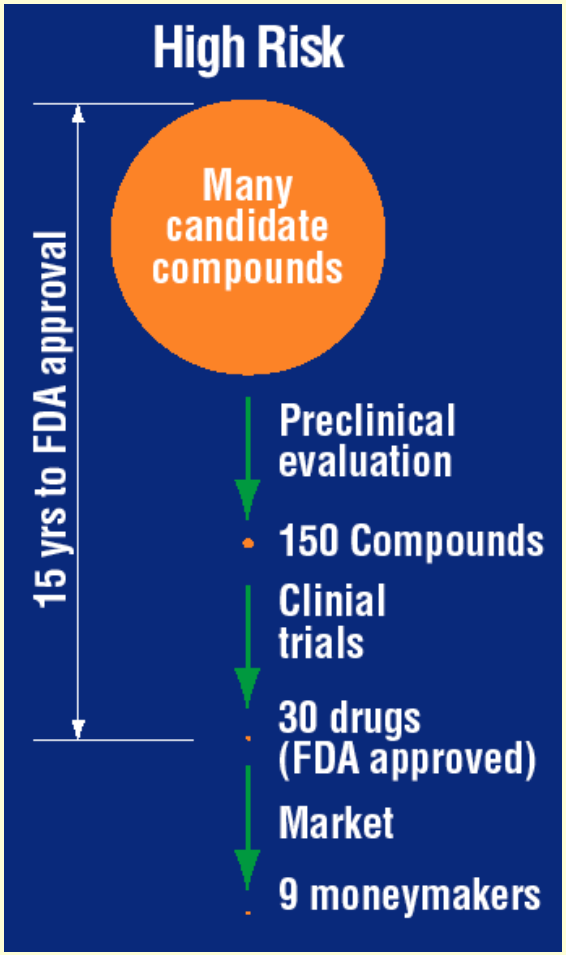
About Pharmaceutical Industry (I)

- Pharmaceuticals are a high-gain enterprise (2008 world-wide pharm. market: ~$700B, Pfizer's 2008 revenue: $48.3B, Lipitor:$13B, profit: $8.1B, 46 in Fortune 500)
- Pharmaceuticals are a high-risk enterprise:
  - Only a small fraction of the thousands of candidate compounds entering discovery/pre-clinical phase makes money!
  - Generics competition (patent cliff: 2010-2012)
  - Highly regulated industry (FDA and other world-wide agencies may change their scrutiny of INDA or NDAs)
  - Payors (goverments, insurance companies) have a huge influence!
  - More combination products (more of the same) than new mechanisms/molecules (harder to discover)
- Pharmaceuticals (drug products) manufacture relies on batch processing; continuous processing paradigm shift is yet to arrive.

About Pharmaceutical Industry (II)



Prilosec (Omeprazole): Top money-maker in 2000

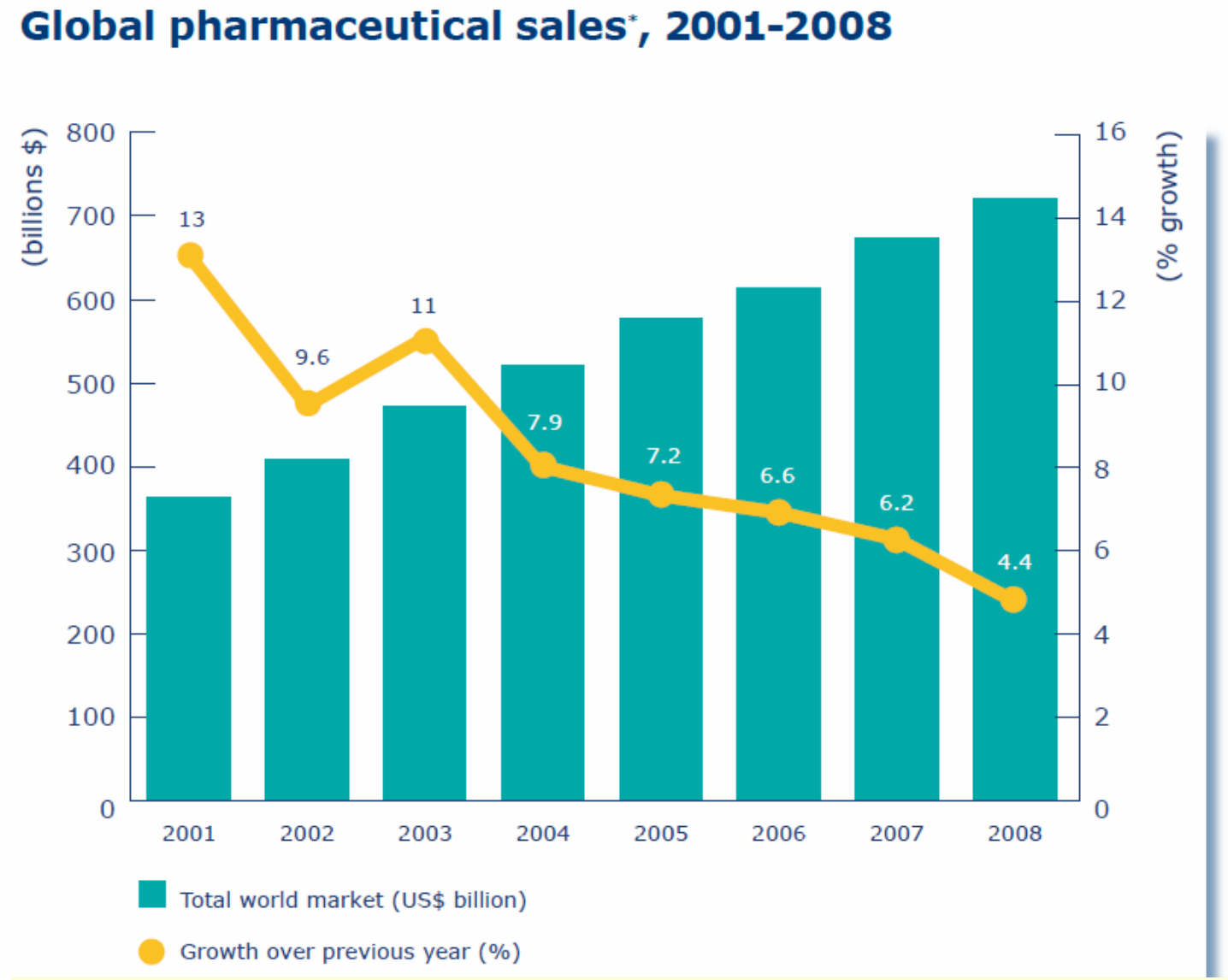


2001 Data

NJIT New Jersey's Science & Technology University

B.A. Berkowitz, G. Sachs, Molecular Interventions
http://molinterv.aspetjournals.org/content/2/1/6.full

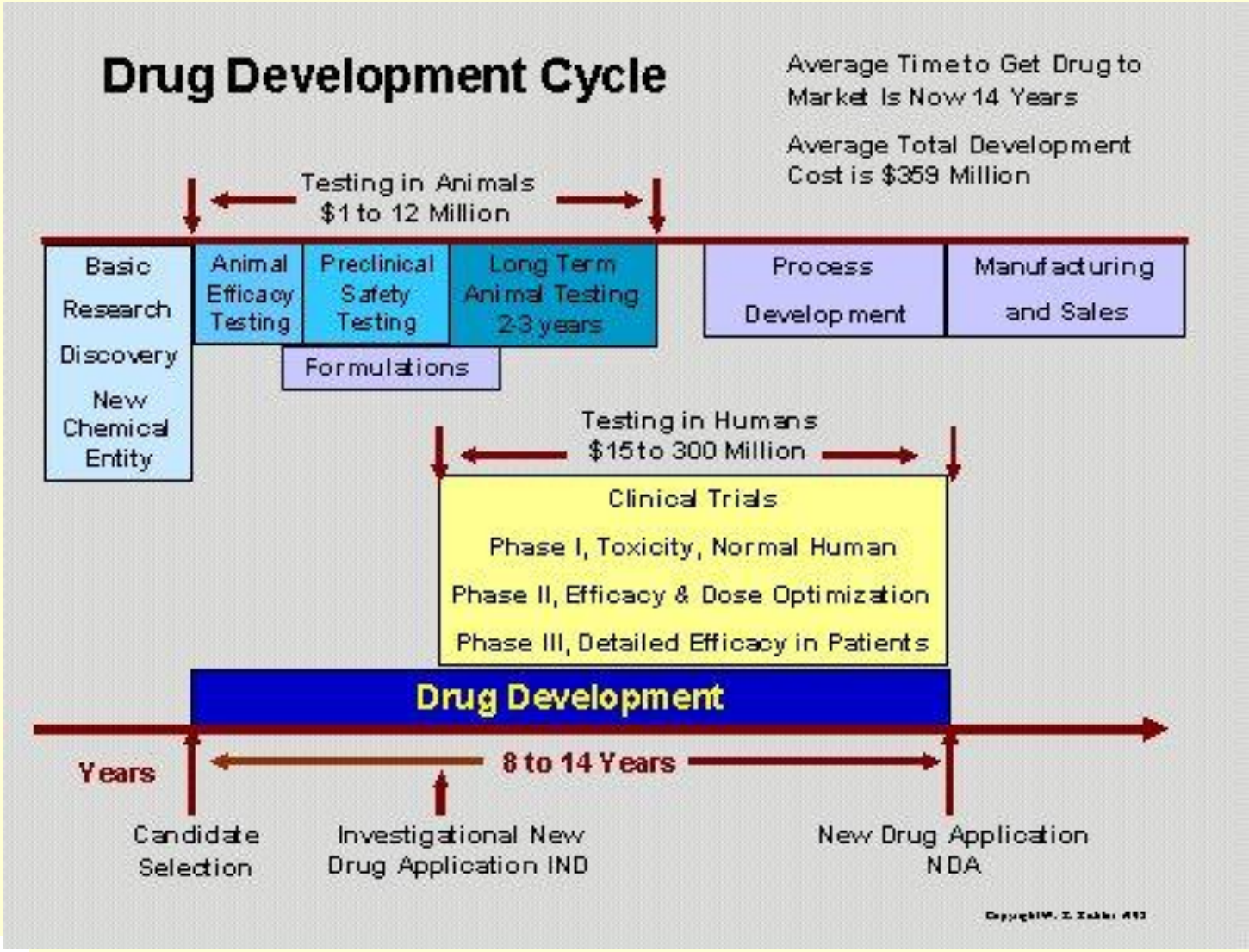
About Pharmaceutical Industry (III)



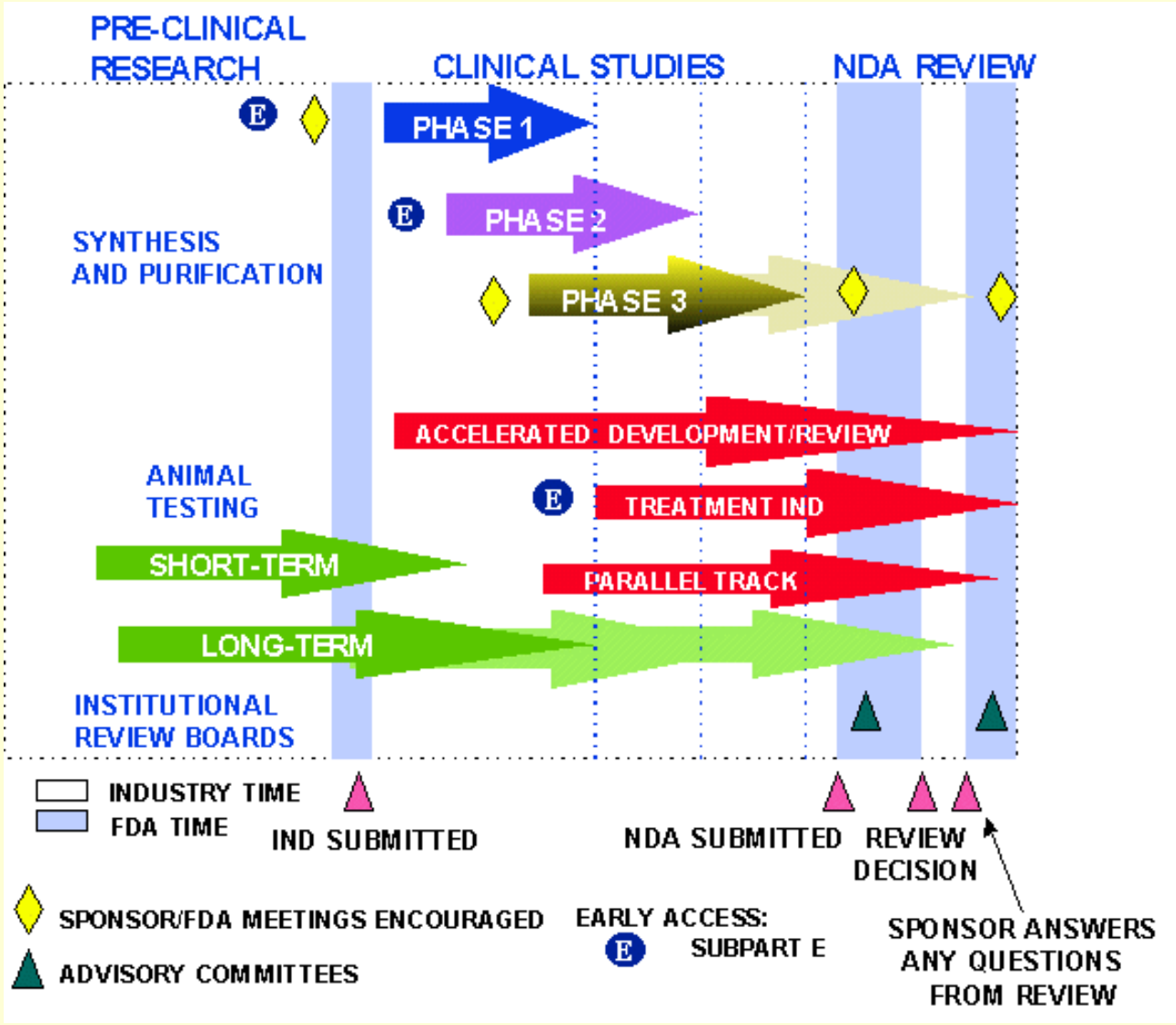
Source: IMS Health, MIDAS, December 2008.

NJIT New Jersey's Science & Technology University

Drug Development Cycle (I)



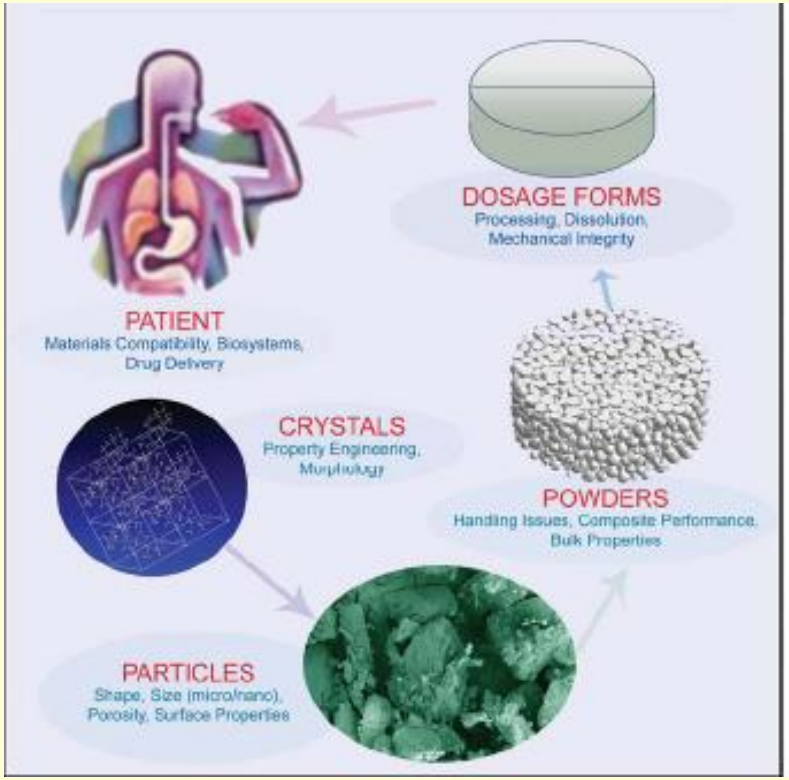
Drug Development Cycle (II)



http://sciencehandy.blogspot.com/2008/08/drug-approval-process-in-us-eu.html

Dosage Form (I)

- The final physical form of a drug formulation prior to delivery to patients
- Drug formulation: API: active pharm. ingredient (drug substance, DS) + excipients
- Each dosage form is unique in terms of physical and pharmaceutical characteristics
- Provides physicians different delivery options to prescribe



Drug Product (DP):
Drug Formulation
+ Package + Device (if any)

Dosage Form (II)

- Medicines as drug delivery systems administer drugs to body in a safe, efficient, reproducible, and convenient manner
- DSs are always administered along with excipients which impart varied and specialized pharmaceutical functions
- Excipient functionalities: aid flow/compression, bind, control/delay/sustain release, solubilize, suspend, thicken, emulsify, stabilize, preserve, color, flavor…
- Drug product requirements:
  - stable, safe, effective (patient/physician/regulatory)
  - attractive and easy to administer (marketing/patient/physician)

Purpose for Different Dosage Forms (I)

- Convenient, reproducible, and accurate dosing
- Masking bitter/salty/undesirable odor and taste of DS (coated tablets, capsules, flavored syrups)
- Protecting DS from oxygen or humidity (coated tablets, sealed ampoules)
- Protecting DS from gastric acid (enteric coated tablets)
- Controlling rate of DS release to decrease frequency of administration (sustained release tablets/capsules/suspensions)
- Providing liquid preparations of water-insoluble/unstable DSs (suspensions)
- Providing clear liquid dosage forms of DSs (syrups)

Purpose for Different Dosage Forms (II)

- Ensuring optimal drug action from topical administration sites (ointments, creams, ophthalmic and nasal preparations)
- Ensuring optimal drug action from inhalation therapies to especially asthma patients (aerosols, DPIs, pMDIs)
- Inserting a drug to into one of the body's orifices (rectal, vaginal suppositories)
- Placing drugs directly into blood stream or body tissues (parenteral injections)

Classes of Dosage Forms by Physical Form

- Solid dosage forms (powders, granules, capsules, tablets)
- Liquid dosage forms (solutions, suspensions, emulsions)
- Sterile dosage forms (parenteral, ophthalmic preparations, and biologicals)
- Semi-solid dosage forms (creams, gels, paste)
- Molded dosage forms (suppositories)

Classes of Dosage Forms by Route of Administration (I)

- Oral dosage forms (capsules, tablets, powders, solutions, suspensions)
  - Pros: most convenient and frequently used, self-administration, systemic effects
  - Cons: slow onset of action, possibility of irregular/food-dependent absorption, destruction of drugs by enzymes and GIT secretions
- Sublingual/buccal dosage forms (quick-dissolve tablets, film-strip, sprays, lozenges)
  - Pros: drug bypasses digestive system and enters the blood stream in minutes, may be used in the unconcious patient
  - Cons: taste, solubility, and dosage limitations
- Rectal dosage forms (suppositories)
  - Pros: local rather than systemic, indicated for drugs that are destructed by GIT fluids, can be administered to vomiting or unconscious patients, drug also enters systemic circulation
  - Cons: inconvenient, irregular/unpredictable drug absorption

Classes of Dosage Forms by Route of Administration (II)

- Parenteral dosage forms (intravenous, intramuscular, and subcutaneous injections in vials/ampoules)
  - Pros: 100% bioavailable, fast-action, preferred when rapid absorption is essential or when drugs are destroyed or poorly absorbed upon oral administration.
  - Cons: inconvenient (usually not self-administered), fear of needles, complications
- Topical dosage forms on skin (creams, gels, lotion, patches):
  - Pros: mostly applied topically for local action (antiseptics, antifungal, anti-inflammatory agents
  - Cons: may slowly be absorbed for systemic circulation
- Respiratory (Inhalation) dosage forms (DPIs, pMDIs, nebulizers):
  - Pros: Lungs provide large surface area and high blood for local and systemic action of inhaled aerosols (mist or micronized drugs), especially effective for respiratory diseases
  - Cons: relatively more difficult to formulate/manufacture, more costly, patient compliance and device issues

Typical Solid Dosage Form Ingredients

Function	Common Examples
API (DS), Therapeutic	Atorvastatin (lipitor), simvastatin, metformin
Compression Aid, Diluent, Filler, Matrix Former/Dry Binder	microcrystalline cellulose, lactose, mannitol, dibasic calcium phosphate, starch, sorbitol, sucrose, fructose, dextrose, calcium carbonate
Solution Binder	(semi)-synthetic polymers (HPC, HPMC, PVP, PEG), natural polymers (starch, pre-gel starch, gelatin, acacia)
Disintegrants	croscarmellose sodium, crospovidone, sodium starch glycolate
Lubricants	magnesium stearate, sodium stearyl fumarate, stearic acid
Wetting Agents	sodium lauryl sulfate, poloxamers, polysorbates (Tween80), TPGS
Flow Aids/Glidants	colloidal silica, talc, magnesium carbonate
Film Coating	HPMC/lactose/TiO2 based suspensions

Other ingredients: flavors, sweeteners, colorants, preservatives (antioxidants), delayed/sustained release controlling polymers, taste-masking fat/wax

Formulations in Different Phases of Development

- Fit-for-purpose formulations (FFP): widely used in preclinical and early development studies (solutions and suspensions as opposed to tablets/capsules)
- Pre-Market Formulation (PMF): Close to FMI, but may not define all intended attributes of the dosage form
- Final Market Formulation/Image (FMI): final dosage form of the formulation intended for filing, market authorization, and commercialization
  - Defines all intended final dosage attributes of the dosage form
  - Exact shape, color, final composition, etc.

Two Worlds of Drug Development

DS(API) Development/Manufacture

- Development and scale-up of chemical reactions and unit operations during the manufacture of DS from pre-clinical to commercialization
- Chemical purity, salt-form, polymorph, stability, other physico-chemical characteristics of DS
- Their product is an intermediate to DP business.
- Chemistry and chemical engineering are at the core of DS Business. Mostly chemical transformations and separations technology. Particle technology plays a role in finishing operations.

DP Development/Manufacture

- Development and scale-up of pharmaceutical unit operations during the manufacture of DP from pre-clinical to commercialization
- Physico-chemical characteristics of intermediates, drug formulation, and DP's functional responses (stability, dissolution, content uniformity, etc.)
- More inter-disciplinary and diverse: chemical transformations undesirable, pharmaceutical sciences, chemistry, chemical engineering, and particle technology all play a major role. Only pharmaceutical unit operations.

Early and Late Development during DP Development

Early Development

- Come up with FFP and PMF for pre-clinical and clinical studies up to PhII in collaboration with Late Dev.
- Manufacture/support of pre-clinical and clinical material production (small scale work)
- Have a formulation focus/mentality, black-box processing
- Must develop proof-of-concept for the formulation and a Target-Product Profile
- Analytical, pre-formulation, quality/regulatory, and formulation development groups
- Little focus on cost, manufacturability, scalability unless given feedback by Late Dev.

Late Development

- Come up with FMI/process for late PhII and PhIII, filing&commercialization in collaboration with Early Dev.
- Manufacture/support of PhIIb/PhIII clinical material production (pilot to commercial scale)
- Have a more process focus/mentality: design and scale-up processes
- Biobatch/FSS/Validation design and Support, commercialization and tech transfer support to global sites
- Analytical, packaging, formulation/ process dev., quality/regulatory groups
- Significant focus on cost, scalability, manufacturability either as part of Manufacturing or in collaboration

Cross-Functional Team(s) in DP Development

Functional Areas in DP Development (I)

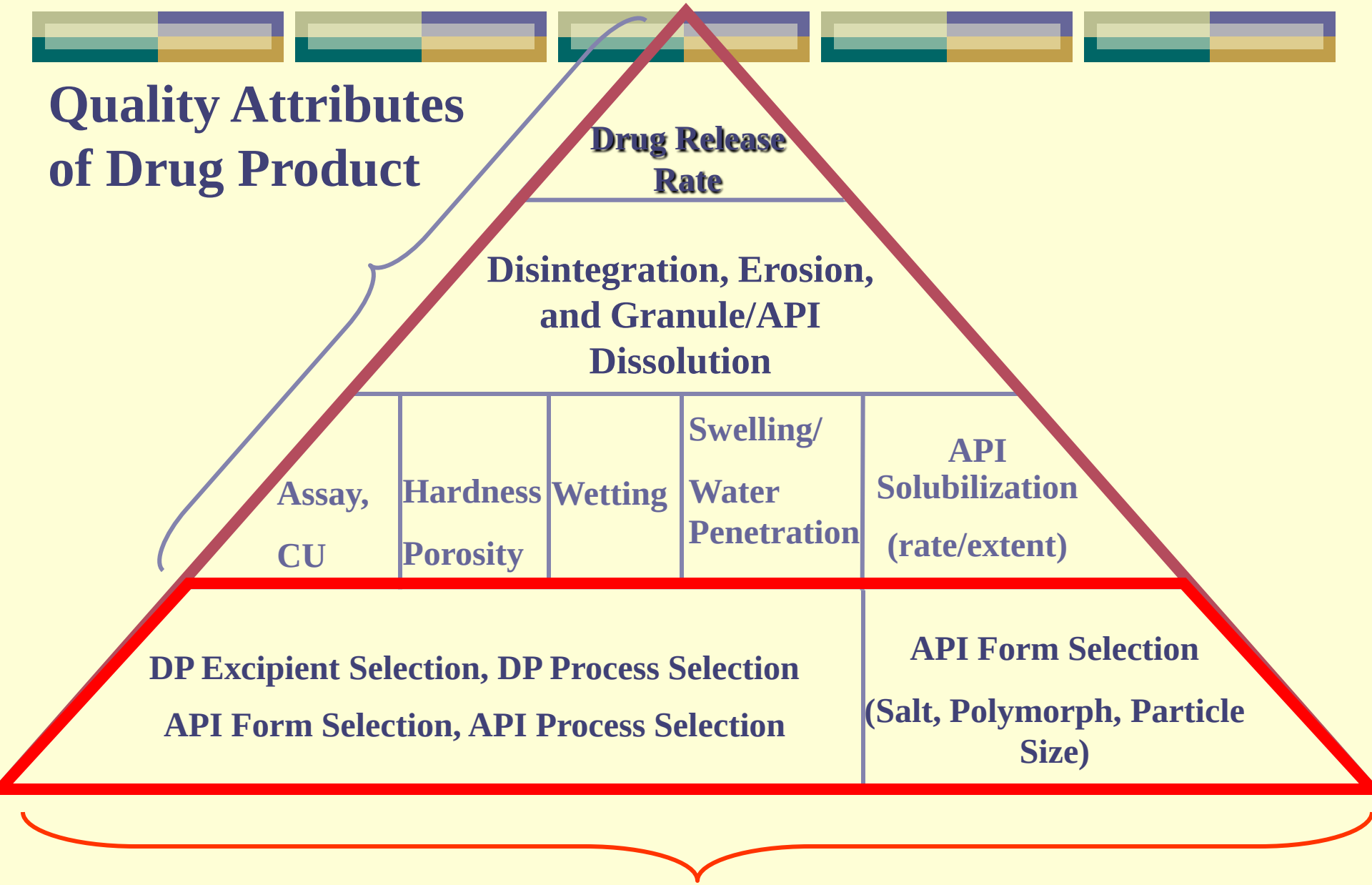
- Formulation/Process Development (Pharm R&D, Manufacturing)
  - Pharmacists, pharmaceutical scientists, chemists, chemical engineers
  - Formulation (FPF, PMF, and FMI) and unit operation development and scale-up
  - Execution/support of experimental, pre-clinical, clinical, Biobatch/FSS, validation batches from pre-clinical to commercialization
  - Collect data, write or help write regulatory documents including filing
- Analytical Development
  - Chemists, pharmacists, pharmaceutical scientists
  - Development of all analytical methods
  - Execution/support of all product characterization and testing for the aforementioned batches
  - Lead/support product characterization and stability studies
- Regulatory Sciences
  - Interface to regulatory agencies
  - Ensures timely feedback from/to agencies, help/write INDA/NDA documents
  - Guides development teams in terms of regulatory aspects (filing strategy)

Functional Areas in DP Development (II)

- Quality
  - Ensures that all work/studies/batches/production are performed per cGMP rules, and operators/scientists/teams get the proper training and follow cGMP.
  - Ensures labs, storage areas, and sites have the capability for cGMP manufacturing and production
  - Audit internal and external sites for cGMP compliance
- Packaging
  - Perform/support product characterization/stability studies in collaboration with Formulation and Analytical development toward the selection of proper packaging
- Others
  - Supply chain/finance/marketing: capacity assessment, make vs. buy decisions, outsourcing, market projections, cost assessment, input FMI design
  - API development: support of API supply in need for DP development while continuing on DS process development and scale-up

Dosage Form Attributes

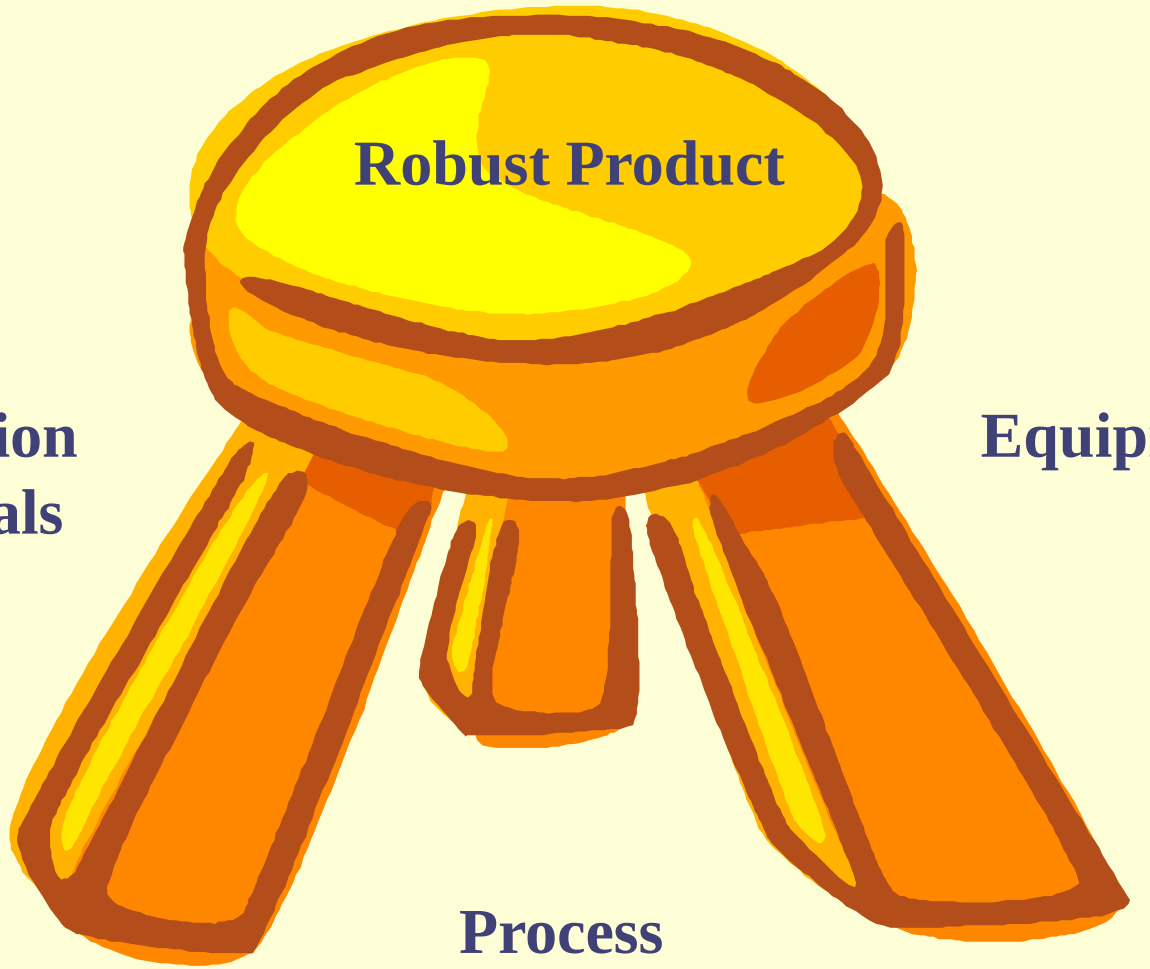
Quality Attributes of Drug Product



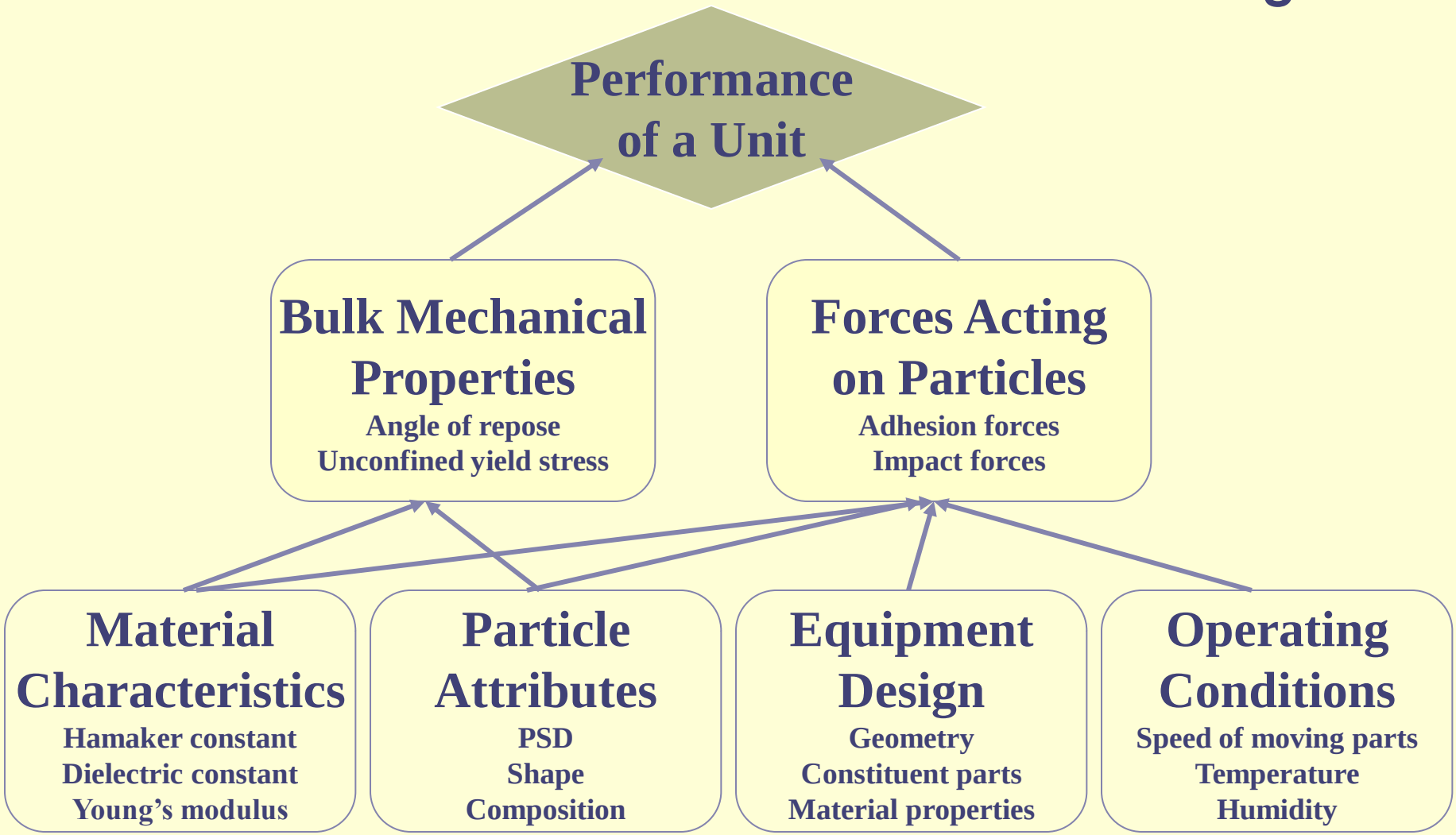
Modified from "Features of "Quality by Design Approach:" Doing things consciously*"

*A Quality by Design Approach to Dissolution Based on the Biopharmaceutical Classification System, R. Reed

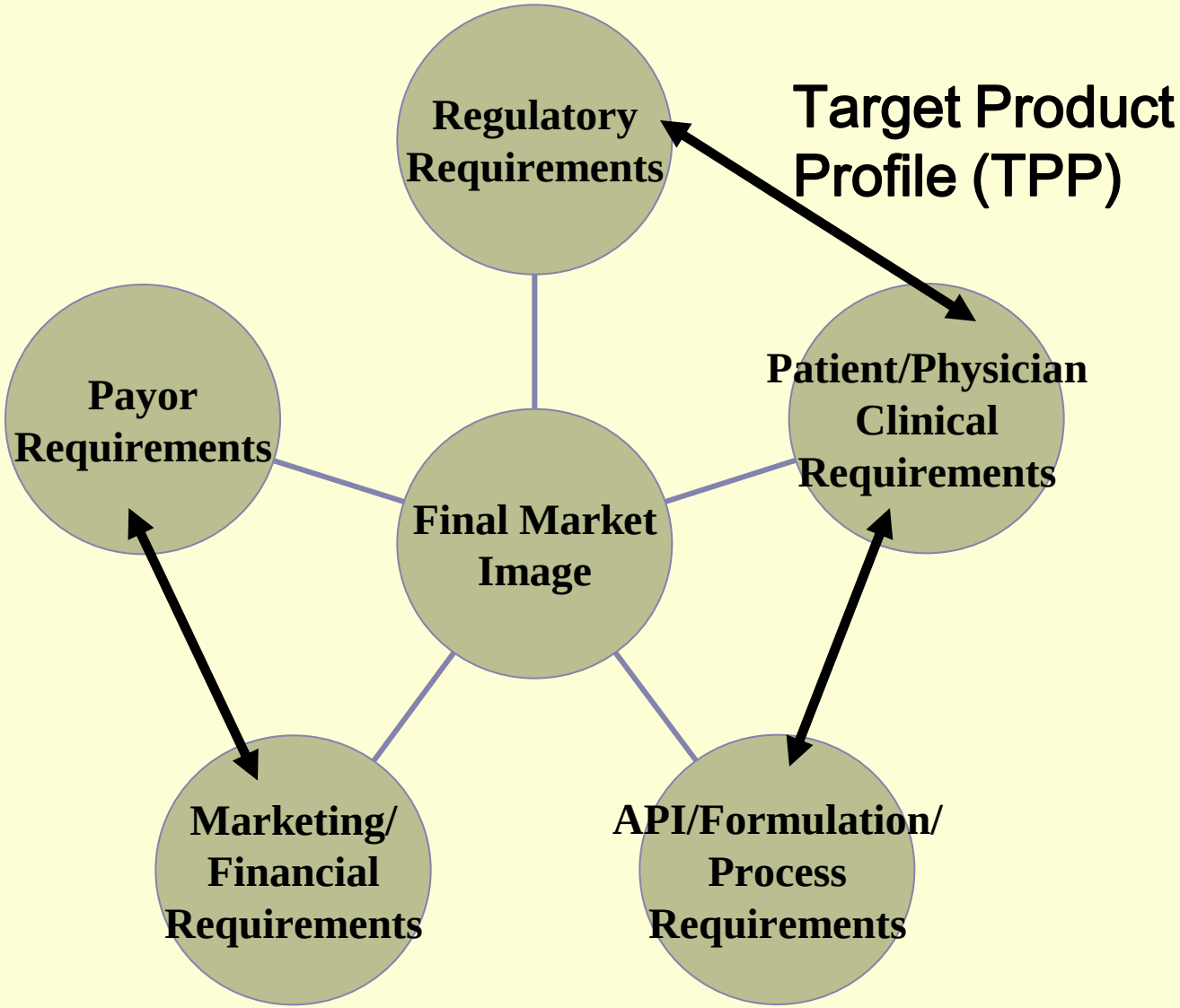
Elements of a Quality-by-Design Program



Performance of Pharmaceutical Solids Processing Units



What determines the FMI Attributes?



Target Product Profile (Voluntary Briefing Document Prepared by Sponsor and Submitted to Agency)

- A strategic process development tool:

The purpose of a TPP is to provide a format for discussions between a sponsor and the FDA that can be used throughout the drug development process, from pre-investigational new drug application (pre-IND) or investigational new drug application (IND) phases of drug development through postmarketing programs to pursue new indications or other substantial changes in labeling.

- The sponsor indicates (among many other aspects):
  - Dosage and administration, dosage forms and strengths
  - Detailed description of dosage form and route of administration, ingredients, formula, pharmacologic and therapeutic class, and other important physico-chemical properties
  - How supplied, storage/handling

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080593.pdf

Pfizer's Exubera: It is not all about Science and Engineering!

- A failure story: Pfizer's Exubera Inhaler Designed for Delivering Inhaled Insulin to Type I Diabetes Patients (see WSJ)

Once on the market, diabetes specialists said it was hard to use. Patients need to insert packets of powder into the device measured in three or nine milligrams -- not the units doctors are used to. The company had problems getting insurance companies to cover the treatment at a favorable rate, and a British medical committee said Britain's health authorities shouldn't pay for it at all because it didn't offer advantages over less-expensive therapies. Exubera costs about $5 a day while injectible insulin costs about $2 to $3 a day.

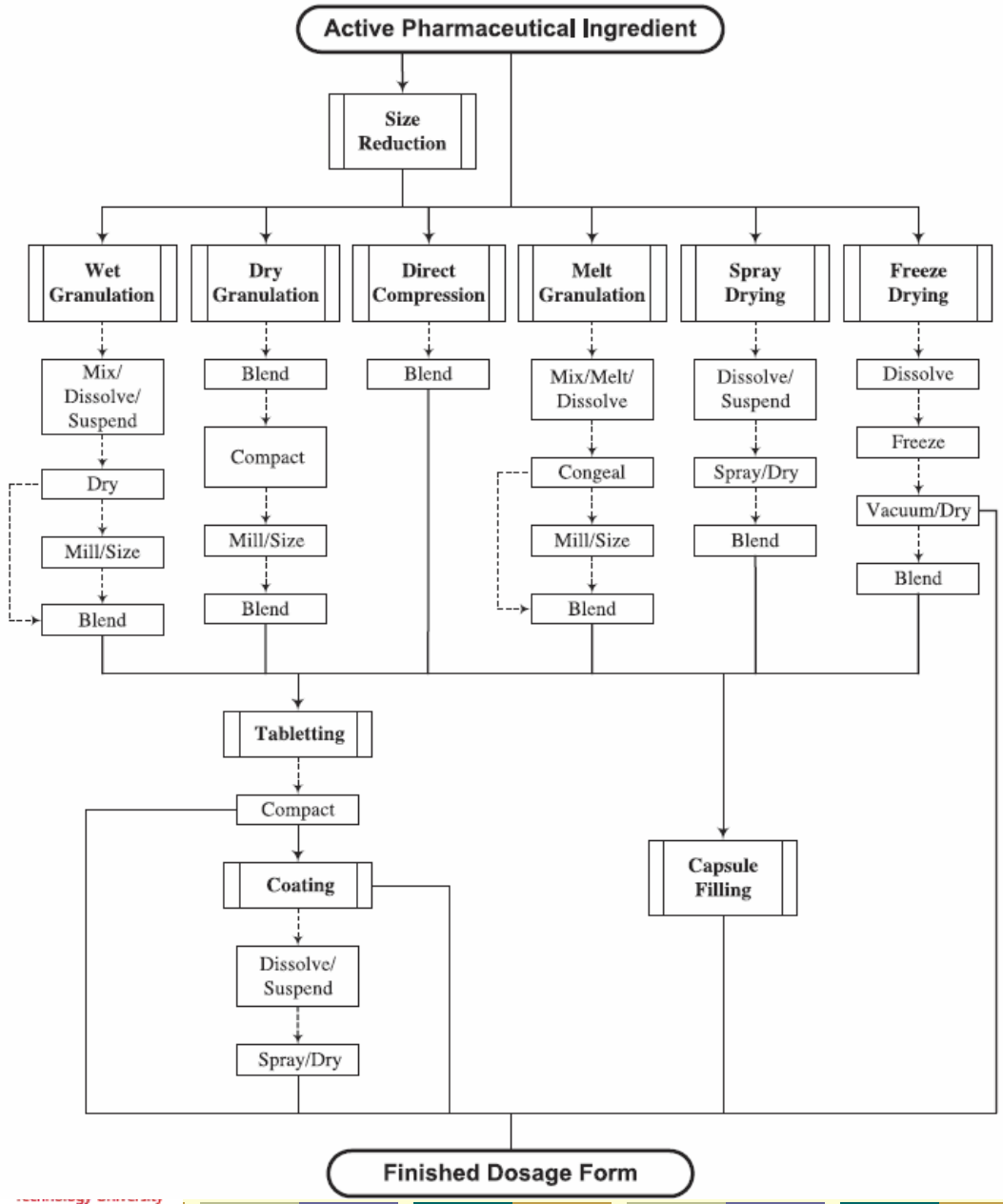
The Exubera device, which some compared unflatteringly to a bong for smoking marijuana, could also be embarrassing to use in public.

"I can teach someone how to use an insulin pen in five minutes, but it would take nearly an hour to teach a patient to use inhaled insulin," says Anastassios Pittas, an endocrinologist at Tufts-New England Medical Center.

http://online.wsj.com/article/SB119269071993163273.html

A Review of Most Common Pharmaceutical Process Trains

Standard Process Trains for Solid Dosage Forms



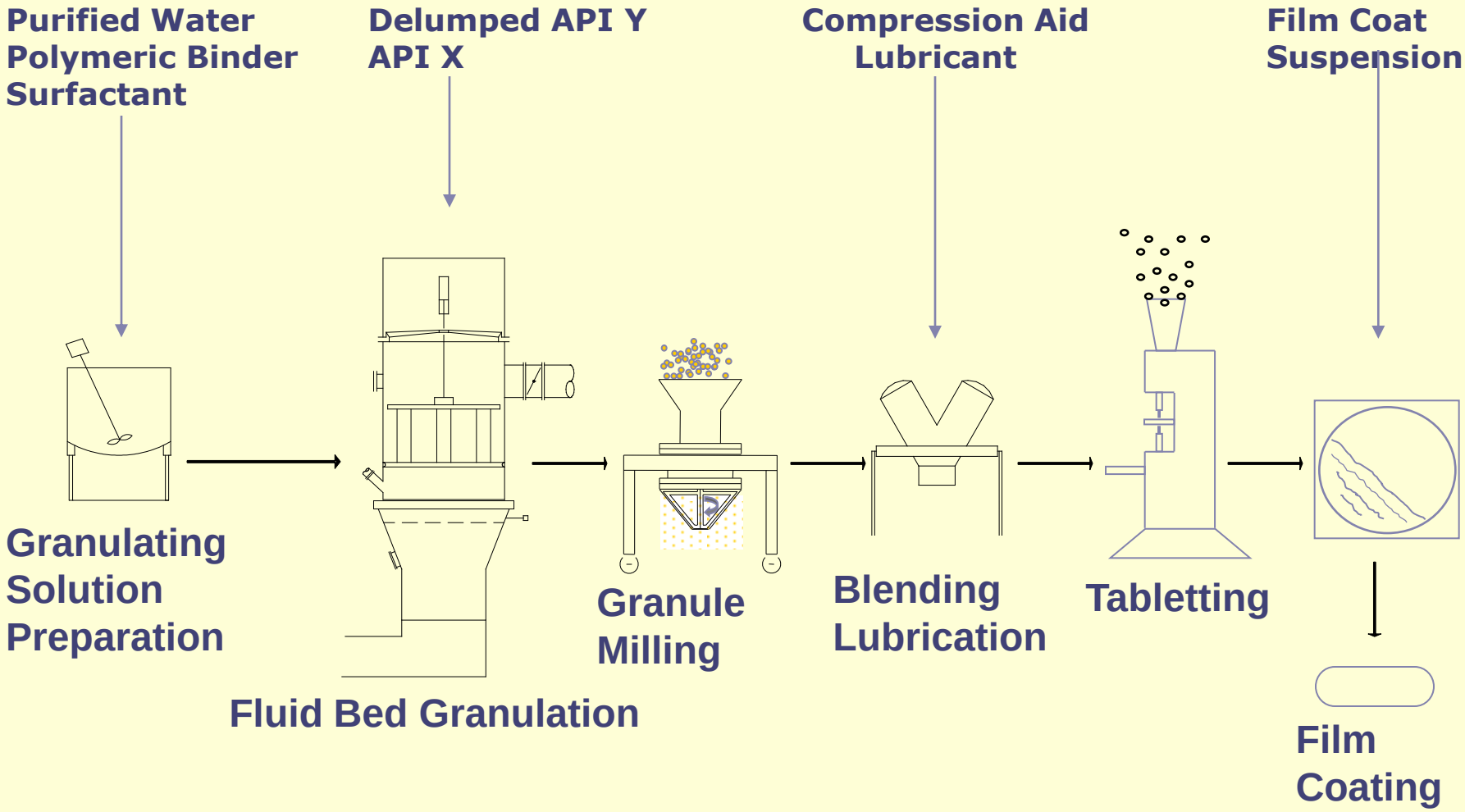
Common Abbreviations:
DC: Direct Compression
WG: Wet Granulation
(HSWG: High-Shear WG,
FBG: Fluidized Bed Granulation)
RC: Roller compaction
(Dry granulation)
SD: Spray Drying

Melt Processing:
-Hot Melt Extrusion (HME)
-Melt granulation in HSWG/FBG

Solid Dispersion Technologies:
-HME
-SD
-Some melt granulations

(*Zhang et al., Adv. Drug Del. Rev. 2004*)

FBG Process Flow Diagram



What Dictates the Choice of Process Train?

- Target Product Profile: detailed description of dosage form and route of administration, ingredients, formula, pharmacologic and therapeutic class, and other important physico-chemical properties
- API Functional Responses: BCS Class (water solubility), PB-ECL, powder flow/cohesion, compactability, stability, degradation characteristics, which are dependent upon intrinsic API particle & physico-chemical properties as well as processing and storage/handling history of the API
- Intended Formulation Characteristics: binary/mixture compatibility of API under stressed conditions, functional responses of the dosage form (flow, compactability, hardness, disintegration/dissolution, stability, etc.)
- Company Culture: Strategy (core/non-core technology), Internal Expertise and Experience, Outsourcing strategy
- Manufacturing Feasibility, Scalability, and Capacity

Rule of Thumb/Decision Trees/Trends (I)

- TPP sets the high-level selection through intended route of administration, drug release mechanism (immediate versus delayed), dose, intended population (pediatric requiring significant taste masking)

- Sustained release/taste masking for pediatric population/orally-dissolving/chewable tablets, and strip-films usually require more specialized process trains/formulations and possibly a combination of standard process trains

- BCS Class II and IV compounds have poor water solubility (<0.01mg/mL). For these compounds:
  - DC/Granulation with improved formulations (solubilizing/wetting agents/melt processing) and/or micronized API
  - Nanomilling, SD, HME or parenteral forms (if erratic absorption, high fast/fed variability, insufficient plasma concentration)

Rule of Thumb/Decision Trees/Trends (II)

- In most immediate release solid dosage forms of soluble compounds, standard process trains are used.
  - Badly flowing-cohesive powders (usually finely milled via hammer or disc/pin mills, fluid-energy mills or otherwise cohesive) or small API loaded formulations are usually granulated. Need to minimize development times by avoiding segregation, assay/CU problems, tablet weight and hardness uniformity/elegance problems.
  - Granulation preference: unless API property is extremely restrictive, companies can make any granulation technology work!!! Company culture/strategy, internal expertise/experience in Early Dev. and feedback by Late Dev., and cost considerations play a major role.
  - Mfg. Cost: Nanomilling, SD, HME>Melt processing>WG>RC>DC

(On the other hand, API cost is the main factor determining tablet cost)

Rule of Thumb/Decision Trees/Trends (III)

- Unless API property is extremely restrictive, companies can make any granulation technology work!!!

- But, HSWG: easiest to perform, most widely used for all kinds of APIs, PSD set by milling, dependence of porosity on processing/formulation

  RC: new fashion, cheaper than HSWG, rely partly on API's compactability, densest granules (lowest porosity), bimodal milled granules, potential dissolution slow-down

  FBG: most versatile, highest quality granulations, apply to all APIs except extremely high loading of micronized/finely milled APIs, requires more elaborate process design

- DC is only chosen when API "behaves" in terms of flow/compactability characteristics, and the drug loading is preferably greater than 10%.

Acknowledgements

I would like to acknowledge the contribution of my NJIT colleagues and students as well as NSF ERC for SOPS.