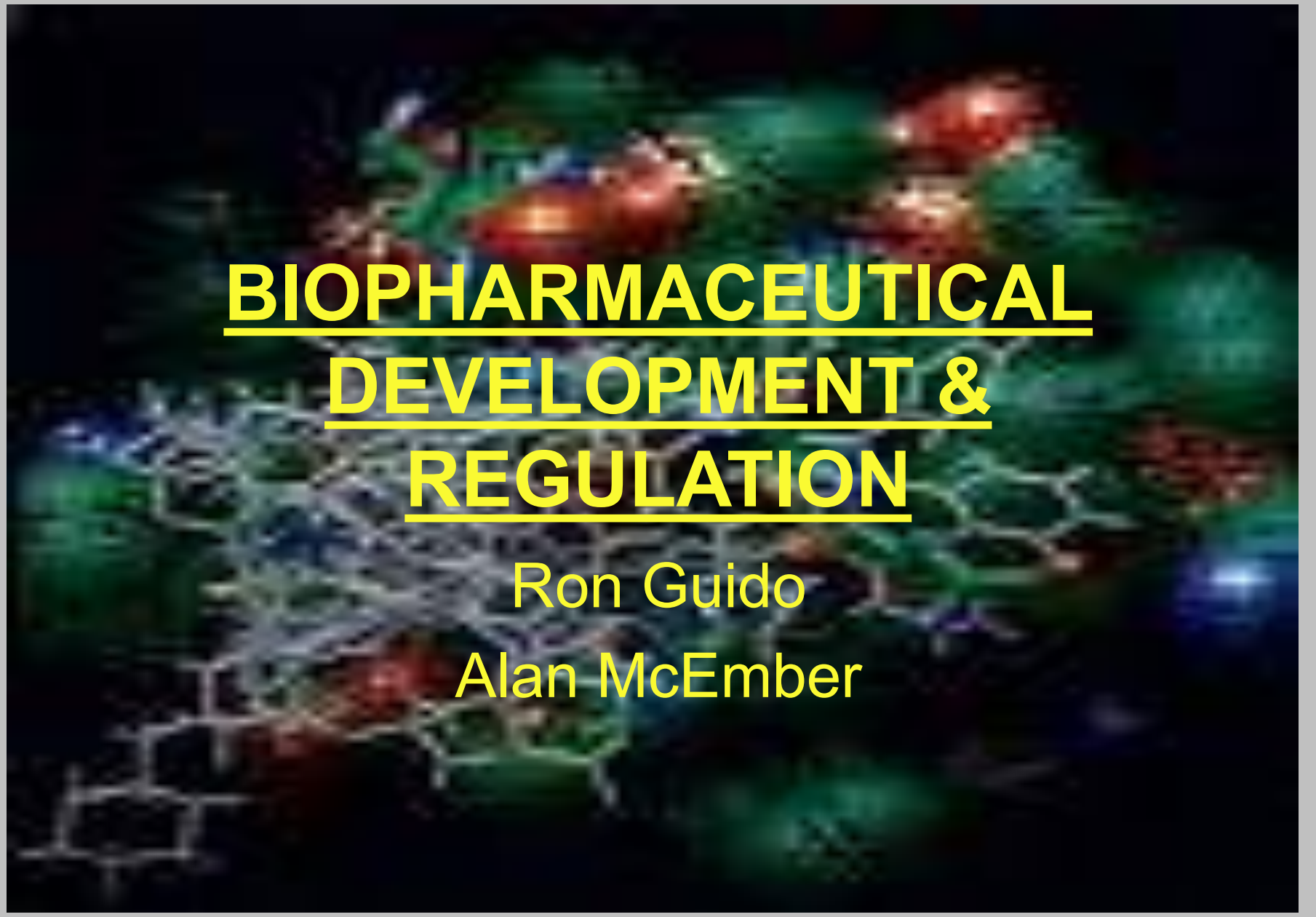

BIOPHARMACEUTICAL
DEVELOPMENT &
REGULATION
Ron Guido
Alan McEmber

Course Details

- **Fall 2007: W4200 Section 001 : BIOPHARMACEUTICAL DEVELOPMENT & REGULATION**
- **Meets: Thursday 2:40pm-4:40pm**
- **Location: 1000 Sherman Fairchild Life Sciences Building**
- **Instructors: Ron Guido, Alan McEmber**
- **Instructor Contact : ron.guido@pfizer.com; alan.mcember@pfizer.com**

Course Details

Class Modules (Subject to Change)

- History of Regulation (incl. Regulatory Defined, Major Regulatory Bodies Worldwide)
- Basics of Drug Discovery and Development
- Pharmacokinetics / Pharmacodynamics (from a Regulatory viewpoint)
- Non Clinical Pharm/ Tox (incl. cGMP)
- Standards of Approval (Rx, OTC, Biologics, Biotech)
- IND / CTD / CTx (inc. cGCP)
- NDA / MAA (US, EU, Japan, National
- Deep Dive US Regulatory
- Deep Dive EU Regulatory
- Clinical Program Development / Labeling Development and Revision
- Post Approval Actions (Studies, Amendments, Supplements, Variations) EU / US
- cGMP and Inspection
- CM&C and Change Control
- Recalls and Field Actions – Product Queries
- OTC / Consumer Products
- Advertising and Promotion
- Agency Meetings and Communication
- Introduction to Regulatory Assessment and Strategy

Course Details

- **Method of Assessment: 3 Take Home (24-Hour) Assessments, 10 short responses per assessment. May require light research and problem solving**
- **Textbook**: Drug Discovery and Development: Technology in Transition, H.P. Rang, Churchill Livingstone (Elsevier) 2006
- NOTE: Supplemental readings will be posted

Drug Development Terminology and Basic Concepts

..from the Regulatory Perspective..

For your consideration

- Drug /Biotech Development requires cutting edge science, but that's not all its about
- Regulation is supported by science, but science and regulation often part company
- Industry, clinical excellence groups lead regulation
- Novelty lowers hurdles for approval, but often complicates review process
- Product is defined by its active, and the associated claims of action
- Product needs to have a meaningful clinical effect
- Burden of proof is on the sponsor to demonstrate the safety, necessity and/or efficacy of any component not already recognized.

Regulatory Affairs

What is it?

A Broad Scope: Regulations and Agencies

- Pharmaceutical products are regulated in essentially every country of the world.
- These regulations are applicable to both the investigation and marketing of compounds.

Regulatory Affairs Defined

- Regulatory Affairs is a specialized profession within the pharmaceutical/biotechnology sector.
- Regulatory Affairs oversees company compliance with regulations and laws pertaining to the manufacture, marketing and development of regulated products.
- Regulatory Affairs acts as point of contact between the company, its products and regulatory authorities
- Regulatory Affairs interacts with worldwide, federal, state, and local regulatory agencies (e.g., FDA (US), EMEA (EU), BfARM (Germany), TPD (Canada), etc) to assure…
  - licensing,
  - registration,
  - development,
  - manufacturing,
  - marketing and
  - labeling

…….of pharmaceutical and medical products are conducted in compliance with all applicable rules

Regulatory Framework

- Development, approval for marketing, manufacturing, and ongoing compliance of pharmaceutical/biotech products is among the most regulated activities of any industry
- Regulations are complex systems of interrelated rules that govern a broad range of activities
- These rules are continuously undergoing amendment and supplementation
- Their main function is to assure that these products are safe (do no harm) and effective (do some good)

Regulatory Framework

Why do we pay so much attention to regulation and process ??

- It takes 8 to 15 years to develop a new drug/biologic product.
- Costs up to $ 800 million.
- Attention to early development, successfully execution of significant clinical studies helps to reduce number of development failures.
- Regulatory affairs provides insight/guidance into this development through agency wisdom collected in guidance, previous experience, market precedence, etc.

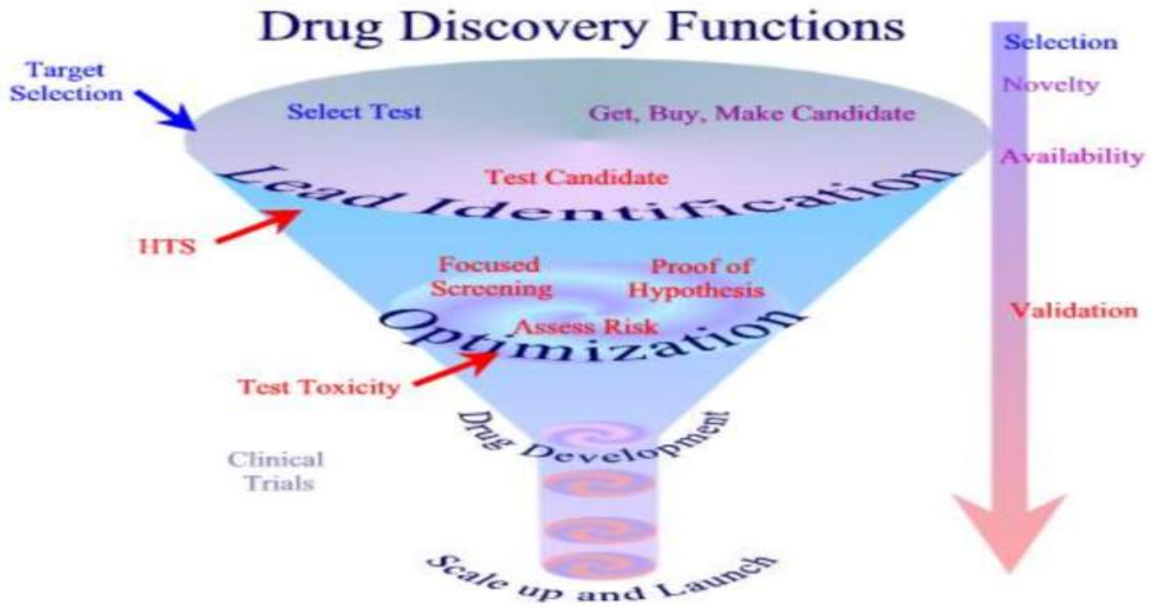
Compliance with Regulator expectations therefore equates with development success. Patient Protection is of greatest importance

Development Costs in Perspective

FROM: The Price of Pills; July 2003; Scientific American Magazine; by Carol Ezzell

- Forty F16 jet fighters, or $802 million. That's how much it takes to develop a new drug, according to the first academic analysis of the process published in 12 years. That number reaches $897 million if postmarketing studies-additional clinical research that the U.S. Food and Drug Administration sometimes requires as a condition for approving a new drug-are taken into account, the report's authors announced in May.
- These sky-high prices (in 2000 dollars) have prompted disbelief and consternation among some critics, who allege that the pharmaceutical industry is inflating the true cost of drug development to justify the escalating price tags of many therapies. The naysayers also accuse big pharma of seeking to justify its tax credits for research and development and to dissuade Congress from rolling back those benefits.

Drug Discovery



US Base Standards for Drugs / Biopharmaceutics

- Drugs must be generally recognized as safe and effective
- Benefits of use must always outweigh potential risk

Definition of a Drug

- The term "drug" means [any] articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.

What is a “new” drug

- The term "new drug" means …any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof (except drugs so recognized subject to the Food and Drugs Act of June 30, 1906) [“Old Drug”]

Chemistry and Manufacturing

Drug Substance

- **Drug substance (Active pharmaceutical ingredient)—**
  - It is the material that is exerting the pharmacological action.
  - Along with other ingredients (excipients, inactives) it subsequently it is used to formulate, the drug product.
- It can be composed of
  - the desired active material,
  - product-related substances,
  - product—or process related impurities (subsequently removed)
- It also may contain other components, including vehicles, or buffers.
- Biologics and biotechnology industry.
  - Alternatively referred to as bulk concentrate, bulk intermediate, or simply bulk

Drug Product

- **Drug product (Dosage form; Finished product)—**
  - one or more drug substances (active pharmaceutical ingredients)
  - usually with excipients
- **Excipients**
  - components of a finished medicinal drug product other than the active pharmaceutical ingredient (API).
  - Included in the formulation to facilitate manufacture, enhance stability, control release of API from the product, assist in product identification, or enhance other product characteristics.

Impurity

- **Impurity**—An impurity is any component present in the excipient, drug substance, or drug product that is not:
  - the desired product,
  - a product-related substance,
  - or excipient, (including buffer components).
- It may be either process- or product-related.
- It may be the result of active principle degredation during holding/processing

Chemistry Manufacturing & Controls

- Analytical Method
- Degradation Products
- Specifications
- In-process controls
- Methods Validation
- Process Validation
- (DP/DS) Characterization
- Container / Closure System
- Characterization
- Stability

Drug Discovery & Approval

Drug Discovery

- **Target Profile** – Intended therapeutic site of action and clinical outcome
- **Lead Identification** – Identified candidate compounds with potential drug activity commensurate with profile from a library of actives (hits)
- **Lead Optimization** –Identification / modification of lead compounds for best action / least side effects, etc
- **Combinatorial Chemistry** – generation of active compounds (hits) from a library of building blocks
- **Structure-Activity Relationship** – determination of the relationship between a specific chemical structure and a pharmacological action

Clinical Investigation

- US: IND – Investigational New Drug (Application)
- EU: CTA / CTX – Clinical Trial Authorization/Clinical Trials Exemption

Marketing Approval

US

- NDA – New Drug Application
  - 505(b)(1), 505(b)(2)
  - ANDA - Abbreviated New Drug Application
- BLA – Biologic License Application

EU

- MAA – Marketing Authorization Application
- CTD – Common Technical Document; common format for organization of information in marketing authorization (registration) applications. Format for CTD acceptable in three regions (US, Europe, Japan). Content requirements are not fully harmonized and there are differences between the three regions.

Label

- **Label**—The label is the document physically attached directly to the packaging materials that are in direct contact with the excipient, drug substance, or drug product.
- **Labeling**—Labeling includes the label and the documents included with, but not attached to, the packaging materials that are in direct contact with the excipient, drug substance, or preparation (e.g., package insert).

Labeling Terminology

- Primary and Secondary Container
- US Package Insert (PI)
- US Patient Package Insert (PPI)
- Structured Product Labeling (SPL)
  - labeling electronically packaged "in a form" that FDA can process, review, and archive
- EU SPC – Summary of Product Characteristics
  - Basis of information for health professionals on how to use the medicinal product safely and effectively.
- EPAR - European Public Assessment Report.
  - Conclusion reached by the Committee for Medicinal Products for Human Use (CHMP) at the end of the centralized evaluation process. Includes summary, list of authorized presentations, and the product information (SPC, labeling and package leaflet)

Basic Concepts – Clinical Pharmacology

Broad Categories of Pharmacology

- Pharmacodynamics
  - How the drug affects the body
- Pharmacokinetics
  - How the body affects the drug
    - ADME
      - Absorption, distribution, metabolism, excretion
    - Clearance

Pharmacodynamic Interactions

- Drug-receptor effects
  - Increased effect:
    - Enhancement by occupancy : diazepam and zopiclone
  - Reduced/blocked effect:
    - Competitive antagonism: salbutamol and propranolol
- Enhanced therapeutic effects
  - Alcohol and sedatives
- Side effects
  - Aspirin and diclofenac (both acting on cytoprotective pathways)

Pharmacokinetic Interactions: Metabolism

- Phase I metabolism
- Phase II metabolism
- Many organs, systems involved

Phase I Metabolism: Functions

- Tend to make drugs:
  - More water soluble
  - Less active
  - Less toxic
- Prepares drugs for greater metabolic conversion and clearance

Phase I Metabolism: Reactions

- Oxidation
  - Cytochrome P450 (CYP)
  - Cytoplasmic:
    - Alcohol dehydrogenase
    - Xanthine oxidase
    - Monoamine oxidase
- Reduction
  - CYP in liver, flora in gut
- Hydrolysis
  - CYP
  - Other (e.g. cholinesterases)

Phase II Metabolism: Functions

- Primary : Conjugation (binding to another molecule)
  - Bigger than the drug alone
  - Less able to cross cell membranes
  - Less likely to reach site of activity
- More likely to be removed

Phase II Metabolism: Reactions

- Glucuronidation (e.g. morphine)
  - Conjugation with glucuronic acid
- Acetylation (e.g. isoniazid)
  - Conjugation with acetyl co-enzyme A
- Conjugation with other molecules:
  - Amino acid (e.g. glutathione, glycine)
  - Sulphate

Clearance

- Removal of drug from the body
- Parent drug and metabolites have individual clearance characteristics
- Linked to ADME characteristics of the compound

Types of Clearance

- Metabolic
  - First pass metabolism e.g. nitrates
  - Mostly liver
  - Other metabolic tissues
- Renal (urinary)
- Biliary (fecal)
- Other (expired air, sweat)

Summary

- Pharmacodynamic interactions:
  - When drugs have similar (additive) or antagonistic effects
    - (potentiation, or diminution of effect)
- Pharmacokinetic interactions:
  - When drugs interfere with each other's mechanisms of clearance
    - (taking one drug in the presence of another causes either accumulation, or greatly expedited metabolism)

Worked Example

What makes something a drug ??

Is this a drug ??

Ingredients Analysis

- Ingredients define the “Drug” Product
- Carbonated Water, sucrose, glucose, sodium citrate, taurine, glucuronalactone, caffeine, inositol, niacinamide, calcium pantothenate, pyridoxine, HCL, Vitamin B12, natural and artificial flavors, colors

Ingredients Analysis - Actives

- Definition of Drug Substance
- Carbonated Water, sucrose, glucose, sodium citrate, **taurine,** glucuronalactone, caffeine, inositol, niacinamide, calcium pantothenate, pyridoxine, HCL, Vitamin B12, natural and artificial flavors, colors

Ingredients Analysis

- Carbonated Water, sucrose, glucose, sodium citrate, **taurine**, glucuronalactone, **caffeine**, inositol, niacinamide, calcium pantothenate, pyridoxine, HCL, Vitamin B12, natural and artificial flavors, colors

Recognition of Taurine

- Recent studies show that taurine supplements taken by mice on a high-fat diet prevented them from becoming overweight.

- Taurine is being tested as an anti-manic treatment for bipolar depression.
- Recent studies have also shown that taurine can influence (and possibly reverse) defects in nerve blood flow, motor nerve conduction velocity, and nerve sensory thresholds in experimental diabetic neuropathic rats.
- Taurine is often used in combination with bodybuilding supplements such as creatine and anabolic steroids, partly due to recent findings in mice that taurine alleviates muscle fatigue in strenuous workouts and raises exercise capacity.
- Taurine has also been shown in diabetic rats to decrease weight and decrease blood sugar.

Caffeine

- Recognized in OTC regulation (monograph) for relief of fatigue
- Sub-monograph potency

Claims Analysis

- Improves Performance
  - **NOT**: Relieves fatigue
- Increases Concentration and Reaction Speed
  - **NOT**: Helps relieve adult attention deficit disorder
- Increases Endurance
  - **NOT**: Helps relieve muscle weakness associated with X disease process
- Stimulates Metabolism
  - **NOT**: Prevents obesity, promotes weight loss

Current FDA Analysis

- FDA position:
- Product is a beverage containing a conditionally active, common amino acid with no known deleterious effects.
- No requirement to scrutinize beverages in the absence of uncharacterized ingredients

Conclusion

- Drugs have action in ameliorating disease
- Actives must have a recognized basis for recognition (S/E), not just scientific substantiation of action
- A drug is defined not only by the provision of an active substance but also by the (therapeutic, disease ameliorating) claims made in its labeling

Article Analysis

- Where does the science and regulatory diverge
- Does anything potentially cross the line
- Does the Agency uphold its mission in the protection of public health
- Are there any ethical considerations ??