Irma Lerma Rangel PHARMACY
TEXAS A&M UNIVERSITY

# NDAs and Postmarketing

## Foundations in Cancer Therapeutics, Commercialization, IBT Houston

## August 15, 2022

Mansoor A. Khan, R.Ph., Ph.D.
Regents Professor and Vice Dean, Presidential Impact Fellow
Texas A&M University Rangel College of Pharmacy
College Station Campus

# Conflict Statement

Consult/Consulted as expert for the following firms*

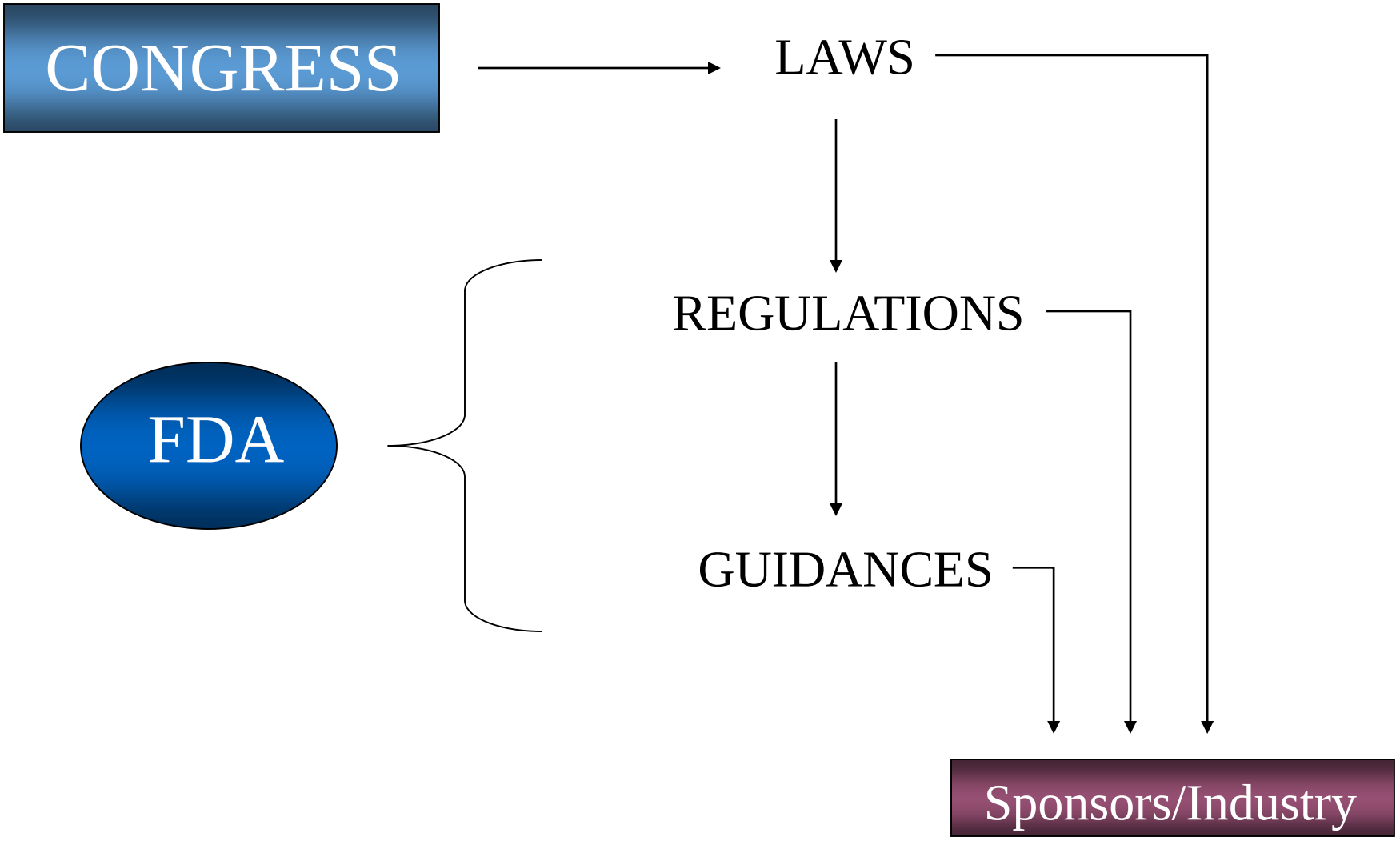
- Pfizer
- Teva
- Amneal
- Lupin
- Mankind
- Sandoz
- Momenta
- Sun Pharma
- Wockhardt
- Cipla
- TherapeuticsMD
- Supernus
- Kashiv Pharma
- FDA
- FTC
- States of TX, NY and CA
- Daiichi Sankyo
- Corning
- Thermo Fisher
- Coherus Biosciences
- Mylan
- Clayton/Absorption Systems

* None of the products of these firms are displayed or discussed. There is no conflict with today's presentation

# Learning objectives

- Understand FDA mission and broad roles of all Centers
- Differentiate between Laws, Regulations, and Guidances
- Outline FDA drug approval pathways
- Learn about NDA Pathways
- Identify main differences of New and Generic Drug Products, OTC products, protein formulations and biosimilars
- Describe the various type of FDA meetings
- Some Postmarketing examples

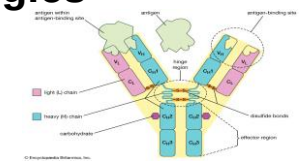
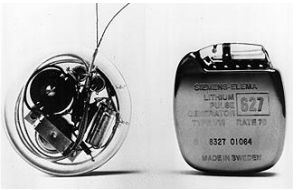
# The legal framework for drug regulation in the United States



# Basic Principle

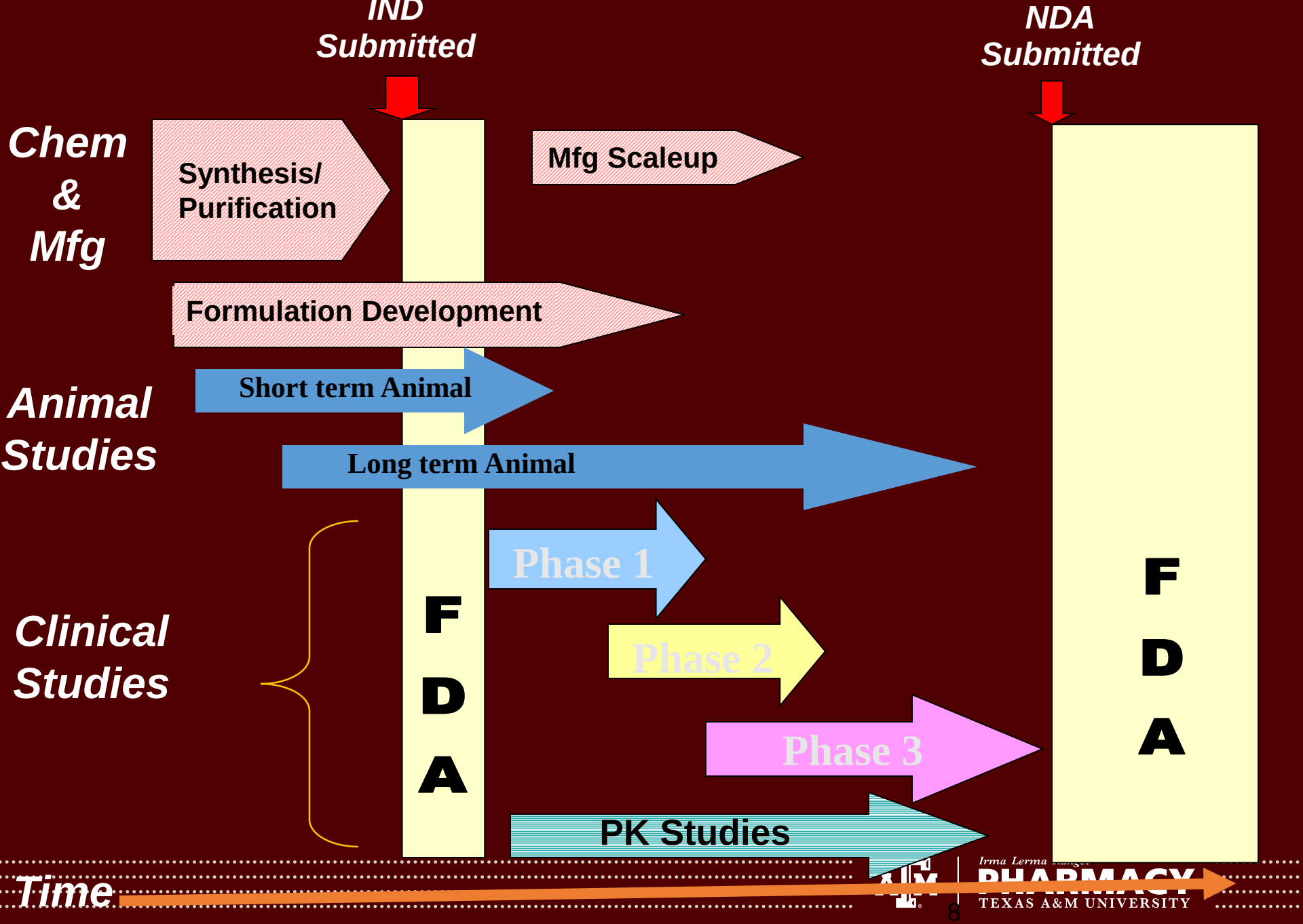
- No drug can be marketed in the United States until "substantial evidence" of its quality, safety and effectiveness has been provided to FDA's satisfaction.
    - *Quality*: the characteristics of the drug, including its manufacturing
    - *Safety*: the relative risk of harm
    - *Effectiveness*: the benefit provided to the patient
    - *Risk/Benefit Ratio*: the degree to which risk is acceptable, given the amount of benefit provided to the patient

# Medical products

| **Drugs**  | **Biologics**  | **Devices**  |
|---|---|---|
| Small molecules | Large molecules | |
| Generally synthetic | Derived from living organisms | Manufactured |
| Analytically simple | Analytically complex:<br>Primary, secondary, tertiary, and quaternary structures | Engineering/physical:<br>Catheters, prosthetics, pacemakers, defibrillators, in vitro diagnostics |
| Heat stable | Heat labile | |
| 21CFR300 | PHS 351a | 21CFR800 |

# FDA Product Reviews

- FDA reviews the results of laboratory, animal and human clinical testing done by companies to determine if the product they want to put on the market is safe and effective.
- FDA does not develop or test products itself.
- FDA conducts this pre-market review for new human drugs and biologics, complex medical devices, food and color additives, infant formulas, and animal drugs.



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# Types of Meetings with FDA

- Type A
  - Necessary for an otherwise stalled drug development program to proceed (i.e., a critical path meeting).

- Type B
  - Pre-IND
  - End of Phase 1
  - End of Phase 2 / Pre-Phase 3
  - Pre-BLA / NDA


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# Types of Meetings with FDA

- Type C
  - All other formal meetings with FDA
- "To promote efficient management of formal meetings, each requestor should try to anticipate future needs and combine drug development issues to the extent practical."

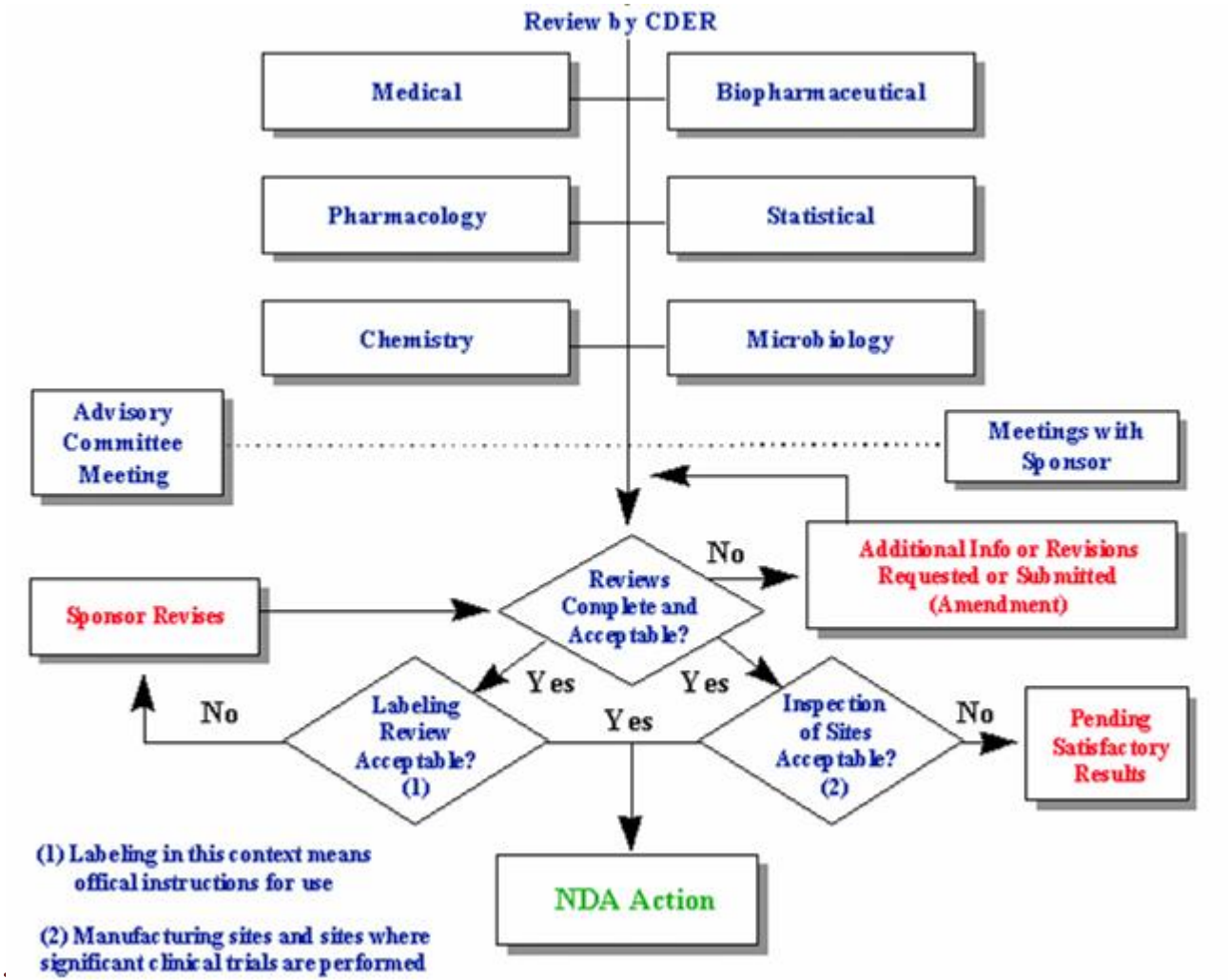
# NDA Content and Format (505)(b)(1)

- Applicants must own or have a right of reference to all studies that are relied upon to support approval
- 356h application form
- User fee cover sheet
- Cover letter
- Index patent statements
- Exclusivity claim
- Financial certification or disclosure
- Labeling
- Summary information on cmc, non-clinical pharmtox, human pk and bioavailability, microbiology, clinical data and statistics

# NDA Content and Format

- Technical sections
  - cmc
  - non-clinical pharmtox
  - human pk and bioavailability
  - microbiology
  - clinical data
  - statistical analysis data
  - pediatric use
  - methods validation

# NDA Review Process




Review times:

60 days filing review
14 days filing letter

Standard – 10 mo
Priority – 6 mo

Subpart-H – Accelerated approval based on surrogate markers

Subpart I – Animal rule

**PMC full text:**

Clin Transl Sci. 2020 May; 13(3): 451–461.

Published online 2020 Feb 6. doi: 10.1111/cts.12745

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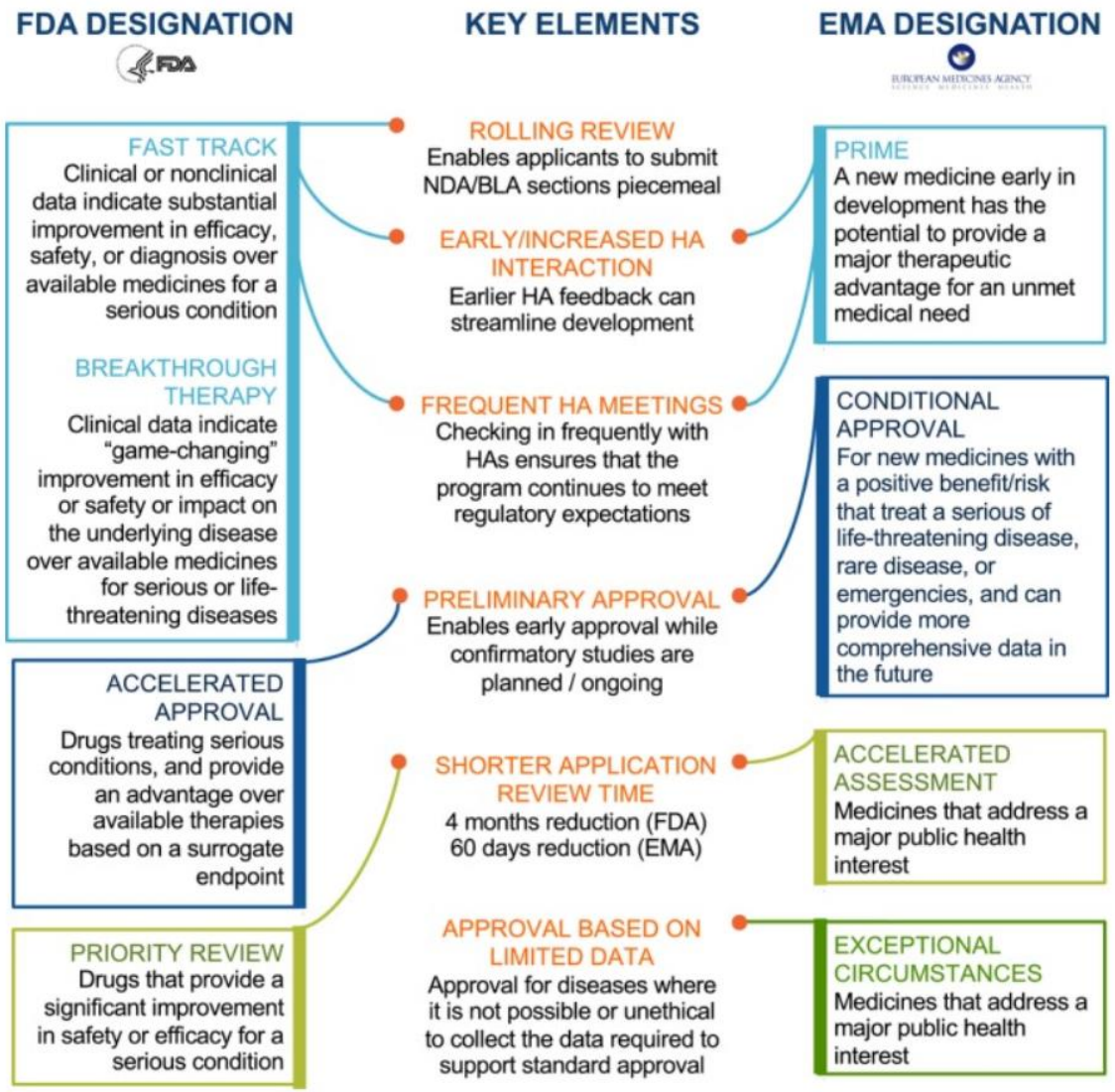
Figure 1



# Generic Drugs 505 (j)

- Sameness is the criteria
  - Same as the RLD in Orange book
  - Active ingredients
  - Route of administration
  - Dosage form
  - Strength
  - Conditions of use recommended in in labeling
  - Some minimal changes are allowed if approved by a suitability petition

# NDA 505 (b)(2)

- Excellent for repurposing or reformulating or for new indications (21CFR 314.54)
- It is an NDA that relies for approval on investigations not conducted by or for the applicant, and for which the applicant does not have a right of reference
- Applicants can rely on literature or the FDAs finding of safety and effectiveness for an approved drug
- For products eligible as ANDA with 505(j), FDA usually refuses a B2 filing as an NDA

# Some examples of changes made in a 505 (b)(2) NDA

- Dosage form
- Strength
- Route of administration
- Substitution of API in a combination product
- Dosing regimen
- Active ingredient – e.g. different salt
- Indication
- Rx to otc switch
- Bioequivalence (both rate and extent, not just rate)
- Naturally derived or recombinant API

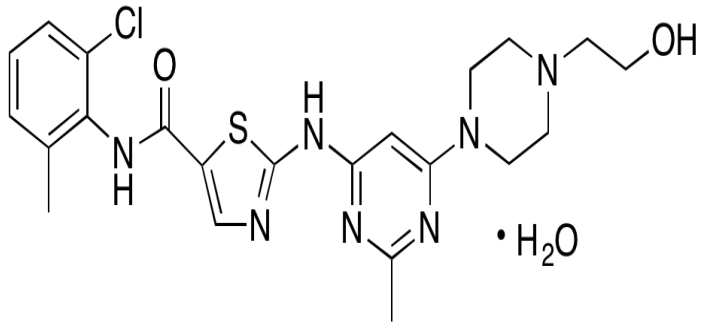
## 505B2 - What is submitted besides cmc?

- BA/BE study between proposed product and RLD
- Patent certification
  - Para1 – patent not submitted to FDA
  - Para 2 – patent expired
  - Para 3 – future patent expiry date – “tentative approval)
  - Para 4 – certification that the patent is invalid, unenforceable
- Statement about indications (same or different from RLD
- Exclusivity of RLD

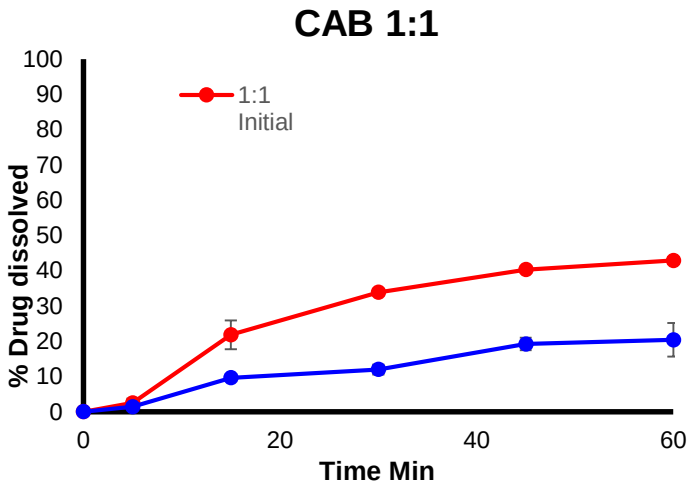
# An example from our lab

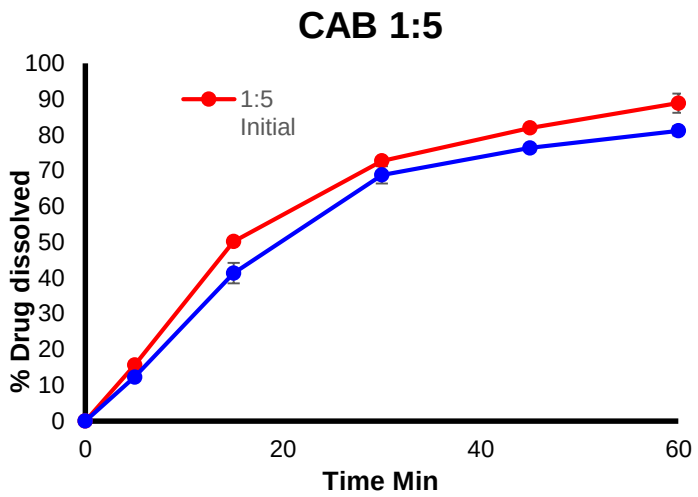
- Dasatinib (DAS), a tyrosine kinase inhibitor is a first-choice oral drug in the treatment of chronic myeloid leukemia (CML) in those patients who are resistant or intolerant to imatinib (coated tablets from 20 to 140mg in strength)

| | | |
|---|---|---|
| Formula | : | $C_{22}H_{28}ClN_7O_3S$ |
| M.Wt | : | 506.02 |
| Water Solubility | : | 0.0128 mg/mL |
| logP | : | 2.77 |
| pKa (Strongest Acidic) | : | 8.51 |
| pKa (Strongest Basic) | : | 7.18 |
| BCS Class 2 Drug | : | Oral BA of 14-34% |



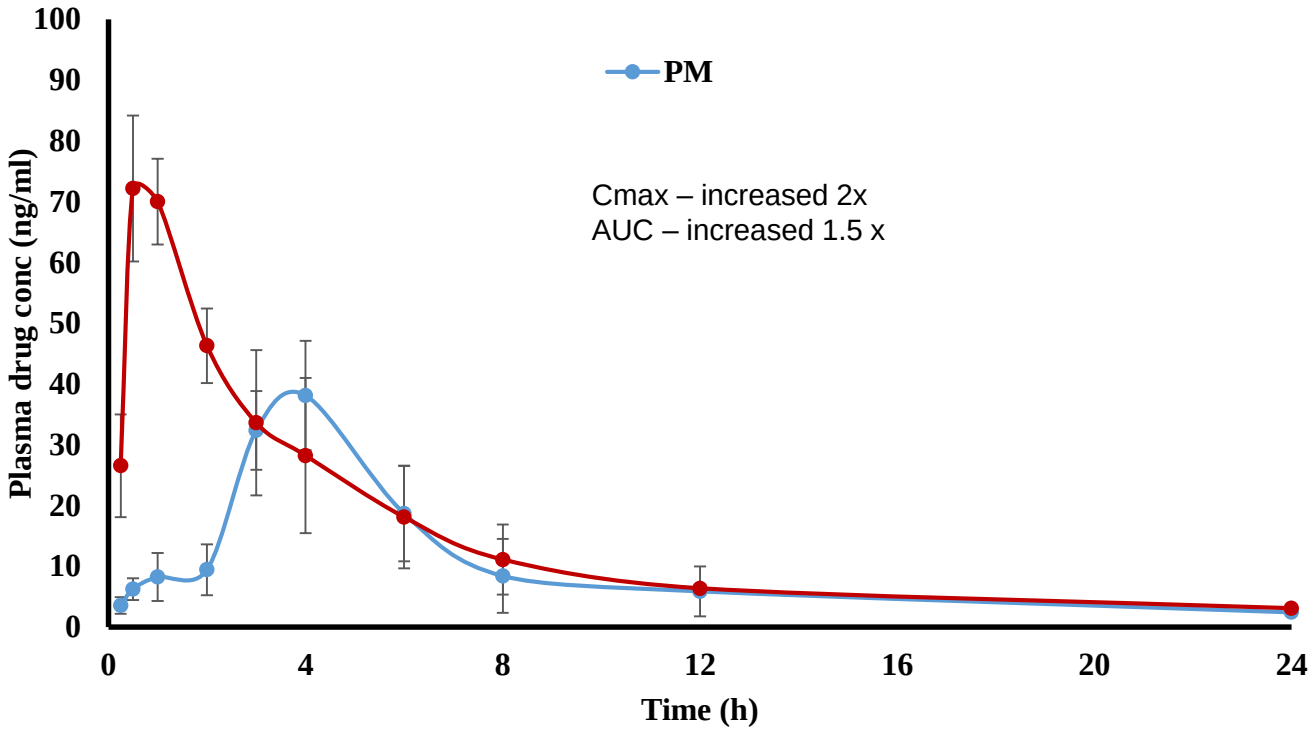
# Dissolution of ASDs prepared by CAB




ASDs prepared with CAB (1:5) showed very good stability compared to other formulations

# Plasma concentration vs Time profile

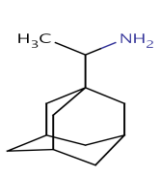


# OTC Products (21 CFR 330)

- Defined as a product that does NOT meet the following criteria
  - Habit – forming
  - Need for physician's supervision
  - Limitations set by an effective NDA for the drugs

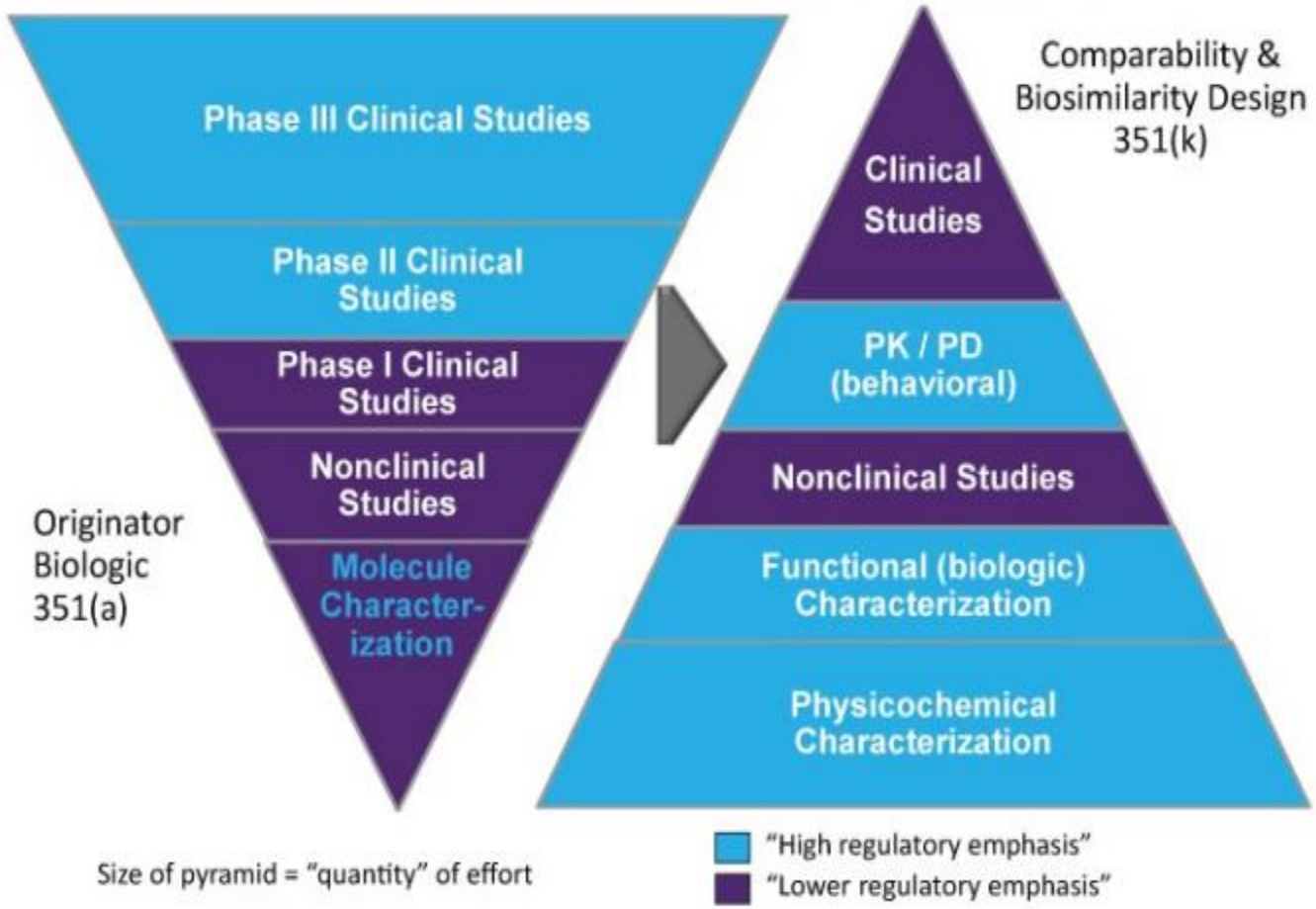
- Two ways to develop
  - GRAS/GRAE ingredients/Official in USP monograph
  - NDA to OTC switch – Deviations from monographs approved for OTC use

# Biosimilars




- "Totality of the Evidence" - Multiple studies are evaluated to determine similarity between a biosimilar and its reference drug. This can be defined as the sum of data from analytical, preclinical, and clinical studies.
- . According to the FDA: "There is no one size fits all approach to biosimilar product development. The goal of a biosimilar development program is to use a "totality of the evidence" approach to demonstrate biosimilarity to the reference product, not to independently establish safety and effectiveness of the proposed biosimilar

## Totality of Scientific Evidence to Characterize the Biosimilar



# Exclusivities

- BLA, 351a: 12 years
- Orphan Drugs: 7 years
- 505 (b)(1): 5 years
- 505 (b)(2): 3 years
- 351k, First biosimilar: one year
- Pediatrics-BPCA – 6 months on adult products
- 505j -First generics – 6 months

# FDA cGMPs

- current Good Manufacturing Practices (cGMPs) and supplements. (21 CFR 210 and 211)

- FDA faces a statutory requirement to inspect facilities every two years.
  - ORA (Office of Regulatory Affairs does domestic inspections for CDER and some from CBER).
  - CDER performs foreign inspections
  - CBER performs biologic inspections for some Biologic.
- Many supplements can require pre-approval inspections.
- Guidance for Industry – cGMPs for phase 1 investigational drugs

# Summary

- IND, NDA (505 B1 and B2), ANDA (generics, 505 j), BLA (351a), Biosimilars (351k), and OTC are ”Pathways” for therapeutic drugs in CDER

- Many opportunities for approvals outside of CDER

- GMP compliance depends upon the stages of drug or drug product development

# Pharmaceutical/Biopharmaceutical Drug Products

Chemistry & Manufacturing
Microbiology
Clinical Pharmacology
Biostatistics
Clinical
Labeling
Compliance
Pharmacology /Toxicology
Safety
Efficacy
Quality

UV, HPLC, UPLC, MS, MS/MS, DSC, TGA, X-Ray
Analytical Methods
Bioreactor/Synthetic
API
Compatibility, Concentration, Solubility, Tg, Particle size dist.
Excipients
Lyophilized powder, Nanomaterials, Microsphere, inhalation solution
Dosage Form
Geometric, Kinematic, Heat transfer, Mass transfer
Scale-up
BLA/NDA/ANDA Pharmaceutical Quality
Product Properties
Ionic strength, Buffer choice, Appearance, Viscosity, pH, Batch size, Yield, Moisture content, Impurities
Container Closure System
Material, Geometry, integrity, Headspace pressure, Leachables, Fill volume, Terminal sterilization feasibility
Processing Conditions
Mixing, Filtration, Sterilization, Freeze-thaw, Agitation, Filling, Spray drying
Environmental Conditions
Storage, Temperature, RH, Light, Handling

**1000+ /YEAR SUBMISSIONS**

**1000+ /YEAR RECALLS**

## Drug Product Life-cycle

**Approvals**
**NDA/505(b)(1)**
**BLA 351 (A)**

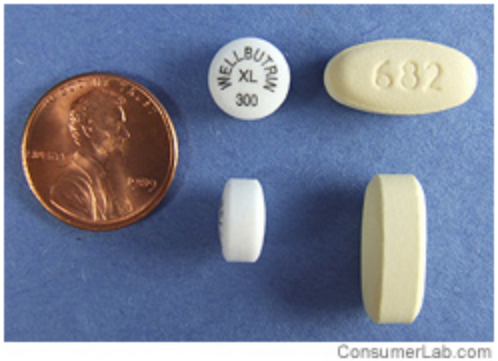
Supplements

**Other NDAs/ANDA(s)/Biosimilars**
**505(b)(2), 505(j)**

Supplements

Mansoor Khan, FDA 2015

Some patients are more sensitive to those differences than others, and people who experience problems with medications are advised to contact their doctors, the drug manufacturer and the FDA's MedWatch. But as an FDA report last week on generic Wellbutrin revealed, consumers who complain may not get much satisfaction.



ConsumerLab.com

Many patients switched from Wellbutrin XL 300 mg to Teva's Budeprion (right); a few have gone back.

Wellbutrin, made by Biovail Corp. of Canada and marketed by GlaxoSmithKline PLC, is one of the best-selling antidepressants in the U.S., with sales of $1.8 billion in 2006. The FDA approved a generic version of Wellbutrin XL 300, a long-acting once-daily version, in December 2006. The generic, named Budeprion XL 300, soon accounted for roughly 40% of the one million monthly prescriptions for the antidepressant.

But patients soon started logging complaints about Budeprion at PeoplesPharmacy.com, a Web site that has become a clearinghouse for medication gripes. "We've received hundreds of complaints about generic drugs in general. But with this one drug, all of a sudden -- kaboom -- right after it was approved," says Joe Graedon, a pharmacologist who runs People's Pharmacy with his wife. Readers' postings cite side effects such as tremors, headaches, anxiety and sleep disturbances. Some consumers said their depression had returned, in some cases bringing thoughts of suicide. Many reported that their adverse effects stopped when they returned to the brand-name drug.

Mr. Graedon alerted the FDA. He also asked ConsumerLab.com, which normally runs tests for dietary supplement manufacturers, to compare Budeprion and Wellbutrin. Using a test-tube test that some industry experts question, ConsumerLab found that

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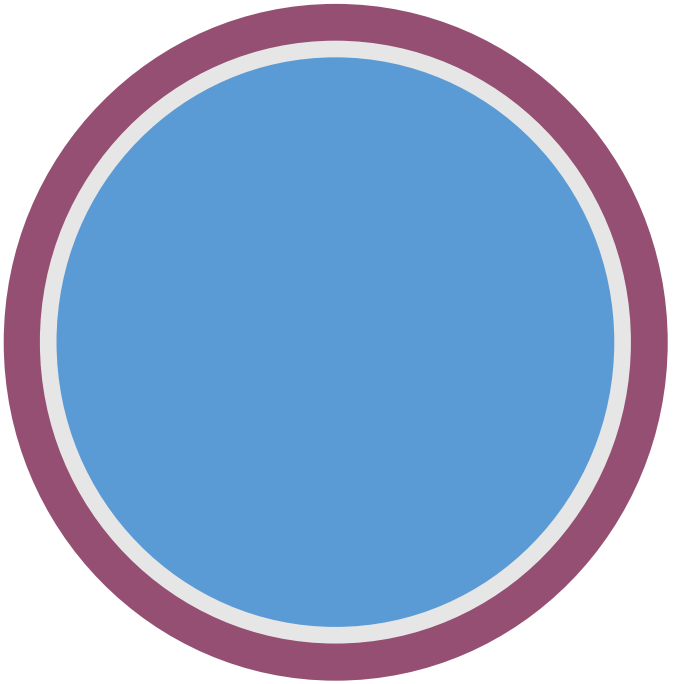
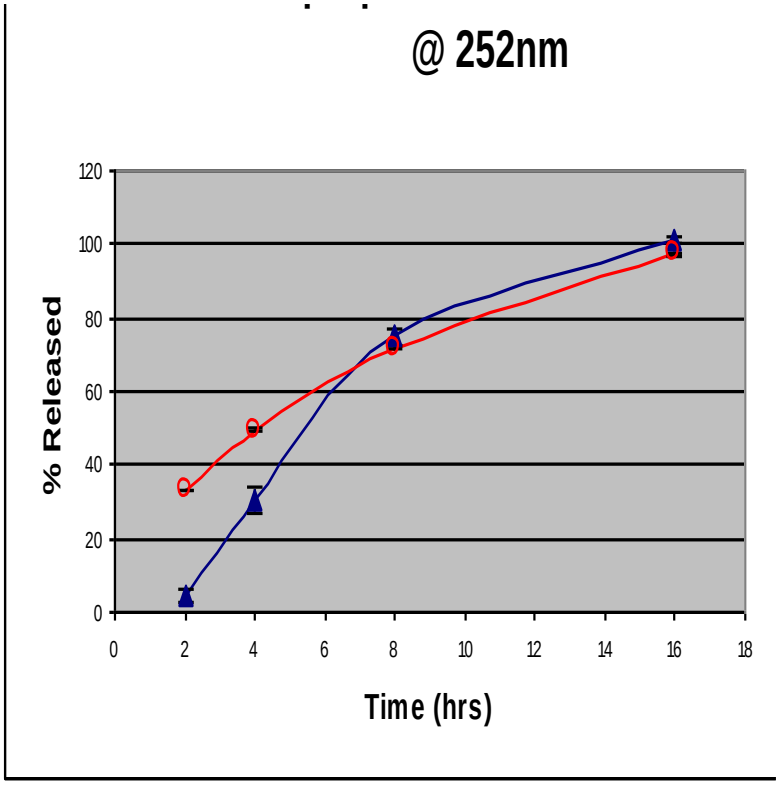
Who Really Shouldn't Eat Gluten

**About Melinda Beck**

As The Wall Street Journal's new Health Journal colur Melinda Beck is returning to her love of reporting after year stint as the editor of Marketplace, the paper's sec Before joining the Journal in 1996 as deputy Marketpl Melinda was a writer and editor at Newsweek magazi wrote more than two dozen cover stories on topics rar the Oklahoma City bombing to the O.J. Simpson trial t and the dilemmas of long-term care. She's always fou health-care issues particularly exciting, as evidenced

# Dissolution Profiles





# Bupropion Statistics

| Summary of Statistical Analysis (n=24) for LS Geometric Means of Bupropion | | |
|---|---|---|
| **Parameter** | **Point Estimate** | **90% Confidence Interval** |
| $AUC_t$ | 0.86 | 76.71-95.82 |
| $AUC_{inf}$ | 0.87 | 78.88-96.97 |
| $C_{max}$ | 0.75 | 65.24-86.81 |

| Arithmetic Means and Ratios of Bupropion | | | | | | |
|---|---|---|---|---|---|---|
| **Parameters** | **Units** | **Test** | | **Reference** | | **T/R** |
| | | **Mean** | **%CV** | **Mean** | **%CV** | |
| $AUC_t$ | ng/mL x hr | 1180.228 | 31.16 | 1400.867 | 38.35 | 0.84 |
| $AUC_{inf}$ | ng hr/mL x hr | 1316.268 | 32.08 | 1527.465 | 38.28 | 0.86 |
| $C_{max}$ | ng/mL | 86.611 | 32.28 | 120.511 | 47.65 | 0.72 |
| $T_{max}$ | hr | 4.000 | 38.14 | 5.000 | 23.37 | 0.80 |
| $K_e$ | $hr^{-1}$ | 0.041 | 61.83 | 0.040 | 52.65 | 1.04 |
| $T_{1/2}$ | hr | 23.689 | 63.99 | 20.980 | 36.04 | 1.13 |

THE WALL STREET JOURNAL.

U.S. EDITION ▾ Wednesday, October 3, 2012 As of 6:39 PM EDT

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HEALTH INDUSTRY | Updated October 3, 2012, 6:39 p.m. ET

# FDA Withdraws Approval of a Generic Version of Wellbutrin

Article | Stock Quotes | Comments (3)

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By JENNIFER CORBETT DOOREN

A A

WASHINGTON—The highest strength of a generic version of the antidepressant Wellbutrin, marketed by a unit of Teva Pharmaceuticals Ltd., TEVA -0.96% will be taken off the U.S. market after tests showed it didn't work as well as the brand-name drug

rticle/SB10000872396390443768804578034794190077594.html#articleTabs_tab_quotes

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Woodcock, Khan, and Yu, New Eng. J. Med., 2012, 367, 26, 2463-2465

COP 32846 0916

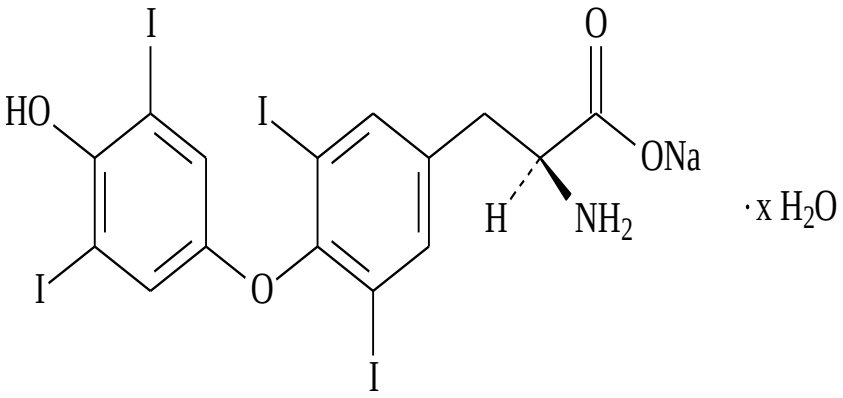
# Just Levothyroxine Recalls – Over 70 recalls with issues of stability and subpotency

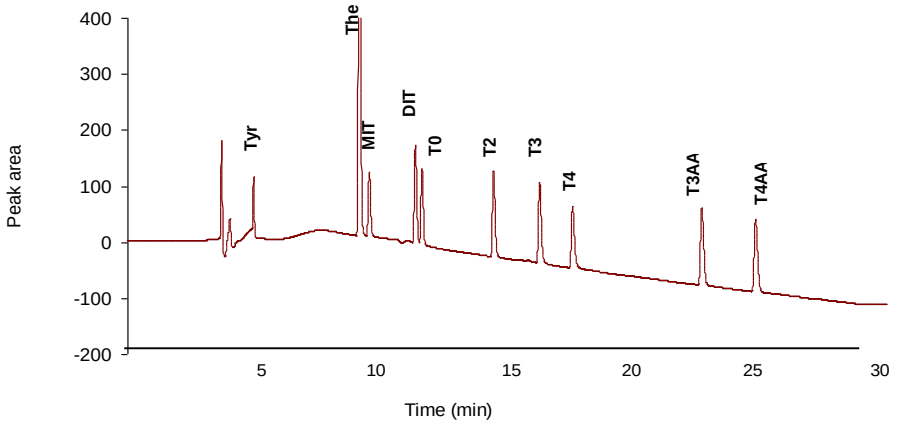
Issue – very low dose drug that degrades with excipient, processes, and environment. The sponsors and reviewers may have missed some basic elements during product development and approvals

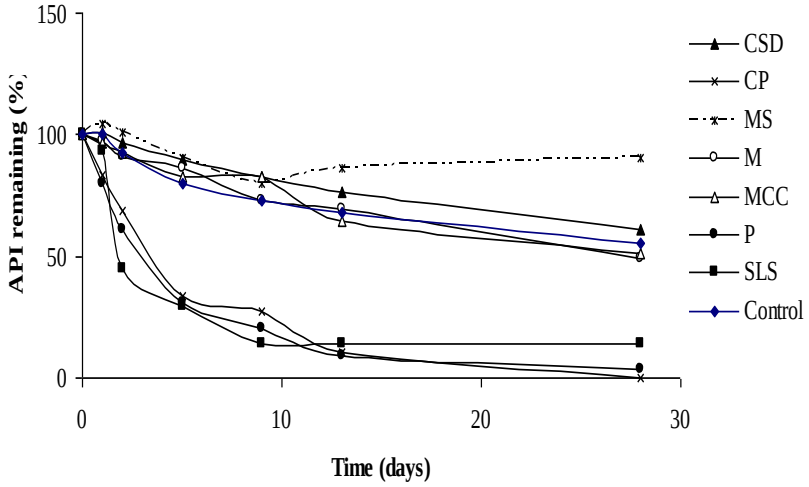
| Stabilty time point | Product1 | Product2 | Product3 | Product4 | Product5 |
|---|---|---|---|---|---|
| Initial eval | 101.16±0.77 | 98.86±0.65 | 98.09±0.91 | 87.25±2.62 | 97.93±0.34 |
| Wk-0 | 106.6±9.77 | 97.98±1.07 | 98.09±0.91 | 87.25±2.62 | 99.22±6.33 |
| Wk-4 | 99.43±0.43 | 96.86±0.63 | 95.3±1.83 | 85.20±0.77 | 101.9±3.70 |
| Wk-8 | 91.43±0.99 | 92.42±0.04 | 94.56±1.27 | 83.49±0.51 | 98.69±4.24 |
| Wk-11 | | | 94.63±2.21 | 88.55±1.78 | |

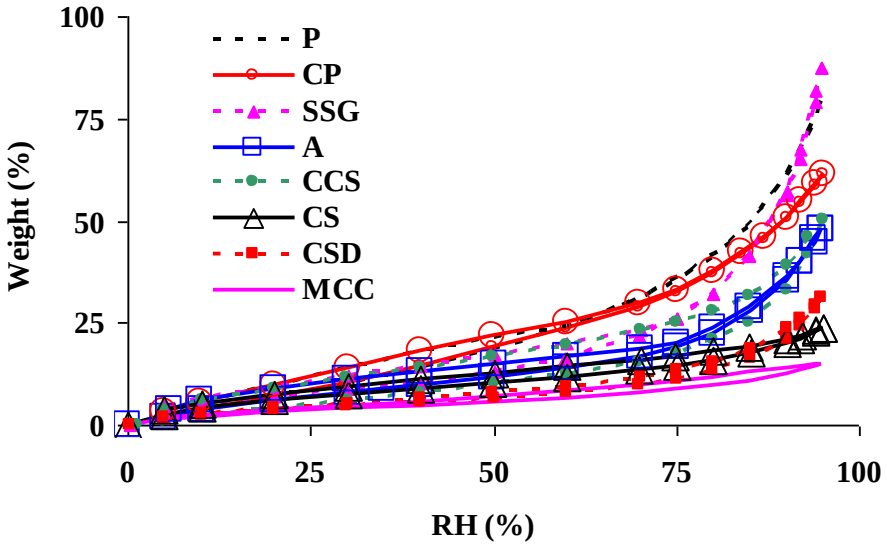
**Several commercial products are failing with our laboratory tests!!**

Collier et al., AAPSPharmSciTech, 54(3), 433-438




Evidence of instability with excipients in approved products by FDA studies


1. *Journal of Pharm. And Biomed. Analysis*, (2011), 433-438.
2. *AAPSPharmSciTech*., (2010), 11(2), 818-825
3. AAPS PharmSciTech. 2010 Sep;11(3):1359-67.
4. *Int. J. Pharm.*, (2008), 360:77-82, 2008

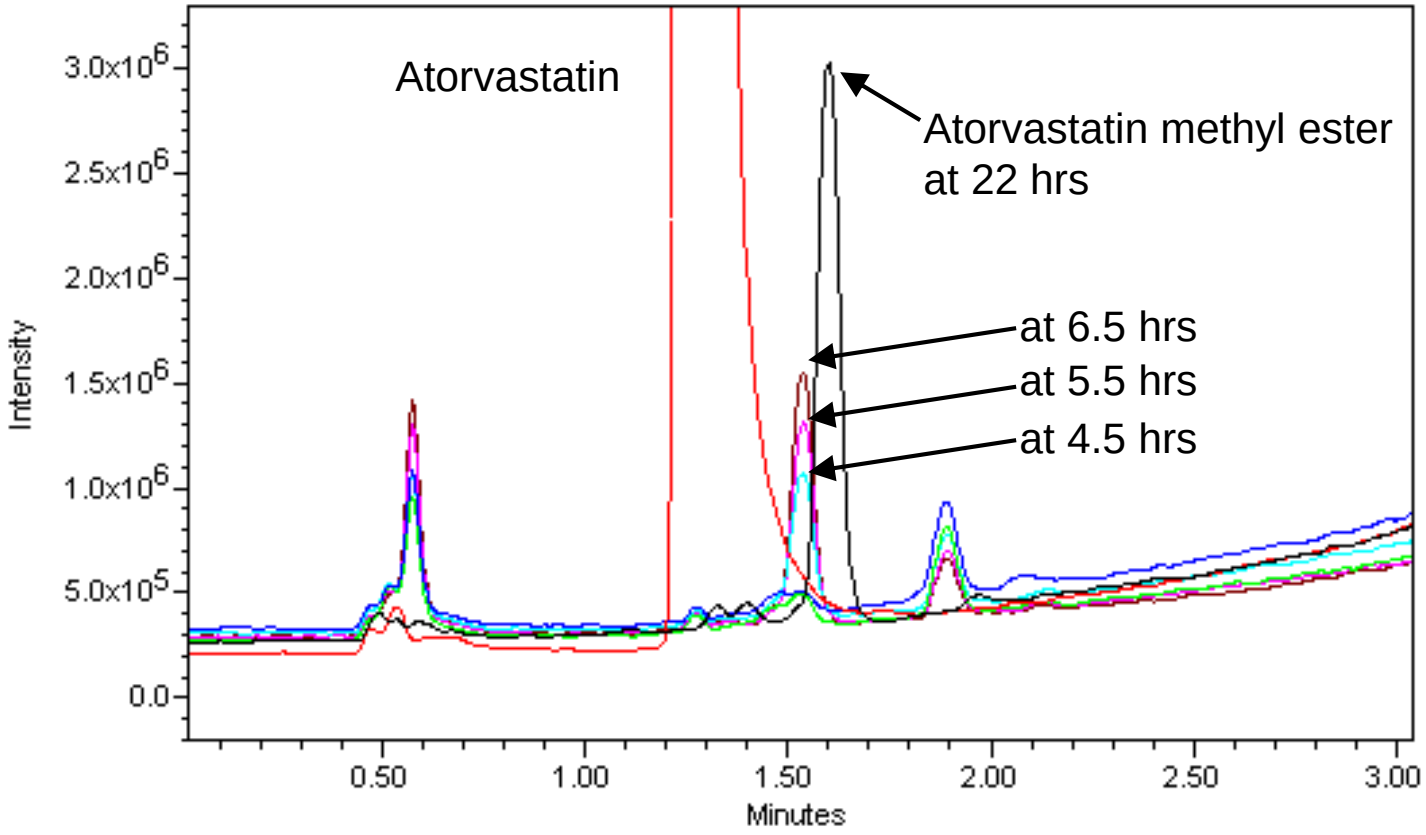
# Atorvastatin Background

- **FDA Failed to Track Substandard Generic Medicines, Congress Told**
- By Anna Edney **February 26, 2014** – Bloomberg News.

- Generic heart drugs made by some India-based companies don't work as they should" said Preston Mason, a researcher at Brigham & Women's Hospital in Boston who has studied the effectiveness of copies of Pfizer Inc. (PFE:US)'s Lipitor made both in the U.S. and abroad.

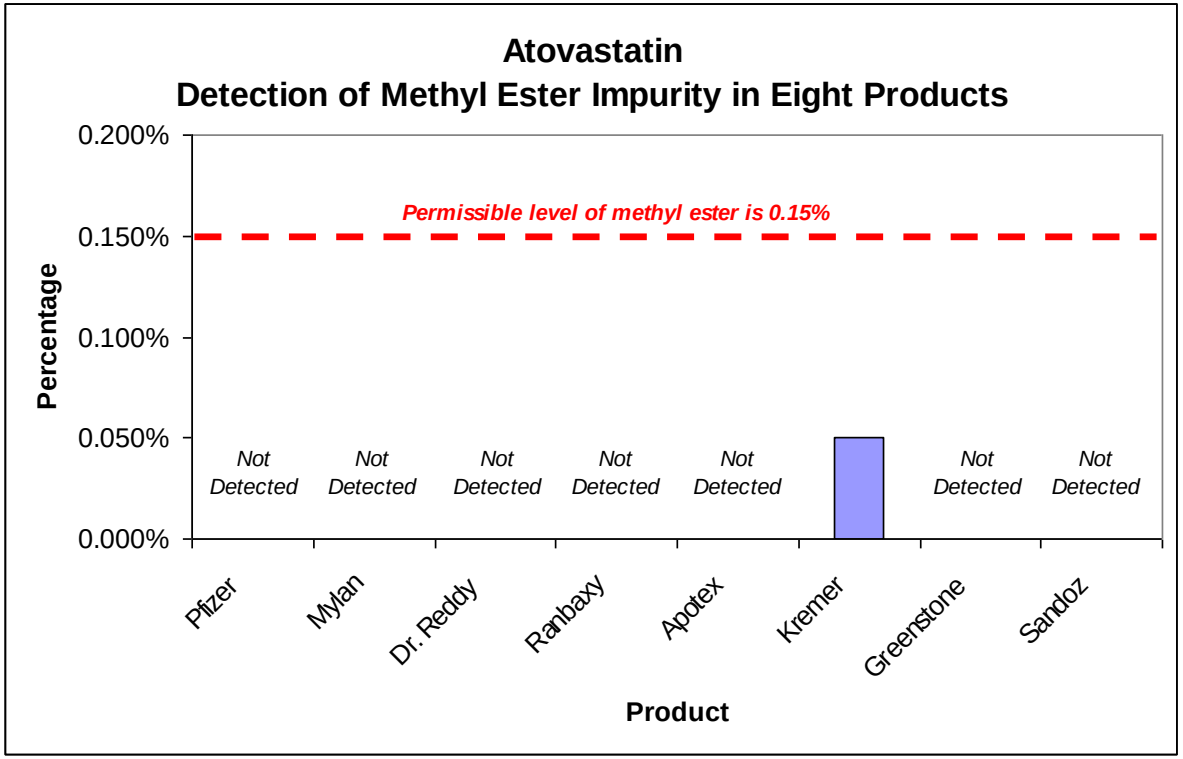
- "This is the Wild West, the whole generics business," Mason told about 50 congressional staff and representatives from the White House, the State Department and FDA…
- _____

# Atorvastatin
# Increase in methyl ester over time



# DPQR: Results

- Additional tests of Atorvastatin products available in the United States, based on USP assay methods without methanol demonstrated that most products had no detectable methyl ester impurity. One product had trace amounts of methyl ester, well below the permissible limit.



# “Harvard” study news corrected and manuscript accepted within two months!!!

Bloomberg News

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By Anna Edney
March 25, 2014 12:01 AM EDT 11 Comments

## Bashing Generics Study, U.S. Regulator Says Heart Drugs Are Safe

A top U.S. regulator is discrediting research published a year ago that found impurities in dozens of generic heart drugs made overseas, saying the investigators contaminated the samples during their testing.

The study by Preston Mason, a researcher at the Harvard-affiliated Brigham & Women’s Hospital in Boston, was one of the first independent probes into generic heart drugs. Outlined by Mason at a congressional briefing last month, it has been at the center of a growing debate over the quality of copycat drugs as insurers increasingly demand their use to trim medical costs.

Janet Woodcock, the Food and Drug Administration’s lead drug reviewer, said Mason’s team “didn’t use the proper method to extract the active ingredient” from samples “and therefore contaminated it themselves

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**FDA Analysis of Atorvastatin Products Refutes Report of Methylester Impurities**

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Therapeutic Innovation & Regulatory Science, 2014, 41(2), pp 239-43.

# Summary

- Differentiated between Laws, Regulations, and Guidances
- Outlined FDA drug approval pathways
- Learned about NDA Pathways
- Identified main differences of New and Generic Drug Products, OTC products, protein formulations and biosimilars
- Described the various type of FDA meetings
- Discussed some postmarketing examples