Regulatory Pathways Panel

Translational Medicine Symposium

February 11, 2013

Agenda

- **Speaker Bio's**
- **Regulatory Discussion of Medical and In Vitro Diagnostic Devices**
- **FDA Regulatory Framework for Drugs**

Haven McCall, DRSc

Moderator

Haven is the Director of the Regulatory Affairs Program at Utah Valley University. He has worked in the medical device industry for over 14 years in the areas of quality assurance, regulatory affairs and clinical research. Dr. McCall teaches graduate level regulatory affairs and clinical research courses at Arizona State University and Utah Valley University. He has a Doctorate and Masters degree in Regulatory Science from the University of Southern California and received a Masters and Bachelors degree in Business Administration from Northern Arizona University.

UVU UTAH VALLEY UNIVERSITY

Patrick Burke, PhD

VP Emerging Products, Myriad Genetics

Dr. Burke is the Vice President of Emerging Products at Myriad Genetics. In this position, he leads the New Product Planning, Business Development and Project Management functions within Myriad Genetics Laboratories. The Emerging Products team delivers new products for commercial launch in each of Myriad's Commercial Business Units. Dr. Burke's previous positions included VP of Strategic Collaborations at Myriad, Vice President of Corporate and Business Development at Myrexis, Inc. , and Licensing Associate at the University of Utah. Patrick earned his Ph.D. in Cell Biology from the University of Utah School of Medicine and received his Bachelor's Degree in Molecular Biology from the University of California, San Diego.

Greg Critchfield, MD

CEO, Sera Prognostics

Dr. Critchfield is the Chairman & CEO of Sera Prognostics. He served as the President of Myriad Genetic Laboratories, Inc. from 1998-2010 and the Chief Medical and Science Officer at Corning Clinical Laboratories/ Quest Diagnostics, Inc. from 1995-1998. Additionally, Dr. Critchfield worked as pathologist and Director of Clinical Pathology at Intermountain Health Care from 1987-1995.

His current and past board service consists of Sera Prognostics, Inc., Saladax Biomedical, Inc, Nodality, Inc, Integrated Diagnostics (Indi), Inc., Metamark Genetics, Inc., Biocius, Inc., BioTrove, Inc., American Clinical Laboratory Association, Chair and Member, Governor's State Advisory Committee on Science and Technology (2003-2006).

He holds a B.S. in Microbiology from BYU, an M.D. from the University of Utah College of Medicine, and an M.S. in Biophysical Sciences from the University of Minnesota.

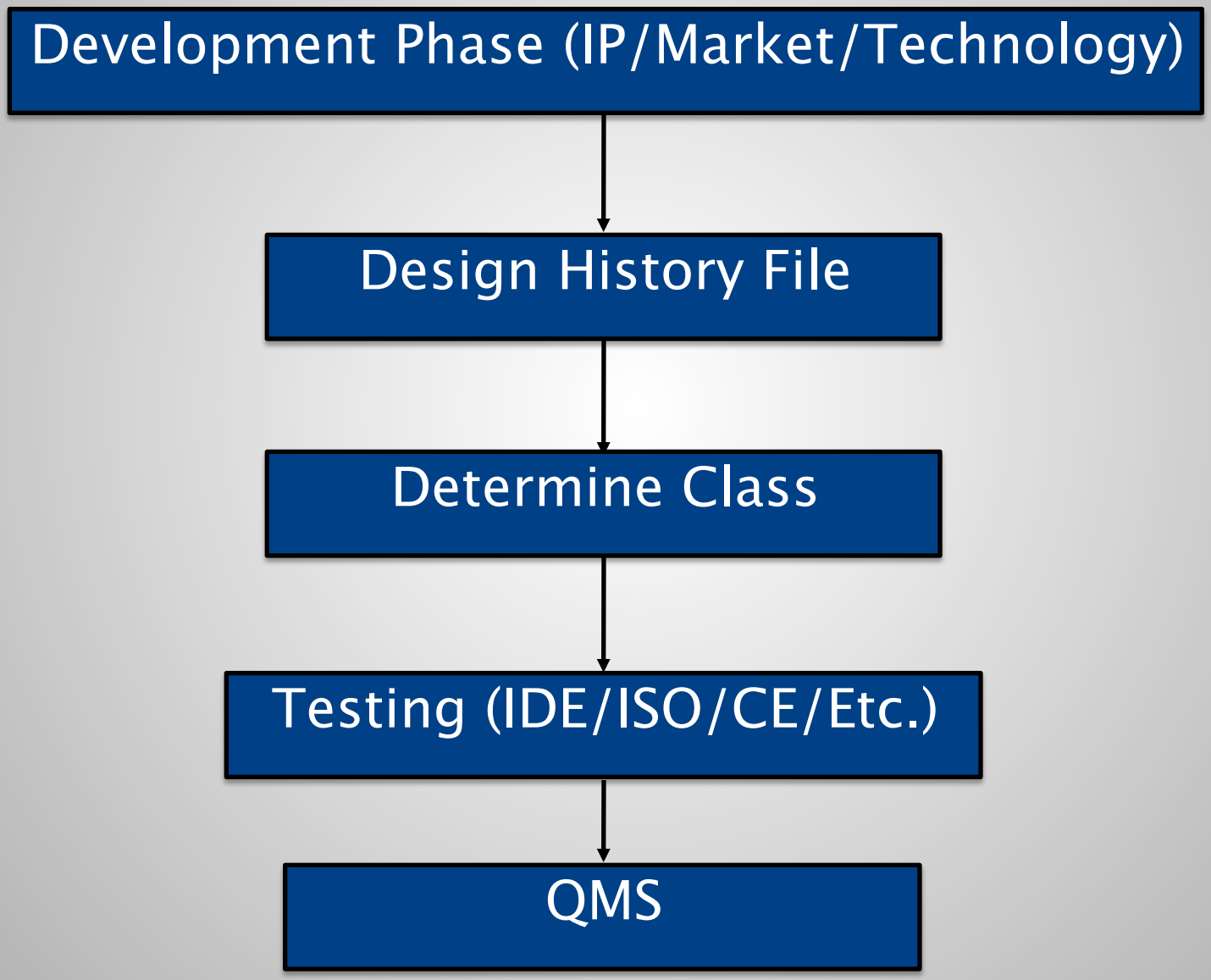
Regulatory Discussion of Medical and In Vitro Diagnostic Devices

Greg Critchfield, MD

Development Phase

- Technology Assessment
  - Does it fit a medical need?
  - Is the technology generally Safe?
  - Can a device be developed that is at least non-inferior to existing therapies?
  - Is there a market for the device?
  - What is the reimbursement strategy?

Typical Device Approval Pathway



Device Class

Class I

- Low risk = generally regarded as safe
- Usually fits a pre-set Class/Panel
- No 510(k) - can market without FDA pre-approval
- QMS - mainly for production controls and post market surveillance
- Registration w/ FDA (annual fee)

Device Class (cont.)

Class II (all of the Class I requirements +)

- Med risk - demonstrable as safe via:
  - ISO 10993
  - IEC 60601 (2nd & 3rd editions)
  - Other specific validations/verifications
- 510(k) required
- Performance Data:
  - Bench
  - Animal (if needed)
  - Clinical/IDE (if needed)
- Formal Risk Assessment
- File with FDA, but no pre-market authorization needed

Device Class (cont.)

Class III (all of the Class I/II requirements +)

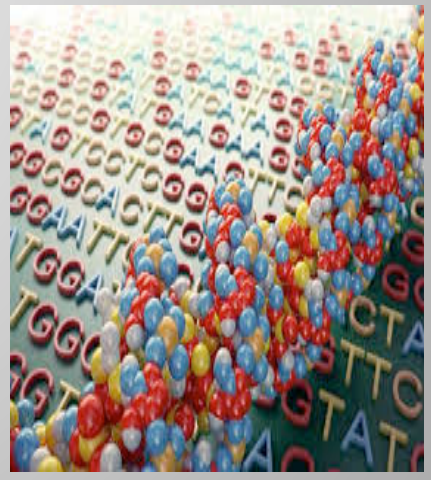
- High risk - demonstrable as safe via:
  - ISO 10993
  - IEC 60601 (2nd & 3rd editions)
  - Other specific validations/verifications
  - Clinical Data (safety and efficacy)
- Full PMA Dossier required
- Performance Data:
  - Bench
  - Animal (if needed)
  - Clinical/IDE
- Formal Risk Assessment
- File with FDA, but pre-market authorization needed

Medical Devices, IVDs and LDTs

- Regulatory Pathways
  - Risk Classification (I, II and III)
    - Based upon "intended use" claims
  - Exempt from FDA Review
    - Class I devices (General Controls only)
    - Some Class II devices
  - Premarket Notification 510(k)
    - Class I and II

Medical Devices, IVDs and LDTs (cont'd)

- Regulatory Pathways
  - –Premarket Approval (PMA)
    - New devices and IVDs
  - –Companion Diagnostics
  - –Laboratory-Developed Tests
    - Clinical Laboratory Improvement Amendments (CLIA)



Types of Submissions

- Pre-Market Notification
- Pre-Market Authorization
- De Novo
  - Humanitarian Use Device
  - Companion Diagnostics
  - Clinical Diagnostic/CLIA

Laboratory-Developed Tests

- Per FDA: Clinical diagnostic test developed by a CLIA-certified clinical laboratory
  - Typically "Non-commercial"
  - Low volume
  - Well-established methods
  - Performed by high complexity laboratories
- FDA's view = LDTs are medical devices
  - Use "enforcement discretion"
- Laboratory view = LDTs are medical services

Regulatory Considerations

- Start with label in mind
  - What will the technology (device/drug/laboratory test) do?
  - What is the intended use population

- What are the safety and efficacy questions regarding the technology?

- How does one build the data needed to justify the claims in the label?

Regulatory Considerations

- What is the regulatory pathway for the product? It depends:
  - FDA
  - CLIA
    - Depending on the situation, a CLIA laboratory test may or may not require FDA review
    - State requirements (US only—e.g., NY, CA, MD, FL, WA)
  - EMEA (Europe)
  - CFDA (China)
  - Others

- What kinds of data will be required by the particular regulatory agency?

Regulatory Considerations

- Consultants can be very helpful as you begin thinking about what to do
  - Have they worked on similar technologies?
  - Have they worked within the agency of interest?
  - Do they have experience with the agency?
  - Have they attended meetings with the agency?
  - Has their work undergone review and resulted in approval by the particular regulatory agency?

A Very Public Illustration: FDA Letter to 23andMe

- 23andMe has been in dialog with FDA for more than 5 years regarding the PGS technology
  - A genetic test marketed to consumers
  - Determines the presence/absence of a number of mutations that have been associated with various conditions

- November 22, 2013: FDA sent the company a letter expressing a number of concerns
  - FDA concerned about claims of performance as a medical test: «"carrier status," "health risks," and "drug response," and specifically as a "first step in prevention" that enables users to "take steps toward mitigating serious diseases" such as diabetes, coronary heart disease, and breast cancer. »
  - FDA highlighted risks of false positives and false negatives, with real health consequences.

A Very Public Illustration: FDA Letter to 23andMe

- November 22, 2013 letter—additional concerns:
  - FDA concerned about expanded uses: "Most of the intended uses for PGS listed on your website, a list that has grown over time, are medical device uses under section 201(h) of the FD&C Act. Most of these uses have not been classified and thus require premarket approval or de novo classification, as FDA has explained to you on numerous occasions."
  - Repeated attempts by FDA to see data supporting claims—none produced; "more than 14 face-to-face and teleconference meetings, hundreds of email exchanges, and dozens of written communications, we provided you with specific feedback on study protocols and clinical and analytical validation requirements, discussed potential classifications and regulatory pathways (including reasonable submission timelines), provided statistical advice, and discussed potential risk mitigation strategies."
  - Concerns about advertising to largely uniformed consumers who could easily misinterpret data

- 23andMe has withdrawn its test from the market, pending outcomes of further discussions with FDA:
  - http://blog.23andme.com/news/23andme-provides-an-update-regarding-fdas-review/

Comments

- Regulation can be complex, and is important.
- Irrespective of pathway, claims must have data backing them up.
- In the US, claims for products/services often will require FDA clearance/review.
- The regulatory pathway depends on a number of considerations.
- Good consultants can help small companies navigate successfully through.

FDA Regulatory Framework for Drugs

Patrick Burke, PhD

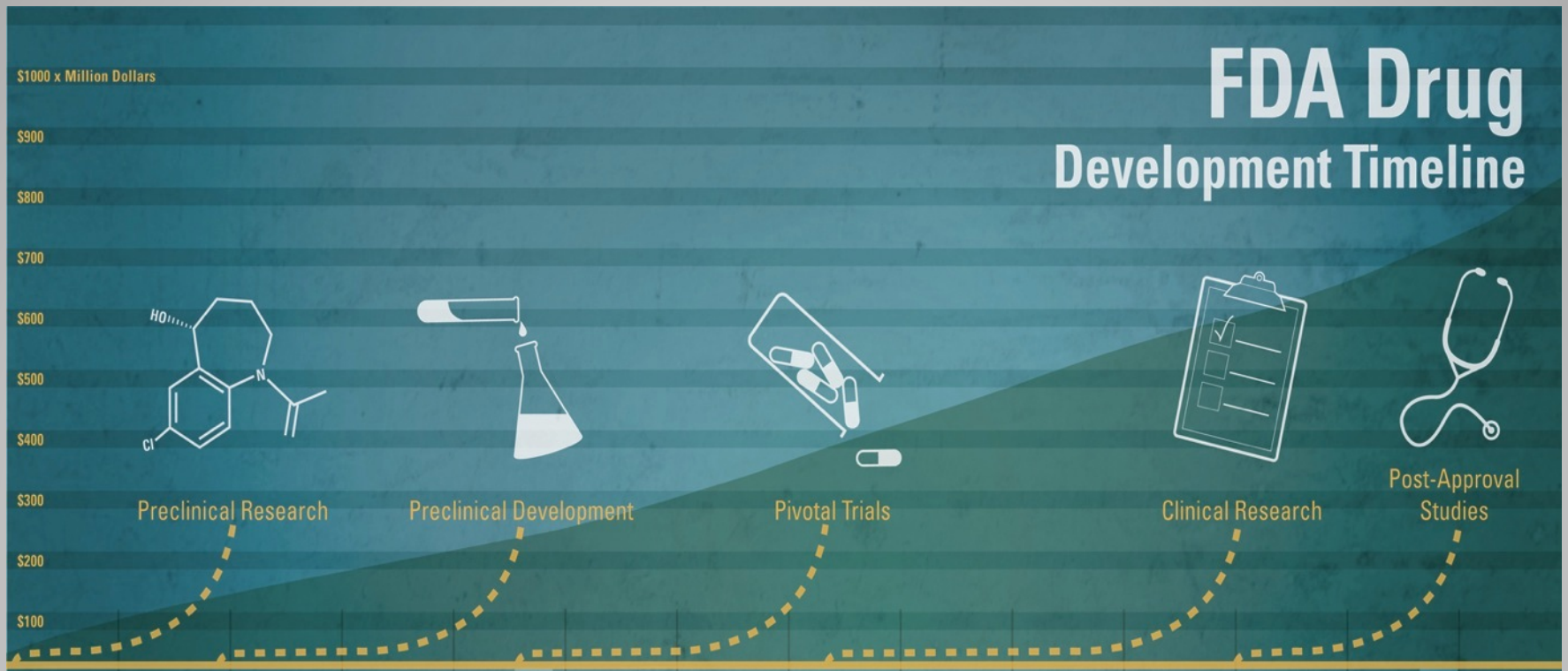
How did this get to you?

FDA Regulatory Framework

Drugs & Biologics

- New Drug Application (NDA); CDER
  - Small molecules
  - OTC
  - Combination Drug/Devices
- Abbreviated New Drug Application (ANDA); CDER
  - Generics
- Biologic License Application (BLA); CBER
  - Vaccines, blood products, devices/tests to safeguard the blood supply, biologics/biologic therapies

FDA Drug Development Timeline



Average Development time:
13 Years
Average cost:
$500 Million - $1 Billion

PKD FOUNDATION
www.pkdcure.org

Phases of a Clinical Trial

Phase I
The drug is tested for safety, dosage and side effects in a small number of healthy volunteers.

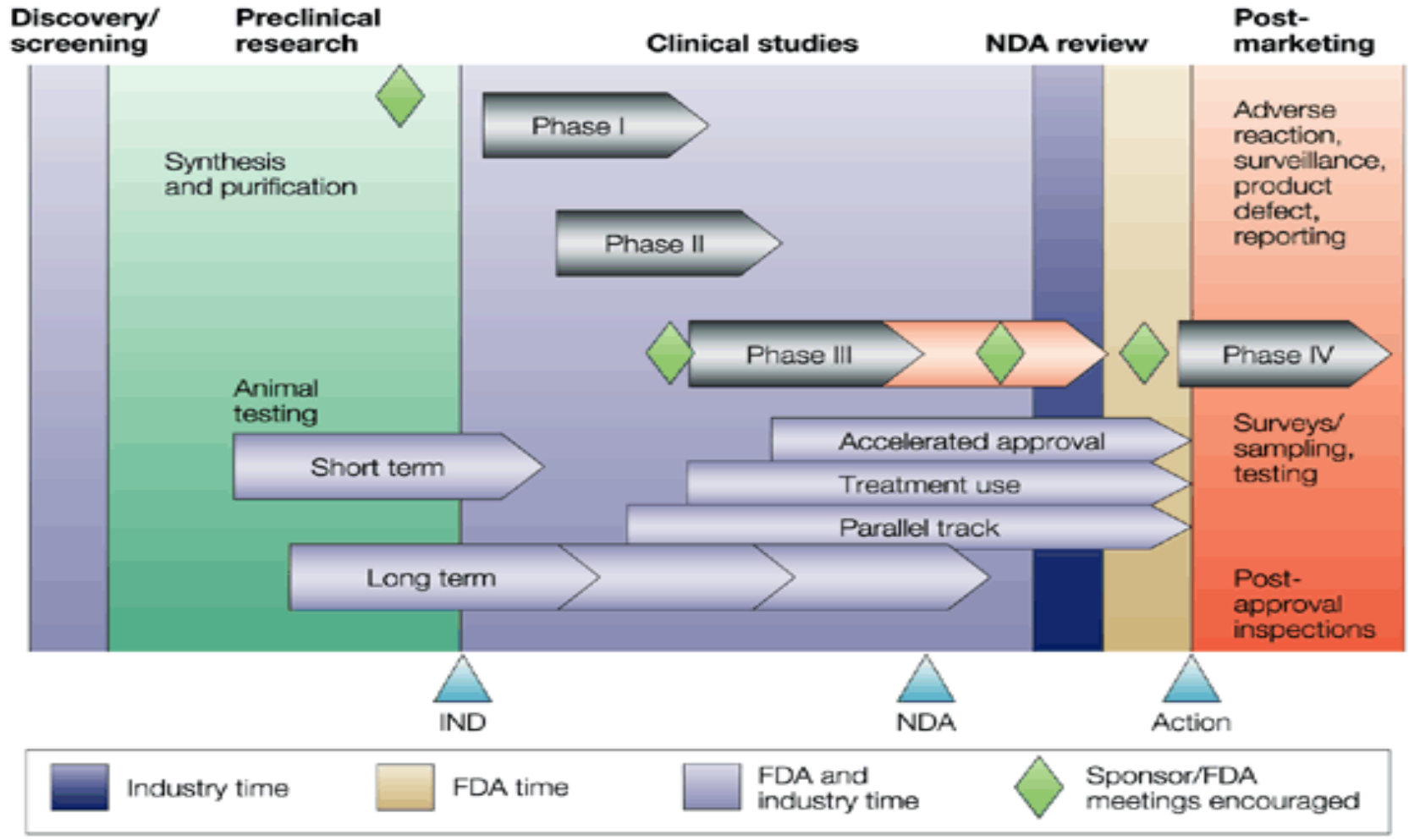
Phase II
The drug is tested for safety and effectiveness in a small number of volunteers.

Phase III
The new drug is tested in a large number of volunteers to confirm effectiveness, monitor side effects and compare results with current treatments.

The data collected during the clinical trial is analyzed and then submitted to the FDA for regulatory review, which can take 1-3 years. Once it is approved, the new drug can be prescribed by physicians.

Phase IV
These studies are done after the drug has been approved and is in use. Additional information about risks, benefits and optimal use is collected and analyzed.

Clinical Studies



Nature Reviews | Drug Discovery

Applications

- **IND** – Investigational New Drug
  - –Supports the **safety** of a drug in order to move into the clinical
    - Incorporates preclinical research, historical clinical data and information on the chemical compound

- **NDA** – New Drug Application
  - –Submission application to market a drug for a specific indication based on pivotal Phase 3 trials
    - Included are manufacturing, CMC, stability, packaging, pharmacokinetics, carcinogenicity and toxicity studies
    - Most important – Risk/ Benefit profile
    - Demonstrate the **efficacy** & **safety** compared to SOC

Purpose of the NDA?

- Allows the company to market and sell a drug for a specific amount of time (exclusivity)
- **NDA** - Needs to demonstrate a comparable or superior risk/ benefit profile
  - Demonstrate that your compound will offer or fulfill a need
    - Novel chemical entity (NCE) must either be non inferior OR superior to a current Standard of Care
    - Offer a treatment where no current treatment exists

END GOAL!!!!

Interactions with FDA

- Pre-IND Meeting
- End of Phase 2 meeting
  - Completed Phase 2b – confirmed your endpoints and your safety/ efficacy
  - Ready to SCALE up
- Type A/B/C Meeting
- Pre-Approval Inspection
- Annual Inspection
- For-Cause Inspection

Companion Diagnostics

- Draft Guidance published July 14, 2011
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf
  - Clearance of an IVD companion diagnostic and therapeutic product
    - Drug usage depends upon use of a diagnostic to meet labeled safety and effectiveness claims
    - Likely Class III device
  - Possible premarket regulatory pathways for each
    - Contemporaneous (preferred); separately
  - Drug labeling identifies an FDA approved/cleared IVD, rather than a specific manufacturer's IVD
  - Example: Roche Zelboraf for melanoma; BRAFV600E mutation

Questions???