Regulatory Issues

FDA's Three Key Development Roles:

* **"Gatekeeper"** to the marketplace -- the new drug approval process
* **"Cop on the beat"** or **"Enforcer"** -- ensuring quality compliance via inspection and enforcement actions (e.g. criminal charges)
* **"Sentinel"** of Safety Concerns - during development and post-approval

FDA regulation of medical products

* Among the products that FDA regulates are three categories of diagnostic, preventative, or therapeutic products:
  + Drugs
  + Biologics
  + Medical devices

The Approval Gate

* Preliminary Considerations -- Determining the Regulatory Status of the product
  + Is it a "drug", "device" or "biologic"?
    - Drug:
      * described in USP (United States Pharmacopeia) or
      * intended (via labeling)
        + to affect the body of man or other animals
        + to be used in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals
    - Device:
      * defined as involving: "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or "similar or related article including any component, part or accessory."
        + in USP/NF (the National Formulary) or
        + intended to be used in diagnosis … cure, mitigation, treatment or prevention of disease or other conditions
        + intended to affect the body of man
    - Thus -- **device** definition can capture products that resemble drugs if they do not achieve their result via being metabolized in the body or via chemical action within or on the body -- regulated by FDA Center for Devices & Radiological Health (CDRH)
      * *Examples of "drug-like" devices:*
        + Ultrasound contrast media
        + Contact lens solutions
    - Biologic
      * Generally, if derived from human or animal tissue;
      * used to be regulated by FDA Center for Biologics (CBER) using approval standards similar to CDER
      * therapeutic biotech products going to CDER
        + vaccines – remain behind
      * ***NOTE:*** "true" biotech products usually are biologics
* OR BOTH??
  + "Combination" or "hybrid" products **--**
    - are regulated per their "primary mode of action" --
    - but this may be difficult to discern -- get clarification very early as will impact FDA Center you deal with
    - can request in writing -- under FDAMA § 416, FDA can't later change its mind w/o your consent or public health reasons exist

What type of submission is needed to get FDA approval or clearance?

* + **Drugs:**
    - Full New Drug Application (NDA)
    - 505(b)(2) NDA or "Paper NDA"
    - Abbreviated New Drug Application
    - The OTC Drug route -- ***Abreva (Avanir/SKB)***
      * NDA
      * OTC Review monograph change
      * What type of submission is needed to get FDA approval or clearance?
  + **Devices:**
    - Premarket Approval Application (PMA) -- *clinical studies will be needed*
    - Premarket Notification under § 510k -- *clinical studies MAY be needed (or wanted)*
  + **Biologics**
    - Biologic License Application (BLA)
    - no generic versions now possible – may change …

What quantity and quality of data will be demanded by FDA to show safety & effectiveness?

* + Will vary -- FDA has extensive discretion here
  + Key task -- try to get clarity as soon as possible in the process -- Ways to do so:
    - Pre-IND meeting -- encouraged by FDA prior to start of human clinicals
    - End of Phase 2 Meeting - also encouraged -- here's where you want to "lock" them in

And the next step…

* You’ve got the device or drug okayed—now you have to manufacture it…

GMPs

* Current good manufacturing practices (GMPs) are the methods by which manufacturers, holders, and transporters of drugs, biologics, or devices assure that every product that they make, hold, or transport is, and continues to be until it is used, safe and effective.
* Failure to comply with GMPs (and for devices, failure to comply with the quality system regulations) makes a product “adulterated” and its distribution or sale illegal.
* The Early Beginnings
  + 1900s house-calls
  + Home remedies, ointments and “miracle elixirs”
  + Entertainment and music
  + No regulations until 1902
* Public Involvement
  + 1905 - The Jungle by Upton Sinclair
    - Sinclair wrote the novel with the intent to portray the lives of immigrants in the United States. However, readers were more concerned with the large portion of the book pertaining to the bad practices and corruption of the American meatpacking industry during the early 20th century
  + Exposure of unsanitary conditions in meat packing plants
  + Public awareness and involvement
  + Pure Food and Drug Act
  + False labeling became illegal
* What is GMP?
  + Good Manufacturing Practice is a set of regulations, codes, and guidelines for the manufacture of drug substances and drug products, medical devices, in vivo and in vitro diagnostic products, and foods.
* Good Manufacturing Practices Worldwide Enforcement
  + Good Manufacturing Practices are enforced in the United States by the FDA
  + In the United Kingdom by the Medicines and Healthcare Products Regulatory Agency
  + GMPs are enforced in Australia by the Therapeutically Goods Administration
  + In India by the Ministry of Health, multinational and/or foreign enterprises
  + Many underdeveloped countries lack GMPs
* 1941 Initiation of GMP
  + Sulfathiaziole tablets contaminated with phenobarbital
  + 1941 - 300 people died/injured
  + FDA to enforce and revise manufacturing and quality control requirements
  + 1941 - GMP is born
* 1962 Kefauver-Harris Drug Amendments
  + Thalidomide tragedy
  + Thousands of children born with birth defects due to adverse drug reactions of morning sickness pill taken by mothers
  + Strengthen FDA’s regulations regarding experimentation on humans and proposed new way how drugs are approved and regulated
  + “Proof of efficacy” law
* 1976 Medical Device Amendments
  + 1972 and 1973 -Pacemaker failures reported
  + 1975 - hearing-Dalkon Shield intrauterine device caused thousands of injuries
  + Class I, II and III medical devices – based on degree of control necessary to be safe and effective
* 1980 Infant Formula Act
  + 1978 - major manufacturer of infant formula reformulated two of its soy products
  + 1979 - Infants diagnosed with hypochloremic metabolic alkalosis
  + Greater regulatory control over the formulation and production of infant formula
  + Modification of industry’s and FDA’s recall procedures

GLPs-Quality Assurance vs. Quality Control

* Quality Assurance
  + An overall management plan to guarantee the integrity of data (The “system”)
* Quality Control
  + A series of analytical measurements used to assess the quality of the analytical data
  + True Value vs. Measured Value
    - True Value
    - The known, accepted value of a quantifiable property
    - Measured Value
      * The result of an individual’s measurement of a quantifiable property
* Accuracy vs. Precision
  + Accuracy
    - How well a measurement agrees with an accepted value
  + Precision
    - How well a series of measurements agree with each other
* Systematic vs. Random Errors
  + Systematic Error
    - Avoidable error due to controllable variables in a measurement.
  + Random Errors
    - Unavoidable errors that are always present in any measurement. Impossible to eliminate
* Quality Control Measures
  + Standards and Calibration
  + Blanks
  + Recovery Studies
  + Precision and Accuracy Studies
  + Method Detection Limits
  + State Laws
* Standards and Calibration
  + Prepared vs. Purchased Standard
  + Signals: Peak Area, Beer’s Law
  + Calibration Curves
  + Continuing Calibration Checks
  + Internal Standards
  + Performance Testing
    - Calibration Curves
      * Graphical representation of the relationship between:
        + The concentration of the analyte and the analytical signal
      * Many methods don’t require that daily calibration curves are prepared
        + A “calibration verification” is analyzed with each batch of samples
    - Sample Batch
      * 10 - 20 samples (method defined) or less
      * Same matrix
      * Same sample prep and analysis
        + Contains a full set of QC samples
    - Internal Standards
      * A compound chemically similar to the analyte
      * Not expected to be present in the sample
      * Cannot interfere in the analysis
      * Added to the calibration standards and to the samples in identical amounts
      * Refines the calibration process
      * Analytical signals for calibration standards are compared to those for internal standards
      * Eliminates differences in random and systematic errors between samples and standards
    - Performance Testing
      * Blind samples submitted to laboratories
        + Labs must periodically analyze with acceptable results in order to maintain accreditation
* Blanks, Blanks, Blanks
  + Laboratory Reagent Blanks
  + Instrument Blanks
  + Field Reagent Blanks
  + Trip Blanks
    - Laboratory Reagent Blanks
      * Contains every reagent used in the analysis
      * Is subjected to all analytical procedures
      * Must give signal below detection limit
      * Most methods require one with every batch
    - Instrument Blank
      * A clean sample (e.g., distilled water) processed through the instrumental steps of the measurement process; used to determine instrument contamination
    - Field Reagent Blanks
      * Prepared in the lab, taken to the field
      * Opened at the sampling site, exposed to sampling equipment, returned to the lab.
    - Trip Blanks
      * Not opened
      * Returned to the lab
      * Not always required in EPA methods
  + Recovery Studies
    - Matrix Spikes
    - Laboratory Control Samples
    - Surrogates
  + Matrix Spikes
    - Sample spiked with a known amount of analyte
    - Subjected to all sample prep and analytical procedures
    - Determines the effect of the matrix on analyte recovery
    - Normally one per batch
  + Laboratory Control Sample
    - Analyte spiked into reagent water
    - Subjected to all sample prep and analytical procedures
* Precision and Accuracy
  + Required for initial certification and annually thereafter
  + A series of four laboratory control samples
  + Must meet accuracy (recovery) and precision (standard deviation) requirements, often in method
* Method Detection Limit
  + The minimum concentration of a substance that can be measured and reported with 99% confidence that the analyte concentration is greater than zero
  + MDLs are determined according to 40 CFR, part 136, Appendix B
  + Seven replicate laboratory control samples, analyzed for precision
  + Must be performed initially for certification
  + Must meet criteria specified in method
  + Must be performed with change in instrumentation or test method
  + Annually with ELCP (Environmental Laboratory Certification Program)
* State Laws (and sometimes city)
  + Each state has laws governing laboratories and their personnel.
  + Some cities (e.g. New York City) have a separate licensure