Planning for Successful, Efficient, Pharmaceutical Product Development

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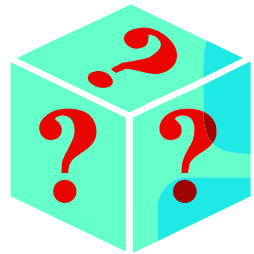
Questions to be answered



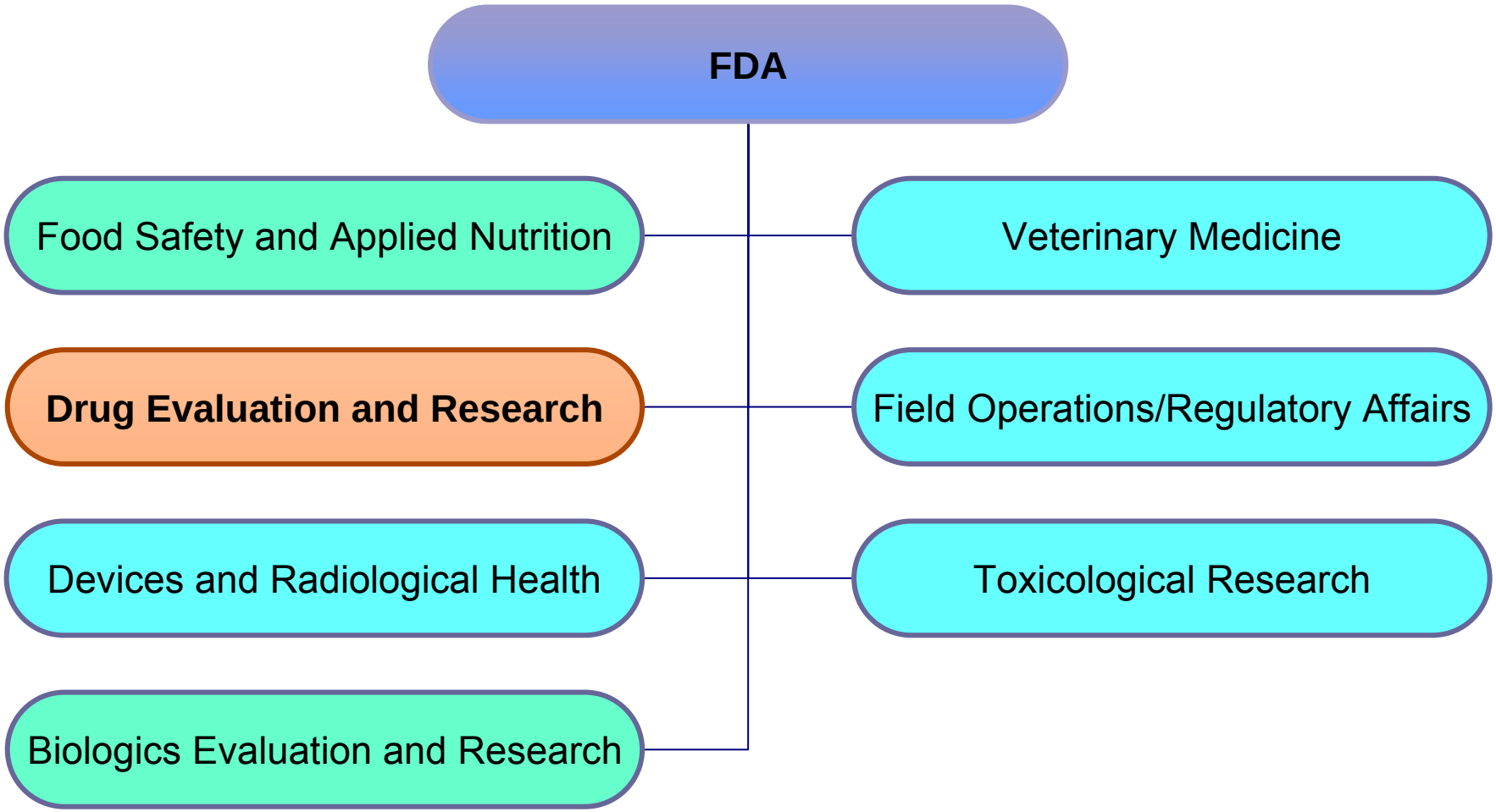
- Who are we?
- What is the process for review:
  - During drug development?
  - Of a marketing application?
- What special programs are available?

Please ask questions!

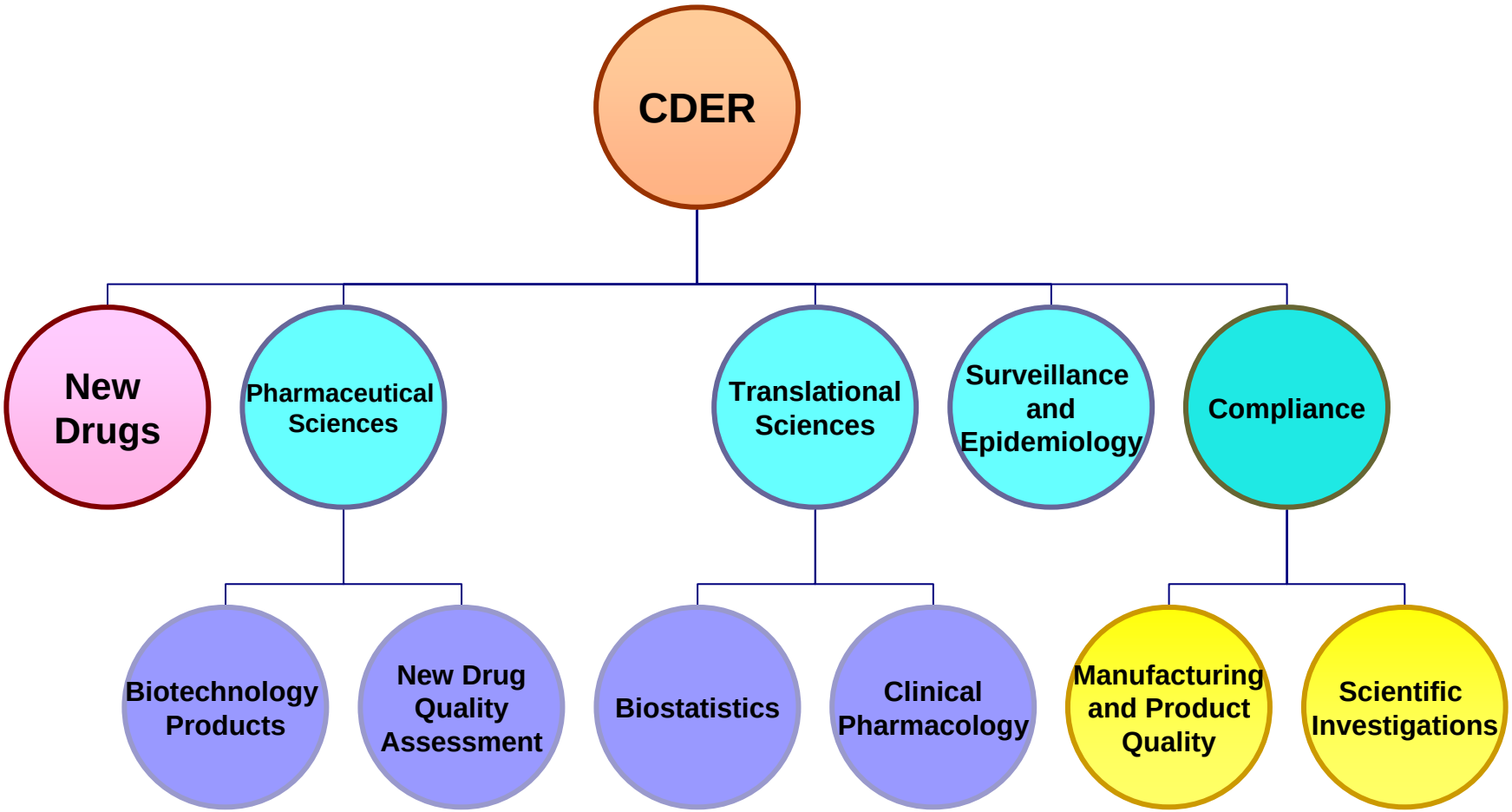
Why are effective interactions important?

- Shared Public Health goal
  - FDA Mission: protecting and "…*advancing* the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable…"
- FDA has expertise and "insider" knowledge; we are uniquely positioned to improve drug development

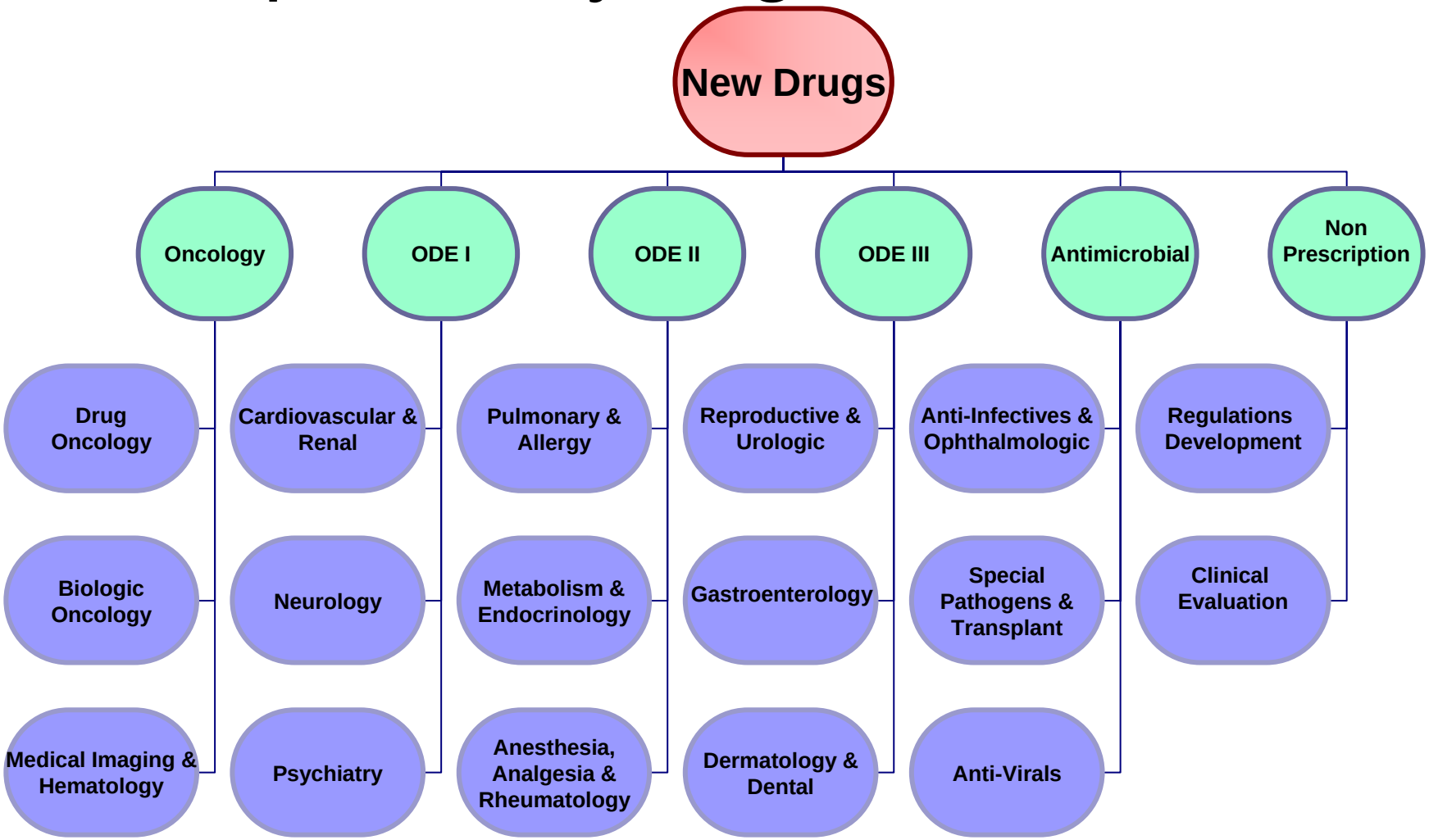
Who are we? A Public-Health, Science-based Agency



Who are we?
A Matrix Organization

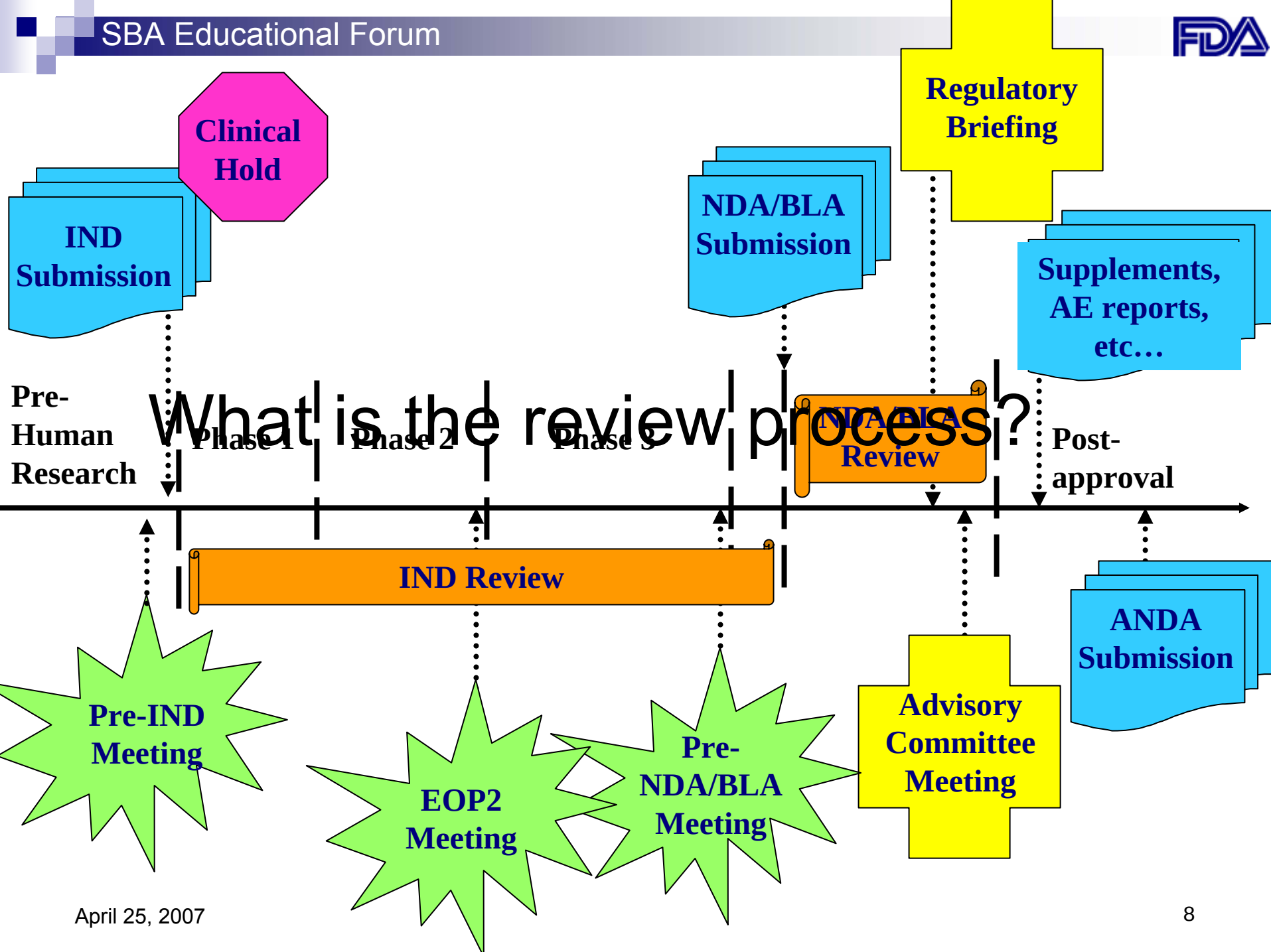


Who are we?
Therapeutically Aligned Divisions



Who are we? Review teams of multi-disciplinary experts

- Clinical
  - Including microbiologists for anti-microbials
- Chemistry/manufacturing
  - Including sterility, if needed
- Nonclinical pharmacology/toxicology
- Clinical pharmacology
- Statistics
- Regulatory (Project Manager)



What is the review process?

When is an IND required?

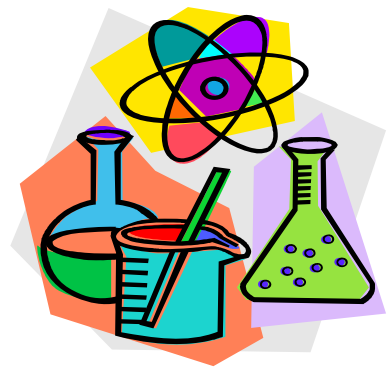
- Generally whenever studies in humans are conducted in the U.S.
- Exemptions:
  - Drug is approved in the U.S. and investigation is not intended to support change in labeling or advertising and does not change the known risk/benefit profile
  - Some bioavailability/bioequivalence studies
  - Still need IRB approval and informed consent

Pre-IND Meeting

- Not necessary for every IND
- Generally focus on nonclinical studies and design of initial clinical protocol
- Opportunity to discuss uniqueness of molecular entity, studies or indications
- Pre-IND meeting ≠ no clinical hold
- ☺ Ask specific, answerable questions
- ☺ Remember: advice given is based on information provided

Basic information needed – IND application

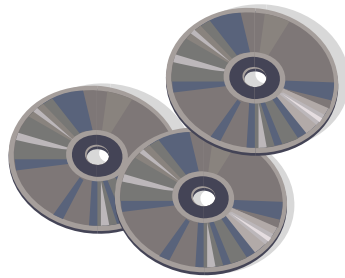
- Nonclinical
  - Enough data to support proposed clinical protocol
  - Basic exposure data
- Chemistry, manufacturing and controls
  - Sufficient information to assure proper id, quality, purity and strength
  - Sufficient information to assess whether batches can be adequately produced and consistently supplied



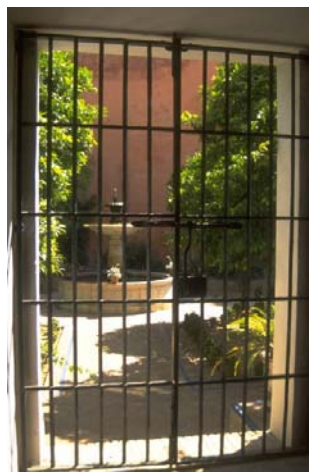
Basic information needed – IND application

- Clinical trial protocol
  - Determine the phase of development
  - Provide supporting data (e.g., from ex-U.S. trials, PK data)
  - Specify how to ensure safety of the subjects/patients in the study

New IND submission



- Content requirements outlined in ***21 CFR 312.23***
- Paper unless in eCTD (electronic Common Technical Document format) on media or via Gateway
- Actions (within 30 days)
  - "Reasonably safe to proceed" = active
  - Clinical hold (partial or full)
- INDs are *not* approved



Active IND = Drug Development!

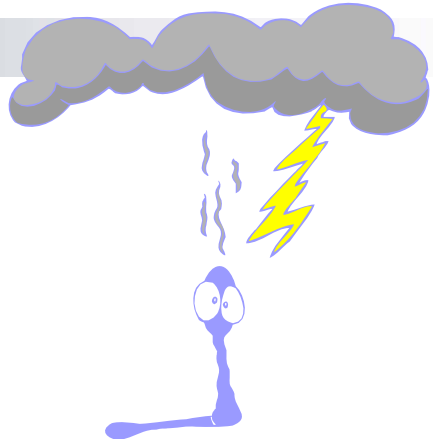
- New trials can be initiated once protocol is submitted and IRB approval is obtained – no waiting!
- Amendments include clinical protocol changes, new protocols, information amendments of nonclinical data, chemistry, etc.
- Safety and annual reports required ***21 CFR 312.32; 21 CFR 312.33***
- ☺ Clearly identify all submissions (e.g., stability protocol)

Review of Active INDs: Things to remember…

- Review builds as development continues
- An active IND can be placed on clinical hold or partial clinical hold at *any time*
- Sponsors may not promote investigational drugs or uses, and may not charge for investigational drugs (unless specifically approved by FDA) ***21 CFR 312.7***
- Housekeeping: inactive, withdrawal, termination ***21 CFR 312.45, 312.38, 312.44***

Why are meetings important?

Meetings are one method of communication between the Agency and industry to facilitate a common goal – more efficient drug development.



Meetings Have Impact

"Review team members generally consider open and frequent communication as having a high impact on the review process."

Independent Evaluation of FDA's First Cycle Review Performance –Retrospective Analysis Final Report, Booz Allen Hamilton, Inc. www.fda.gov/oc/pdufa

What happens when a sponsor requests a meeting?

- Requests evaluated for appropriateness, generally surrounding the issues/draft questions for discussion
- Decisions to grant/deny the request issued within 14 days

~ 2,500 requests/year; ~10% denied

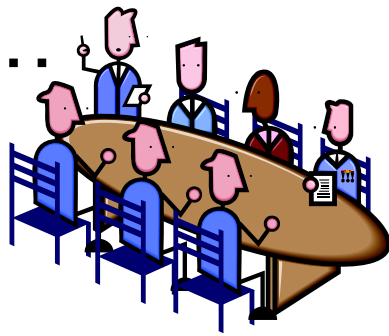
Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products

What happens when CDER grants a meeting?

- Scheduling is the biggest challenge and is dependent on the attendees requested/needed
  - "Reciprocal" attendees – who *really* needs to attend?
- Background package with final questions is received, reviewed and discussed at an internal meeting and preliminary responses drafted and provided to sponsor in advance
  - Goal: make meeting more focused and efficient

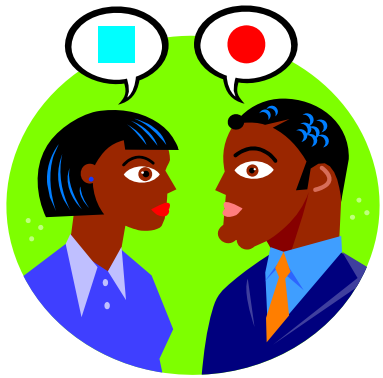
What happens at the meeting?

- Teleconferences just like face-to-face meetings without the suits
- Seating assignments not made but…
- Elements of a “good” meeting
  - Discussion is focused on issue
  - Outcome is clear and summarized at conclusion
  - Participants remain professional



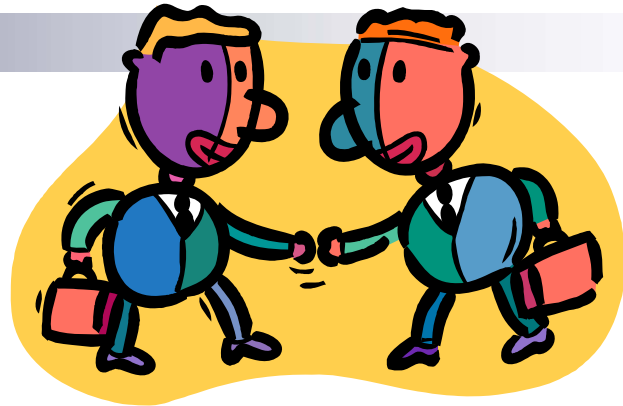
What happens after the meeting?

- Minutes for all meetings are provided in 30 days



  - FDA version is “official” – submit disagreements in writing

Key Meetings – End of Phase 2



- Held after Phase 1 and 2 studies are complete
- Discuss and reach agreement on clinical studies that will provide definitive support for efficacy and safety
- ☺ Most important meeting during development!
- ☺ Be honest about possible problems identified during development
- ☺ Mock-up a label so we can help ensure that your trial design supports your labeling goals

http://www.fda.gov/cder/guidance/6910dft.pdf

Key Meetings – Pre-NDA/BLA

- Request when all studies designed to support the desired claims of safety and efficacy have been completed
- Discuss whether evidence of effectiveness was seen in the Phase 3 trials, the need for risk management, technical aspects (format), plans to address potential problem areas
- ☺ Address all previous advice not taken, and unresolved issues
- ☺ Be honest – are you really ready to submit?

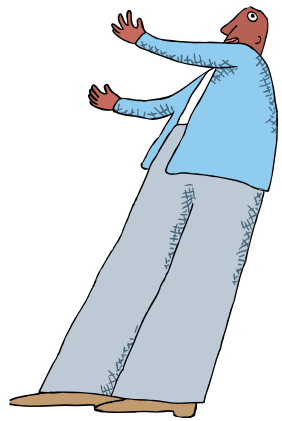
Other interactions – Guidance/Advice

- Guidance meetings can be held at request of sponsor or FDA to discuss any issues
- Written feedback can be provided upon request for amendments to the IND (not always provided)
- Regulatory and procedural advice can be given over the phone or by e-mail
- ☺ Keep in touch with the Regulatory Project Manager on an informal basis – provide updates, “Heads up!”, etc.
- ☺ Never assume – be clear

Meetings are critical – Here are a few reminders…

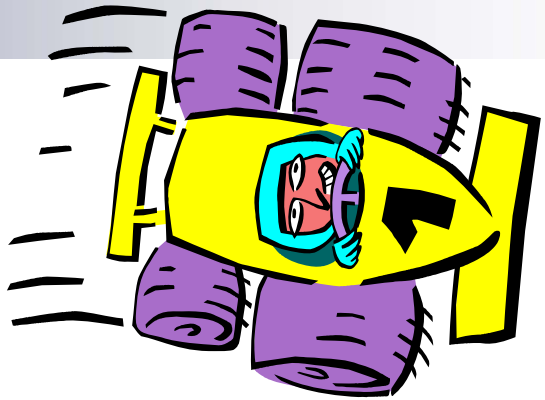
- **Rule #1** – follow the guidance! Submit requests in writing
- Identify your questions before you request a meeting and don't ask unanswerable questions
- Don't hide concerns – share them and propose solutions
- Skip the presentation – use the time for discussion
- Minimize surprises
- Listen closely and strongly consider what is being recommended

Meetings are critical – More Helpful Hints!



- Stay focused on the agenda
- Stay professional
- Listen closely and strongly consider what is being recommended
- Have someone (either you or FDA) summarize the outcome and any action items

Special Programs – Drug Development



Subpart E Accelerated development of drugs intended to treat life-threatening and seriously debilitating illnesses

- Highlights critical nature of close, early communication (e.g., Pre-IND and end of Phase 1 meetings)

21 CFR 312.80 through 312.88

Fast track designation

- Overarching program encompassing available development and application review programs meant to accelerate the development and approval of drugs intended to serious and life-threatening diseases where there is unmet medical need
  - Includes Subpart E and accelerated approval

Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review

Special Programs – Drug Development

Screening INDs

- Allows for the review of multiple active moieties or formulations within a single IND to screen for the preferred compound or formulation for early exploratory studies (short-term Phase 1 tolerance, PK/PD, and pilot efficacy)
- Covers only the protocols in the initial submission; new IND submission required once candidate selected

Manual of Policy and Procedures 6030.4, INDs: Screening INDs

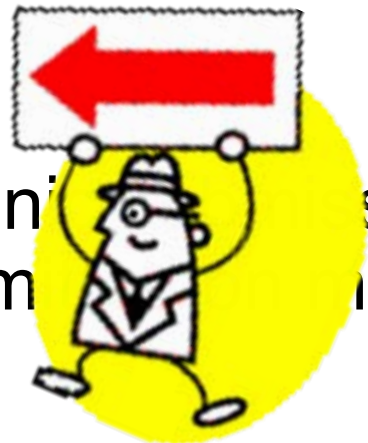
Special Protocol Assessment

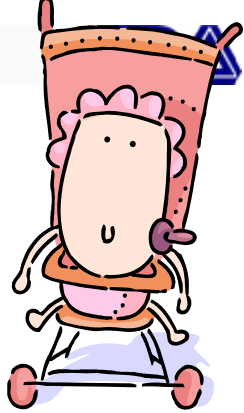
- Applies to carcinogenicity protocols, stability protocols, and clinical protocols for trials intended to form the primary basis of efficacy
- Assessment provided in writing within 45 days of receipt

Guidance for Industry: Special Protocol Assessment

Development Complete – May You Market?

- NDA/BLA submission User Fees
  - Current fee: $896,200
  - Small Business Exemption!!
- Beginning in 2008, all electron sions must be in eCTD format subm edia or via Gateway





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- Physicia… … labeling format fe… … d table of contents
- Structur… … h electron… … arch function… … oduct labeling … cine

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Imdicon safely and effectively. See full prescribing information for Imdicon.

IMDICON® (ibollmast) CAPSULES
Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Imdicon immediately if any of the following occur:

- Neutropenia/agranulocytosis (5.1)
- Thrombotic thrombocytopenic purpura (5.1)
- Aplastic anemia (5.1)

RECENT MAJOR CHANGES

Indications and Usage, Coronary Stenting (1.2) 1/200X
Dosage and Administration, Coronary Stenting (2.2) 1/200X

INDICATIONS AND USAGE

Imdicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:

- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)

Important limitations:

- For stroke, Imdicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

DOSAGE AND ADMINISTRATION

- Stroke: 50 mg once daily with food. (2.1)
- Coronary Stenting: 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in recently impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 5.6, 12.3)

DOSAGE FORMS AND STRENGTHS

Capsules: 50 mg (3)

CONTRAINDICATIONS

- Hematopoietic disorders or a history of TTP or aplastic anemia (4)
- Hemostatic disorder or active bleeding (4)
- Severe hepatic impairment (6, 8.7)

WARNINGS AND PRECAUTIONS

- Neutropenia (2.4 % incidence; may occur suddenly; typically resolves within 1-2 weeks of discontinuation), thrombotic thrombocytopenic purpura (TTP), aplastic anemia, agranulocytosis, pancytopenia, leukemia, and thrombocytopenia can occur (5.1)
- Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Anticoagulants: Discontinue prior to switching to Imdicon (5.3, 7.1)
- Phenytoin: Elevated phenytoin levels have been reported. Monitor levels. (7.2)

USE IN SPECIFIC POPULATIONS

- Hepatic Impairment: Does may need adjustment. Contraindicated in severe hepatic disease (4, 8.7, 12.3)
- Renal Impairment: Does may need adjustment (2.3, 8.6, 12.3)

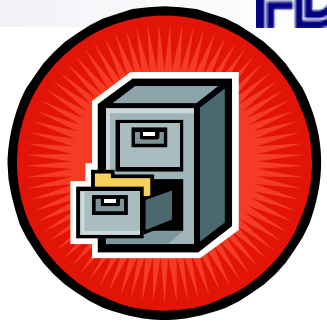
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 5/200X

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

First Milestone - Filing

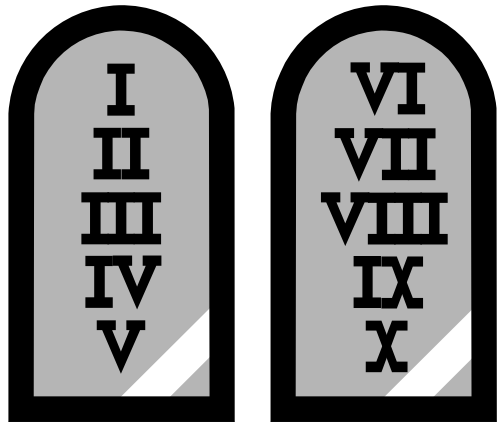


- Internal filing meeting held ~day 45
  - Decision by day 60 including review classification (priority?)
- Quantitative vs. qualitative assessment: Is there sufficient information to be reviewed, in a format that allows review?
  - Yes: filed!
  - No: refuse to file

OR

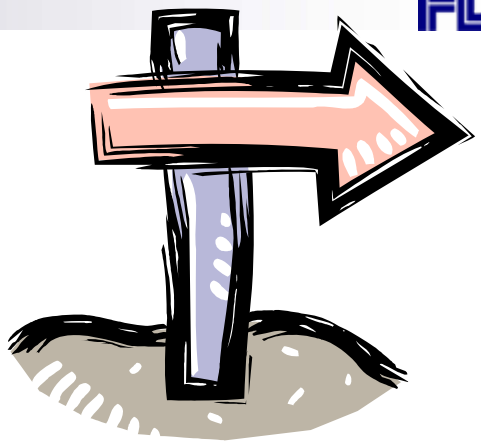
- Are there deficiencies identified during the filing review?
  - "74-day" filing issues letter

Good Review Management Practices and Principles



- Best practices for *both* applicants and FDA review staff
- Quality enhanced by consistency
- Efficiency but not at the expense of quality
- Clarity in communication
- Transparency but not at the expense of efficiency
- Ongoing process improvement initiative to implement or “operationalize” these practices and principles

Road Map to Success! Review Planning



- Review team meetings
- Mid-cycle review
- Advisory Committee?
- Regulatory Briefing?
- Preapproval safety conference
- Labeling negotiation

Review Team Meetings

- Attended by primary review staff and (usually) Team Leaders; management involvement as necessary
- Opportunity to keep entire team informed of issues discovered during review
- Keeps review team “on track” for efficient review management

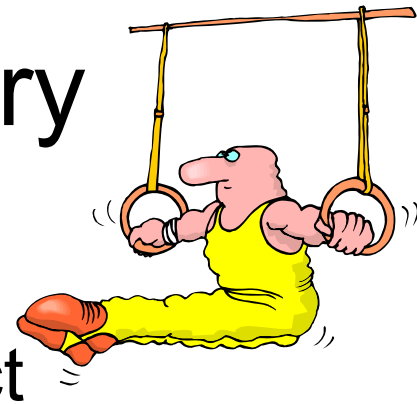
Mid-cycle Review

- Briefing for signatory authority
- Update on the progress of the review to date, including consults
- Includes all review disciplines
- Includes overview of any labeling or risk management issues and planned postmarketing study commitments

Advisory Committee Meetings – Should you worry?

- Opportunity to gain input from experts in the field
- Often held for new molecular entities, particularly for first in class products, first in class Rx to OTC switches, new indications, risk management planning, controversial products, specific safety or efficacy concern
- Applicant can request but Agency must concur
- Recommendations are advisory only and not binding

How to prepare for an Advisory Committee meeting



- Work closely with the Regulatory Project Manager and Advisors and Consultants Staff
- Be aware of requirements and timelines for information disclosure
- Watch one in advance (in person or via commercially available sources) to familiarize yourself with the typical format
- Remember that the press will usually be present
- Open public hearing time is dependent upon the topic

What is a Regulatory Briefing?

- Opportunity to present complex or controversial issues to CDER Senior Management
- *Not* a decisional meeting – advisory only
- Gain insight and broader perspective
- Helps to achieve consistency within Center

Preapproval Safety Conference

- Meeting between Office of Surveillance and Epidemiology and review division for all marketing applications for new chemical entities (or others as appropriate) that are likely to be approved
- Opportunity to educate OSE about the existing safety database, especially aspects which may be important postapproval

Labeling Negotiations

- Labeling recognized as an integral part of the review; no longer simply at the “end of the day”
- Generally internal meetings followed by interactions with the applicant
  - Ranging from an exchange of written versions, to teleconferences, to day-long meetings with appropriate decision-makers

Wrapping it up

- Primary review completed
- Secondary review by Team Leader
  - Concurrence or documented disagreement
  - Discipline review letters as appropriate
- Labeling
- Postmarketing Study Commitments

More about Postmarketing Study Commitments

- Two types of commitments: required and voluntary
  - Required: deferred pediatric studies, confirmatory studies for accelerated approval using a surrogate endpoint, or confirmatory evidence for approvals based on animal efficacy
  - Most are voluntary and agreed to by the applicant to increase knowledge about optimal use of a newly approved product
- Posted on the internet upon approval (excluding CMC commitments)

http://www.fda.gov/cder/pmc/

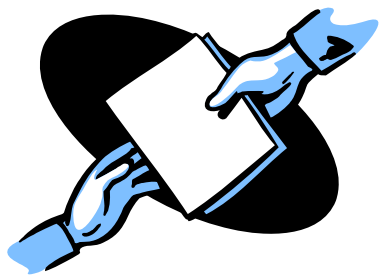
The Action Package

- Compilation of documents to facilitate the final review of NDAs/BLAs and efficacy supplements
- Includes internally generated reviews, pertinent correspondence and labeling
  - For each review cycle
- Includes draft action letter
- Redacted for post-approval release

How does the review end?

Approval

Approvable



Complete Response

BLAs only…for now!

Not Approvable

Marketing Applications – Special Considerations

- Accelerated approval
  - Approval under accelerated approval regulations requires the submission of promotional materials for review
  - Postmarketing/confirmatory studies required for surrogate endpoints

21 CFR 314.500 (Subpart H); 21 CFR 601.40 (Subpart E)
Also covers restricted distribution

Marketing Applications – Special Considerations

- Rolling review
  - Allows submissions of sections of an application for early review (as resources allow)
  - User fee (if applicable) required with first section
  - Review clock starts with last submission

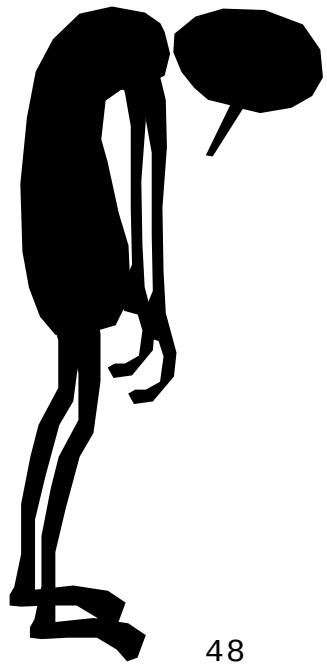
Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review

Marketing Applications – Special Considerations

- Best Pharmaceuticals for Children Act (BPCA)
  - Extends existing patent and/or exclusivity by 6 months for the conduct of requested pediatric studies
  - Studies are requested via a “Written Request”
  - Used in conjunction with PREA
  - Exclusivity determinations are distinct from the review of the data submitted (in an efficacy supplement)

What to do if you are not approved in the first review cycle…

- Request an end-of-review meeting with the signatory authority to ensure clear understanding of deficiencies and information needed to resolve them
- Resubmit!
  - Class 1/Class 2 resubmissions
  - No additional user fee



Reality Check

- Each reviewer has multiple applications at any given time
- ☺ "Do your homework" in advance of calling
- ☺ Discuss an approach with the RPM for communications to balance the "tension" of constant calls vs. information voids

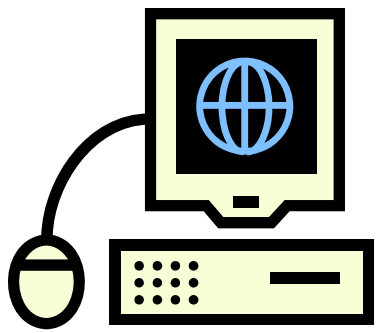
- Start with the Regulatory Project Manager
- Follow the chain of command
- Scientific, regulatory, procedural disputes above the Division follow formal dispute resolution
- Utilize the Ombudsman's office

Helpful Resources (*Why* FDA does what it does…)

- Legislation (FD&C Act, PDUFA, FOIA, FACA, PREA, BPCA, and many more)
- Regulations CFR Title 21
  - 50 Human Subject Protection
  - 54 Financial Disclosure
  - 56 Institutional Review Boards
  - 201 Labeling
  - 312 IND
  - 314 NDA

Helpful Resources (*How* FDA does what it does…)

- Guidances
  - Current Agency thinking to Industry; some directed to review staff
- Manual of Policy and Procedures (MAPPs)
  - Internal processes
- Where to go?
  - www.fda.gov/cder



Contact me at:

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Questions?