FDA Overview – CDER vs. CBER

Tacey E.K. White, PhD Director of Operations & Senior Consultant Aclairo Pharmaceutical Development Group, Inc. April 2017



Aclairo PDG Overview

- Consulting firm specializing in nonclinical drug development services
- 12 years in business as Aclairo
 - Wholly owned subsidiary of Experimental Pathology Laboratories, Inc., Sterling, VA (1 year)
- 14 employees:
 - 7 Senior Consultants, 3 Consultants
 - 9 consultants/senior consultants with PhDs, 1 consultant w/ MS
 - 3 ex-FDA supervisor/pharm-tox reviewers, 5 ex-Pharma, 1.5 ex-CRO
 - 1 Research Assistant, 3 staff
- Focused technical expertise:
 - Toxicology/Pathology PhDs and DVM Pathologist
 - DMPK Clinical pharmacology and nonclinical ADME (2 snr consultants)
- Deep expertise:
 - Small molecules, biologics, devices, gene therapy
 - Most therapeutic areas
 - Early development through NDA and beyond

ACLAIRO ® pharmaceutical development group, inc.

Aclairo Services - Scientific Advisors Group

- Strategic advice by Senior Consultants
- Attend FDA meetings represent technical areas of DMPK and pharm/tox
- Regulatory writing by technical experts; 100% QC'ed
 - IND, NDA, BLA, eCTD format, briefing documents (FDA submissions)
 - Position papers; scientific issue resolution and risk mitigation
- Virtual project team members
- Full range of toxicology support including specialty areas genetox, carcinogenicity, reprotox, juvenile, safety pharmacology, abuse liability
- Program management for nonclinical toxicology and DMPK studies plan, execute, monitor
- PK/PD modeling, simulation, translational PK (dose selection, special populations); GLP TK analysis
- Due diligence, gap analysis
- <u>www.Aclairo.com</u>; email: <u>twhite@aclairo.com</u>; <u>info@aclairo.com</u>;



Tacey E.K. White, PhD

- Toxicology consultant specializing in drug development for small and large molecules – 4+ years
- Pharmaceutical Experience 12 years
 - Toxicology project team representative small molecules, gene therapy
 - Developmental and reproductive toxicology (DART) and juvenile specialist (study director, strategic advisor to project teams – small and large molecules)
 - Head of investigative teratology laboratory
- Covance Laboratories Global Director DART 2 years
 - Scientific strategy and technical offerings; consultant to sponsors
- Drug development experience in wide range of therapeutic areas
 - Metabolism, endocrinology, neurology, psychiatry, GI, anti-infectives, oncology, ocular
 - Liaison with discovery teams, regulatory and clinical
- Pregnancy labeling specialist

US Teratology Society – Standing Past President



Outline

- What is FDA's purpose?
- FDA Organization Overview
 - CDER, CBER, CDRH, Office of combo products
- Types of Interactions
 - Meeting Types
 - Other Opportunities for Advice



Selected FDA Laws and Regulations

Selected Regulations:

- 1938: Federal Food, Drug and Cosmetic Act (FD&C Act)
- 1944: Public Health Service Act (PHS) Biologics
- 1992: Prescription Drug User Fee Act (PDUFA I)
- 1997: FDA Modernization Act (FDAMA) & PDUFA II
- 2003: Pediatric Research Equity Act (PREA)
- 2012: FDA Safety and Innovation Act (FDASIA) & PDUFA V

Important Sections for Drugs:

- FD&C Act, Chapter V:
 - Section 501 Adulterated drugs
 - Section 502 Misbranded drugs
 - Section 505 New Drugs
- PHS Act Section 42 USC 262 Regulation of Biological Products



FDA Mandate

FD&C and PHS Acts: Two Key Principles

- No drug or biologic can be legally distributed in the US until its safety and effectiveness have been established and the product has been approved by the FDA
- FDA can take enforcement action against products that violate the law i.e., if it is "adulterated" or "misbranded"
 - Adulterated = impure or contaminated
 - Misbranded = mislabeled, i.e., efficacy was not demonstrated for the marketed indication



Laws, Regulations and Guidances



From Drug Information Association (DIA) IND Training, October 2013

pharmaceutical development group, inc.

Drug Development Phases



IND = Investigational New Drug application – permission to dose people
NDA = New Drug Application – permission to market drug
BLA = Biologics Application – permission to market a biologic



Types of INDs - FDA



FDA Organization

FOOD AND DRUG ADMINISTRATION



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What Products Does Each Division Regulate?

CDER – Center for Drugs

- Small molecules (organic chemicals)
- Monoclonal antibodies (mAbs)
- Peptides and proteins
- Oligonucleotide therapies

CBER – Center for Biologics

- Blood products (biologic)
- Vaccines
- Gene therapy
- Cell therapy
- Tissues



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Be Careful!! – Biologic therapies are regulated under both CDER and CBER



What Are Other Differences between These Divisions?

CDER	CBER
 Reviewing divisions based on therapeutic categories 	 Reviewing divisions based on type of molecule
 Standard review process applied to all drugs Generally rely on ICH guidelines, when available Work with sponsors starting at IND stage 	 More case-by-case reviews Use more FDA-specific, EMA or WHO guidelines Work with sponsors prior to IND – often grant pre-/pre-IND meetings



How Does FDA Regulate Devices? - CDRH

- Device = "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is ... intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals... which does not achieve any of its primary intended purposes through chemical action within or on the body"
- No ICH guidelines exist for devices; regulated differently in every country
- FDA relies on ISO Standards to evaluate safety of devices
 - ISO = International Standards Organization
 - Standards must be purchased from ISO
- ISO 10993 Defines "Biocompatibility" (safety/toxicity) Testing for devices
 - Extent of testing is determined by degree of contact with body



Why do we care about devices?

- Some products are considered **drug-device combinations**
- Combination products must be tested based on requirements for both drugs and devices
- Sponsors must be aware of this and plan ahead to avoid marketing delays

Examples of drug-device combination products:

- Drug-eluting cardiac stents
- Pre-filled syringes (i.e., drugs sold within their delivery device)
- Drug-filled inhaler
- Hormonal birth control that is delivered using:
 - A patch, a vaginal sponge, an IUD (intrauterine device), etc.



Drug-Device Review Process



- 1. New drug-device in development is reviewed by Off. Combination Products
- 2. OCP decides if it is substantially a device (CDRH) or a drug (CDER or CBER) and OCP assigns product to appropriate division
- 3. Non-assigned division also reviews
 - BUT review might only take place at the NDA stage!!!



CDER – Center for Drug Development and Research



(DKKNVH)

(DKKNUD)





CDER Toxicology Organizational Chart

Karen Davis-Bruno, Associate Director for Pharm/Toxicology, OND

Toxicology Staff -Office Directors and Divisional Supervisors

ODE I	ODE II	ODE III	Office of Anti-Microbials	Office of Oncology
Paul Brown	Tim McGovern	Abby Jacobs	Abby Jacobs	John Leighton
Cardiology & Renal Al DeFelice Tom Papoian	Pulmonary , Allergy & Rheumatology Tim Robison	Gastrointestinal & Inborn Errors Sushanta Chakder	Anti-Infectives Terry Miller	Oncology Drugs Whitney Helms Todd Palmby
Neurology Lois Freed	Metabolic & Endocrine Todd Bourcier Ronald Wange	Reproductive & Urology Mukesh Summan	Anti-virals Hanan Ghantous	Radiology & Imaging Bayo Laniyanou
Psychiatry Aisar Atrakchi Ikram Elayan	Anesthetics & Analgesics Daniel Mellon	Dermatology & Dental Barbara Hill	Transplantation / Ophthalmology Lori Kotch	Hematology Haleh Saber

CBER Office of New Drugs Organizational Chart



Previously – Off. of Cell, Tissue and Gene Therapy



Interacting with the FDA



Interacting with the FDA

- July 9, 2012 signing of "Food and Drug Administration Safety and Innovation 60 Act (FDASIA) of 2012"
 - includes "Prescription Drug User Fee Amendments of 2012" (PDUFA V).
- FDA Goals under PDUFA V (CDER and CBER) for 2013-2017
 - Strengthen interactions between FDA and Sponsors
 - CDER Established:
 - Dedicated drug development communication and training staff
 - Enhanced Communications Team (ECT) liaison staff
 - CBER:
 - Enhanced their Manufacturer's Assistance Staff
 - Established Ombudsman = secondary point of contact if sponsors have communications challenges with FDA
 - Published joint guidance: "Best Practices for Communication Between IND Sponsors and FDA During Drug Development, Draft Dec 2015"



FDA Communication Philosophy

"IND sponsors and FDA work collaboratively during the drug development process"

- <u>Sponsor Responsibilities</u>:
 - Manage overall development
 - Determine nature and timing of submissions
 - Solicit input and guidance from FDA
 - Provide well-organized and complete submissions



FDA Communication Philosophy, cont

• <u>FDA Responsibilities</u>:

- Ensure safety and rights of clinical subjects
- Ensure quality studies demonstrating safety and efficacy
- Enforce Good Clinical Practice (GCPs) regulations and Human Subject Protections (HSP)
- Advance regulatory science
- Provide advice and feedback to sponsors on specific <u>clinical</u> <u>trials</u> and <u>overall development plans</u>
 - IND, NDA / BLA Submissions
 - Formal Meetings
 - Informal Advice



Examples of FDA Advice

- **Regulatory** e.g., Adequacy of technical data to support an investigational (drug development) plan; waiving of certain studies;
 - Whether proposed investigations are likely to meet requirements for NDA/BLA
- **Clinical/Statistical** e.g., Design of clinical trials: trial size, outcomes and endpoints, alternative designs
- **Safety** e.g., issues related to nonclinical studies; size of safety database; risk mitigation strategies
- Clinical pharmacology and PK e.g., dose selection; specific populations
- Nonclinical pharmacology, PK, toxicology e.g., specialized studies such as genetic tox, developmental and reprotox, carc, mode of action
- **Product quality** e.g., CMC, shelf life, stability, delivery systems, characterization of drug substance/product
- **Pediatrics** proposed pediatric development plan, dosing
 - All drugs must be tested in pediatric clinical trials unless a waiver is granted



FDA Advice, continued

- <u>Important</u> FDA wants sponsors to use all available guidances and talk to experts/consultants first
 - Do not ask basic questions that are clearly explained in guidance documents
- FDA determines the extent of review and feedback
- Expedited Programs (fast track, breakthrough) sponsors receive more extensive guidance



Types of FDA Interactions

- Submission Reviews
 - IND Investigational New Drug Application
 - Permission to test drug in people in clinical trials
 - NDA New Drug Application
 - Permission to market/sell a drug therapy
 - BLA Biologics Application
 - Permission to market/sell a biologic therapy
- Formal FDA Meetings
 - Type A, B, C meetings
 - See: Guidance for Industry: Formal Meetings Between the FDA and Sponsor or Applicants of PDUFA Products
- Special Protocol Reviews
 - Carcinogenicity studies, juvenile toxicity studies, clinical studies



CDER and CBER Culture

- Each CDER and CBER review division functions independently
- Divisions handle meeting requests differently
 - Some divisions grant most meeting requests e.g. Cardio-Renal, Reproductive and Urology, Gastrointestinal, Anti-virals, CBER divisions
 - Some divisions routinely deny meeting requests (e.g., pre-IND) but provide responses in writing – e.g. Neurology, Metabolism and Endocrinology
 - End-of-Phase 2 and pre-NDA meetings are milestone meetings that are granted by all review divisions



CDER and CBER Culture

- Divisions handle communications with sponsors differently
 - Some divisions respond to informal inquiries or review protocols on request - e.g., Biologics oncology, Anti-virals, CBER divisions
 - Some divisions require all communications via the project management staff or formal submission – e.g., Neurology, Anesthetics and Analgesics
- Divisions vary in their regulatory flexibility and responses to requests for waivers and deviations from ICH and FDA guidances
 - Some divisions stringently enforce all ICH guidance documents and rarely grant exceptions or waivers – e.g., Pulmonary/Rheumatology and Neurology
 - Some divisions are more flexible and will consider scientific justifications for nonclinical study waivers or novel study designs – e.g., Oncology, Cardio-Renal, CBER divisions



Investigational New Drug Application (IND) Decisions

- First–Time-In–Human studies with new product **OR** first clinical study in the US with a new drug **OR** for a new clinical indication
- Non-clinical study requirements described in ICH M3(R2) for small molecules OR ICH S6 for biologics OR CBER-specific
- IND is assigned to the review division based on the clinical indication (CDER) or type of therapy (CBER) and reviewed on a 30 day clock
- IND includes nonclinical data to support FTIH **AND** Clinical protocol
- Divisional review team includes:
 - Chemist and supervisor Quality review Drug substance
 - Pharmacologist and supervisor Pharmacology, DMPK, Toxicology
 - Medical reviewer and supervisor Clinical
 - Division director, deputy director, and project manager



IND Decisions

- Chemistry and pharmacology reviewers evaluate non-clinical data submitted to IND. Medical reviewer evaluates adequacy of clinical protocol and planned safety evaluations.
- Reviewers discuss data and recommendations with supervisors.
- Review team meets prior to 30-day IND safety date to discuss any safety concerns or clinical hold issues.
- If no safety concerns or modification to protocol, clinical study may proceed without feedback from FDA – but should confirm
- If reviewers have questions, project manager will contact sponsor to request additional information. Sponsor should provide requested info ASAP to prevent a clinical hold.
- If FDA has safety concerns, tcon is scheduled with sponsor to discuss modifications to dose selections, study design, safety monitoring or implementation of a clinical hold.



Formal Meetings

- FDA Procedural Guidance: *"Formal Meetings Between the FDA and Sponsors or Applicants, May 2009"*
- Types of Meetings:
 - Type A for stalled development (clinical holds) or dispute resolution
 - Type B PDUFA-authorized meetings such as pre-IND, End-of-Phase 2 (EOP2), or pre-NDA meetings
 - Type C any meeting other than Type A or B
 - Executive or Full Carcinogenicity Assessment Committee (CAC)
 - Advisory Committee meetings



Meeting Procedures

- Goals for FDA response to meeting requests
 - 14 days for Type A meeting and 21 days for Type B or C meeting
- Goals for meeting scheduling
 - Type A within 30 days
 - Type B within 60 days
 - Type C within 75 days
 - ECAC (for special protocol assessments/SPA) within 45 days
- Deadlines for submitting meeting background packages
 - Type A two weeks prior to meeting date
 - Type B or C one month prior to meeting date



Meeting Procedures

- **Meeting requests** must be made in writing, addressed to the division director, and **should include the questions for discussion**
 - Also include Briefing Book proposed agenda, brief history, current status questions and support info & company position
 - Pre-IND: send request to the supervisory project manager in review division
 - Open INDs: send request as an amendment to the IND
- Questions should be carefully crafted and address product specific issues since the nature of questions can determine whether a meeting is granted or denied, especially for Pre-IND and Pre-NDA meetings
 - Avoid open-ended questions!
- FDA grants only one of each type of milestone meeting pre-IND, EOP 2, and pre-NDA for each application **Plan carefully!**
- Written advice can be sought via questions submitted to the IND; however, there are no formal response timelines as with meetings.



Meeting Procedures

- CDER review divisions have internal pre-meeting within one week prior to the formal meeting to formulate responses to questions
- Preliminary responses to questions are drafted and sent to the sponsor 24-48 hours prior to the scheduled meeting; Sponsors can respond by email to address any concerns ahead of the meeting
- Sponsor can cancel meeting if preliminary responses are adequate, or request a teleconference in lieu of the formal meeting if limited discussion is needed.
- Agenda of the meeting can be revised to focus on discussion of the unresolved issues.
 - Face-to-face meetings are likely to result in more comprehensive discussions
- CDER goal to generate meeting minutes within 30 days of meeting
- FDA provides the official meeting minutes bulleted summaries of questions and responses



Type B Meeting – Pre-IND Dos and Don'ts

Type B Meeting = PDUFA-authorized meetings such as pre-IND, End-of-Phase 2 (EOP2), or pre-NDA meetings

Please Note:

- A pre-IND meeting is not required
- If there are no issues, submit your IND without asking for a meeting
- Questions that don't need responses prior to the IND can be posed in the IND submission

Do Schedule a Meeting when you need to discuss the following:

- Safety issues identified in the IND enabling toxicity studies
- Need for additional studies
- Proposals for a unique or abbreviated toxicology program e.g.,
 - Alternative regulatory path
 - Toxicology program to support a biosimilar
 - Plans for toxicology studies to bridge to previous applications or literature (505(b)2)



Type B Meeting – Pre-IND Dos and Don'ts

Do Not Schedule a Pre-IND Meeting when:

- You have general questions e.g., whether a standard ICH M3(R2)enabling program is adequate to open the IND
- You want "Face Time" with FDA prior to generation of toxicity data
- When there are no significant issues for discussion or when the IND will be submitted shortly thereafter (2-4 weeks)



Type B - End of Phase 2 (EOP2) Meetings

- EOP2 Meeting = Most important milestone meeting and is granted by all divisions
- Provide a comprehensive summary of the preclinical and clinical data from the completed studies Get buy-in for your Phase 3 trials are they adequate for NDA
- Tabular summaries of the data are most useful (doses studied, target organs, NOAELs, safety margins, toxicokinetics)
- Identify potential deficiencies or safety issues in the toxicology program for discussion (e.g., toxicological characterization of impurities, excipient, or metabolites)
 - Don't risk FDA finding problems during the NDA review
- If possible, submit reports from completed toxicology studies for review one month prior to the EOP2 meeting.
- Many divisions review all outstanding data to permit identification and discussion of safety issues and to ensure appropriate monitoring during the Phase 3 clinical trials



Type A meeting – Stalled Development / Clinical Hold

If put on Clinical Hold:

- First a clinical hold complete response should be submitted and reviewed by FDA
- If the FDA does not accept the response, and the sponsor and FDA agree that development is stalled, a meeting can be held to discuss a potential path forward.
- Meeting permits further discussion and clarification of FDA's concerns and recommendations for data to address those concerns.
- This meeting is unlikely to result in the removal of the clinical hold. It will help to determine additional sponsor activities.



Type A Meeting – Dispute Resolution

- Used in the case where FDA review staff and sponsor don't agree on an FDA request (other than clinical hold)
- Procedures outlined in the guidance entitled "Formal Dispute Resolution: Appeals Above the Division Level"
- Sponsor can seek review and input from CDER senior staff above the division level – Medical or Pharmacology /Toxicology, OND management, medical policy
- Provides sponsor a forum to present their data and views unfiltered by FDA review staff



Special Protocol Assessments / Carcinogenicity Studies

- Special Protocol Assessment (SPA) Guidance, May 2002
 - Consider for: animal carcinogenicity and juvenile studies, phase 3 clinical studies
- The FDA expects that protocols for all animal carcinogenicity studies be submitted before start of study
- Send a letter notifying the division intention to submit SPA at least 30 days prior to the SPA (Phase 3 and carcinogenicity protocols)
- Each SPA should be sent as a separate amendment to the IND (i.e., mouse and rat protocols sent as two separate submissions).
- Divisions vary in timeliness of review of Phase 3 Special Protocol Assessments



Special Protocol Assessments Carcinogenicity

- Executive Carcinogenicity Assessment Committee (ECAC) meets and reviews SPAs and final carcinogenicity study reports on a weekly basis.
- ECAC meetings held and feedback on adequacy of dose selections and protocol designs provided within 45 days.

Potential Questions to Ask ECAC -

- Does ECAC agree with dose selection and protocol design?
- Does ECAC consider the major metabolites will be adequately qualified in the planned carcinogenicity studies?
- Will novel excipient(s) be adequately qualified in the planned carcinogenicity studies?
 - Divisions can differ on recommendations for carcinogenicity assessments of excipients and/or metabolites.



Other Meetings

- Pre NDA primarily format, content, and labeling questions for which written responses suffice. CDER discourages requests for submission of additional data during the NDA review cycle. Questions regarding Phase 4 toxicology study waivers often posed in pre-NDA meeting to ensure timely response.
- Advisory Committee Meetings -scheduled by CDER review division to discuss NDA approvability or safety issues.
- Labeling meetings generally conducted via teleconference during the last month of the review cycle, if drug is going to be approved.



Informal Negotiations

- Position papers /White papers clear, concise, data rich arguments have the highest probability of success.
- Expert reports usefulness in US vs. EU
- Use of regulatory precedents- most effective when precedents are from the same division, mechanistic class, or for similar toxicity issue since inter-divisional regulatory differences are common.
- Develop the strongest possible data-based scientific justification prior to initiating the negotiation. Multiple submissions of the same argument lessens the likelihood of success.
- FDA <u>always</u> agrees to review scientific justifications or waivers. This in no way implies likely acceptance.



Thank you for your attention.

• Questions ?

