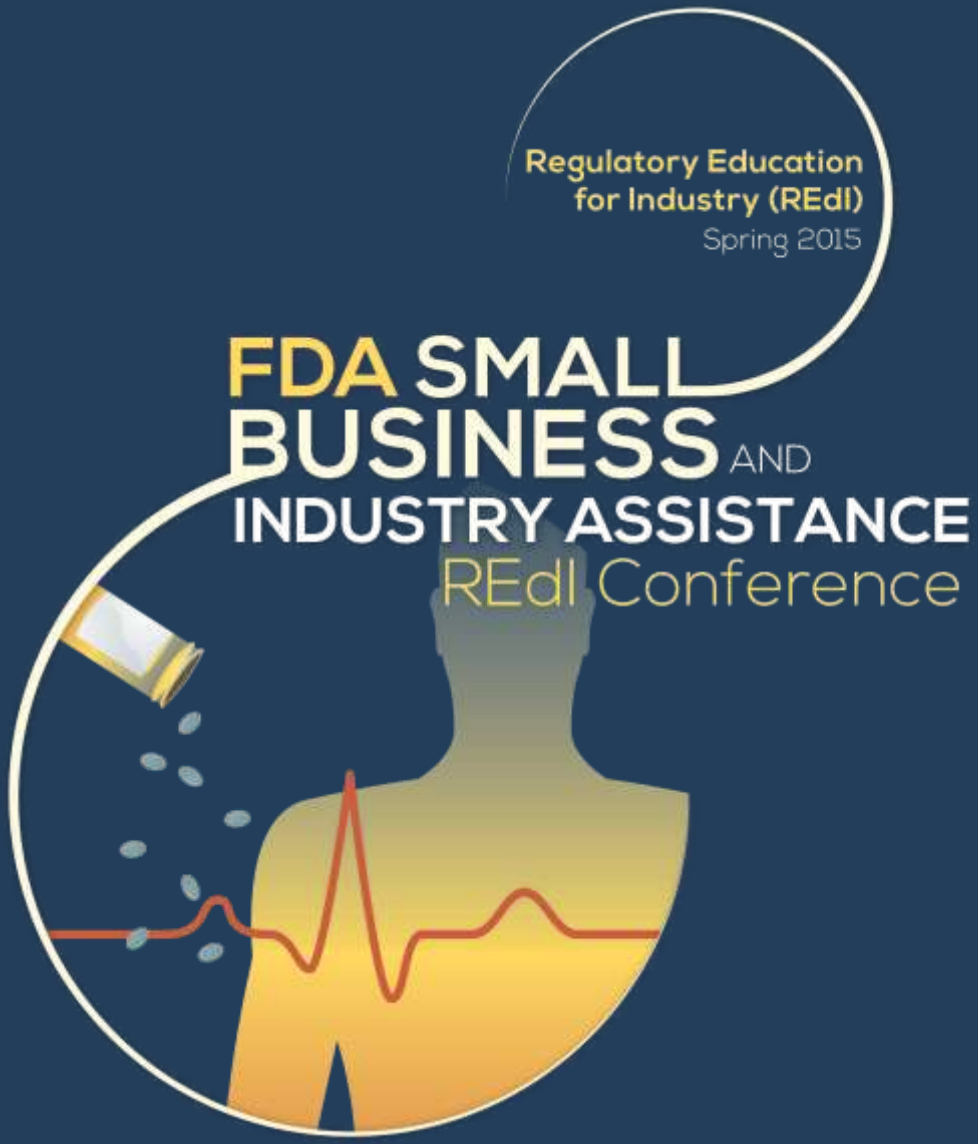


Evidence of Clinical Effectiveness and Data Requirements For an NDA

Eileen Navarro, MD, FACP

Disclaimer

Opinions expressed do not reflect official FDA policy

Outline

- Evidence of Clinical Effectiveness
  - Adequate and well controlled trials
  - Endpoints of direct clinical benefit
  - Evidentiary requirements in incentive programs
- Submission Requirements
  - Content
  - Format

Statutory Requirement (Sec 505 FFDCA)

(a) Need an approved application to market

(b)(1) Full reports of investigations = safe and effective
Details components, composition, methods & controls

(c) FDA must give positive approval (change - 1962 KHAA)

The Food, Drug and Cosmetic Act of 1938

Required premarket notification.

Required a demonstration of safety for approval.

Basis of refusal:

(a) did not include ALL tests reasonably applicable to show whether drug is safe when used under proposed labeling

(b) testing shows drug unsafe or do not show that it is safe

(c) information submitted or any other information available are insufficient to determine whether safe

(d) labeling is false or misleading in any particular

Keyfauver Harris Amendments 1962

1. FDA had to actively grant approval before a drug could be marketed

2. Requirement to study drugs under an IND; informed consent

3. The effectiveness requirement:

   Substantial evidence that the drug will have the effect it purports or is represented to have under proposed labeled conditions of use.

Drug Regulation History

- 1970s drug lag
- 1980s access to investigational drugs
- PDUFA 1992 review timelines S/P 10/6 m
- FDAMA 1997 fast track (drugs for serious disease that fill an unmet need)
- BT PRA 2002 electronic applications and submissions
- FDAAA 2007 authorities for safety assessment
- FDASIA 2012 broad ranging changes:
  -UFA expansion, innovative incentives, patient perspectives on benefit risk, supply chain, shortages, standards mandates, subgroup outcomes

Benefit - Risk

LABELING 21CFR 201.56-57

Adequate directions for use and not false or misleading

- dose-response
- outcomes by relevant subgroup (age, gender, race)

21 CFR 314.50 mandates

FDASIA Section 907 trial participation, safety & efficacy outcome by age, gender, race

Regulations that affect an NDA Submission

21CFR 314.50: Content & Format of an Application

21CFR 314.126: Adequate & Well-Controlled Studies

21CFR 314.500: Accelerated approval (use of surrogate endpoints and approval with restrictions)

Clinical Effectiveness

"Substantial evidence consists of adequate and well-controlled investigations including clinical investigations…on the basis of which it could be concluded that the drug will have the effect it is represented to have under the conditions of use proposed in labeling."

FDAMA 1997 – allow 1 study in certain circumstances

Effectiveness – "clinically meaningful" added in court

Evidence

"Well controlled studies of adequate design must show effectiveness, ordinarily a STATISTICALLY significant effect on a CLINICALLY meaningful endpoint, usually replicated, as a basis for approval. "

Robert Temple

Adequate & Well-Controlled Studies

Is it the drug or spontaneous change or influence of bias?

CONTROL & TEST groups identical save for exposure to test agent

How are test & control selected, treated, observed or analyzed

pre-study, during post study ?

DESIGN CONDUCT ANALYSIS

Characteristics of an AWC Trial 21 CFR312 (b)Cliff notes version

- PRE - define a win, and by how much
- Design - powered to show difference or no difference
- Who is included/excluded in the trial? In the analysis?
- How to protect vs bias? Randomization, blinding
- What is measured? How reliably is it measured?
- PROTOCOL and STUDY REPORT – enable validation of study findings

ENDPOINTS

Distinct and measurable characteristics of treatment outcome

21 CFR 314.126(b)(6)

"The methods of assessment … are well-defined and reliable."

Well defined

"effect on how a patient survives, feels or functions.

others …. are surrogate measures of benefit"

p33 http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf

Endpoints

- Composite Endpoints – multiple ways to win?
  - When outcomes are discordant
  - Which component drives a win
  - Which component is sensitive to drug effect
- Measuring Endpoints
  - Patient Reported Outcomes, Biomarkers
- Methods of Collection
  - Standards enhance replication, balance with flexibility

2 Studies, each convincing on its own, except..

"excellent multicenter study with statistically strong finding," OR

"where .. an important clinical benefit, (e.g. superiority in mortality), ma(d)e a confirmatory study difficult to conduct on ethical grounds".

SO, A VERY HIGH BAR to conduct a SINGLE AWC study.

Regulatory Flexibility : Clinical Effectiveness Guidance

1 **AWCS + independent substantiation confirming efficacy**

- different doses, regimens, dosage forms, endpoints
- another disease phase or population
- similar purpose, pharmacologic/pathophysiologic correlation

Regulatory Flexibility : Clinical Effectiveness Guidance

1 AWCS (no confirmatory data needed)

- multicenter study, consist across sites & patient subsets
- factorial studies
- multiple endpoints, different events
- statistically persuasive finding

FDA fast-tracks drug to treat Duchenne muscular dystrophy

August 31, 2015 12:00 AM

Related Media:
New drug gives hope for pa
with Duchenne

New drug works differently from statins to lower "bad" LDL

The FDA has approved Repatha for people with hereditary forms of high cholesterol or a high risk of cardiovascular disease whose LDL cholesterol can't be controlled with current medications.

"Repatha provides another treatment option in this new class of drugs for patients with familial hypercholesterolemia or with known cardiovascular disease who have not been able to lower their LDL cholesterol enough with statins," says John Jenkins, M.D., director of the FDA's Office of New Drugs, Center for Drug Evaluation and Research. "Cardiovascular disease is a serious threat to the health of Americans, and the FDA is committed to facilitating the development and approval of effective and safe drugs to address this important public health problem."

2013 Guidance: Expedited Programs for Serious Conditions

What is a Serious Condition? 57 FR 58942, 1992

For which products are these incentives available?

https://www.federalregister.gov/articles/2013/06/26/2013-15250/draft-guidance-for-industry-on-expedited-programs-for-serious-conditions-drugs-and-biologics
*superceded Guidance for Industry: Fast Track Drug Development Program –Designation, Developnment and Review

Guidance: Expedited Programs for Serious Conditions

What is Unmet need?

What is Existing or Available therapy ?

Is Unapproved or unregulated Rx “available therapy” *?*

https://www.federalregister.gov/articles/2013/06/26/2013-15250/draft-guidance-for-industry-on-expedited-programs-for-serious-conditions-drugs-and-biologics
*superceded Guidance for Industry: Fast Track Drug Development Program –Designation, Development and Review

Guidance: Expedited Programs for Serious Conditions

Even when not shown to have an efficacy or safety advantage –

"a novel mechanism of action with a well-understood relationship to the disease pathophysiology.

a reasonable basis for concluding that a significant number of patients may respond differently"

For example, mechanistic diversity, …..could be advantageous in disease settings in which drugs become less effective or ineffective over time."

"preferable to have more than one treatment approved under accelerated approval regulations because benefit may not be verified in confirmatory trials for already approved products."

https://www.federalregister.gov/articles/2013/06/26/2013-15250/draft-guidance-for-industry-on-expedited-programs-for-serious-conditions-drugs-and-biologics

*superceded Guidance for Industry: Fast Track Drug Development Program –Designation, Developnment and Review

Harmonized Critical Guidance

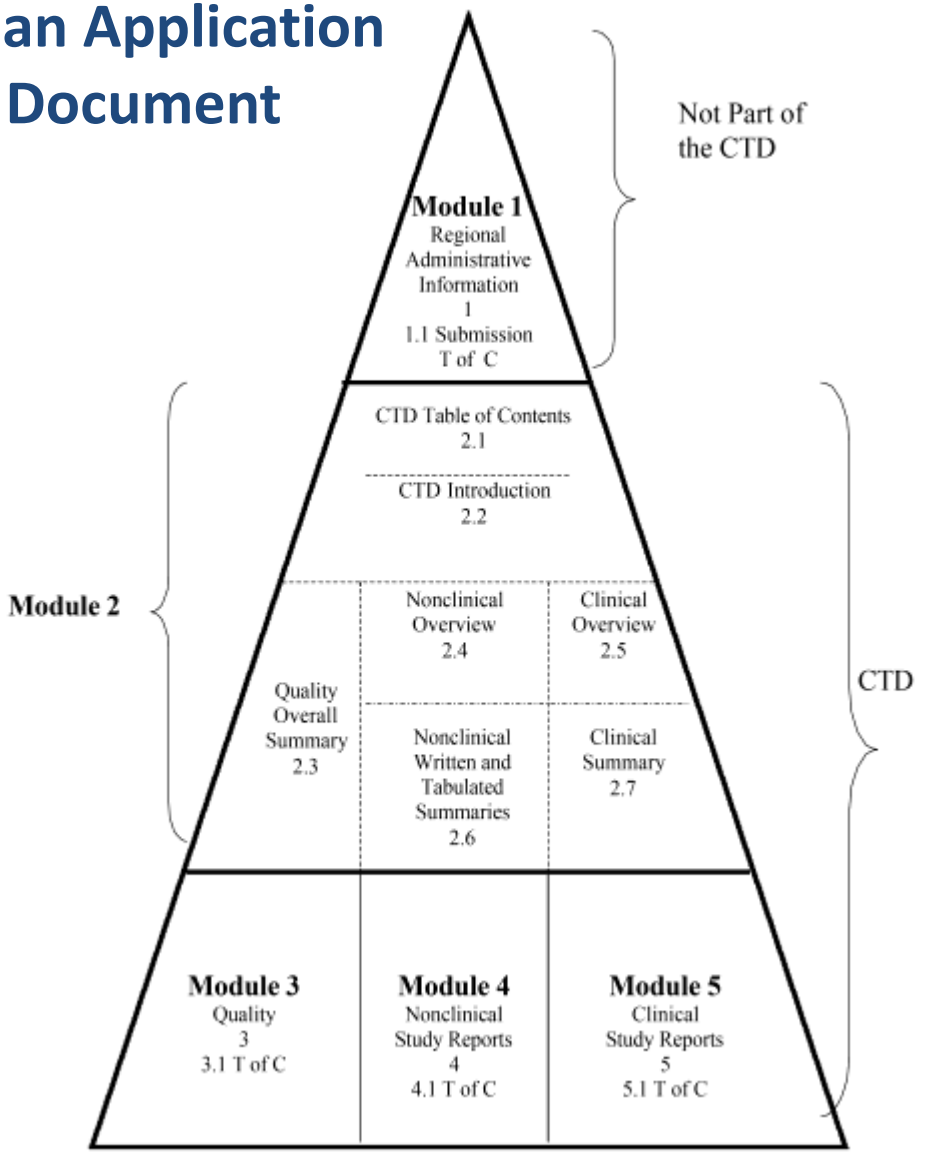
ICH E3	Structure and Content of Clinical Study Reports
ICH E4	Dose-Response Information
ICH E5	Ethnic Factors
ICH E6	Good Clinical Practise
ICH E9	Statistical Principles
ICH E10	Choice of Control Group
ICH M4	electronic Common Technical Document
ICH M4	Efficacy / Safety

http://www.fda.gov/RegulatoryInformation/Guidances/default.htm

Content and Format of an Application
ICH Common Technical Document

Modules

- M1: Administrative
- M2: Summaries
- M3: Product Quality
- M4: Non-clinical
- M5: Clinical



Content and Format of an Application (21 CFR 314.50), ICH Common Technical Document

Module 5
Clinical
Study Reports
5
5.1 T of C

(1) human pharmacokinetics
(2) microbiology
(3) clinical data
(4) statistical section
(7) pediatric use
(8) CRF and CRT

Clinical Section 21 CFR 314.50

Design
Conduct
Analysis

1. Description & analysis of every study. Reports of everything .. pertinent to safety and effectiveness from any source

2. Summary of ..effectiveness, support (for) dosage and administration, modifications for subgroups (e.g age, renal function)

3. Safety summary, 4 month update of all available information (animal data, adverse effects, drug-drug interactions)

Clinical Section (continued)

4. Case report forms for deaths and discontinuations
   Others on request. Pre 1985, all CRFs required.

5. Case report tabulations. (replaced "all CRFs")
   - All data from well-controlled studies
   - All data from earliest clinical pharm studies
   - Safety data from other studies

Module M5

M5: Clinical Study Reports

- Integrated Summary of Safety (ISS)
- Integrated Summary of Efficacy (ISE)

- Datasets (5.3.5.1.25)
  - Electronic datasets (5.3.5.1.25.3)
  - Define files (5.3.5.1.25.3.3)

Clinical Filing Checklist for Day 45 meeting:

- Are datasets available for all pivotal trials?
- Are they reliable, transparent and traceable to the CRF?
- Do the datasets reflect the Sponsor's report of dosage, treatment arms, adequate exposure of doses and duration?
- Are the datasets in a format to allow review of patient data? Are endpoints, adverse events evaluable?
- Is the raw data available to derive the composite endpoints? Do the data allow replication of findings?
- Request data needed that is not submitted
- Pick the trial sites for audit

Clinical Filing Checklist- selected sections:

	Content Parameter
FORMAT/ORGANIZATION/LEGIBILITY	
1.	Identify the general format that has been used for this application, e.g. electronic CTD.
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?
5.	Are all documents submitted in English or are English translations provided when necessary?
6.	Is the clinical section legible so that substantive review can begin?
LABELING	
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?

PDUFA V Included the Requirement to Submit Standardized Electronic Data

- **2002 PDUFA III**
- **2012 PDUFA V**
- **2014 progress in implementation**
  - Final 745A(a) Guidance

  Guidance for Industry - Providing Regulatory Submissions in Electronic Format - Standardized Study Data ("eStudy Data Guidance")
  - Data Standards Catalog
  - Technical Conformance Guide
  - Study Data Reviewer's Guide (SDRG)

When will Study Data Standards will be Required?

24 months post estudy guidance issuance, December 2016

What Study Data Standards will be Required?

http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

How will Study Data Standards be Required?

ttp://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

Study Data Standardization Plan

IND:

List of the planned studies,
Study phase,
Study design
Planned data standards, formats, terminologies OR
justification of studies that may not conform

NDA:

cover letter should describe if Standardization Plan was executed

Resources

Data Standards Catalog

Study Data Technical Conformance Guide

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.
- http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

FDA Webpage

eDataTeam

eData@fda.hhs.gov

CDER OCS

CDER OSP

Data Standards Program

CDER OBI

eData Team

eSub Team

eSubs@fda.hhs.gov

Conclusions

- Adequate and well controlled studies are the basis for a successful NDA; planning starts in IND
- Adequate evidence: rooted in science, codified in regulation, validated in review, described in label
- GCP is reflected in quality submissions; standards facilitate labeling of efficacy and safety
- The electronic submissions and data standards are required by law

Crystal Ball

- Greater harmonization of regulatory requirements
- Key requirements for Phase III and Market authorization -Understand differences and similarities to EU drug approval process -Available advise and support by FDA for small enterprises
- Will Drug Products be discussed along with Drug Substances where applicable? Aids, cancer, diabetes, viral autoimmune
- DMF document via ectd

Thanks!

Slides from colleagues and OND/CDER training

Questions?

Please complete the session survey:

surveymonkey.com/r/DRG-D2S7