University Hospitals
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Maintaining your IND with the FDA: Keys for Success

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Agenda

- How an investigator should prepare and submit and annual report/renewal to the FDA
- Required elements to be included in the annual report/renewal to the FDA
- How to submit to the FDA a IND safety report
- How to properly respond to an FDA protocol inquiry
- Understanding the FDA Guidance documents and how to successfully navigate

Purpose of an IND

“ By assuring that a clinical investigation is performed in accordance with Good clinical practices, an IND helps to affirm a body of knowledge of a drug to support its use in human testing by focusing on the safety of human subjects and the efficacy of the test product.”

Section 520 (g) of the Food, Drug, and Cosmetic Act

Upon Approval of an IND…..
Never Forget

The approval of an IND application is just the **BEGINNING**

An investigator must never forget that an IND application is a "living" project that must be constantly monitored, updated, and nurtured from approval to closure to maintain compliance

Maintaining an IND
Requirements for Every Sponsor Investigator

To maintain an IND, the Sponsor Investigator has 3 primary reporting responsibilities

- Protocol Amendments
- Safety Reports
- Annual Reports

REMEMBER: Each type of report is time sensitive and has a specific structure

Maintaining an IND
Requirements for Every Sponsor Investigator

- IND Protocol Amendments
  - Intended to inform the FDA of the following:
    - New Study protocol
    - Change in an existing protocol
    - New Investigator
- IND Annual Report
  - Submitted once a year
  - Due within 60 days of the date IND went into effect
- IND Safety Reports
  - Submitted when an update or unforeseen circumstance occurs
  - Consists of Med watch form and Cover letter
  - Due within 15 calendar days of initial SAE report

Foundation of 21 CFR 312 Reporting Requirements

Annual Progress Reports

The Submission of an IND Progress Report (Annual Report) to the FDA

At regular intervals and at least yearly, the IND sponsor must provide a progress report to the FDA and all reviewing IRB's.

If the FDA requires a progress report more frequent than on an annual basis, the IND approval letter will indicate the review cycle.

The Submission of an IND Progress Report (Annual Report) to the FDA

- An investigator must always remember that the progress report date is based on the approval date, which will be stamped on the top of the IND approval letter (as follows):

INE Number: X160041

Indications for Use:

Dated: January 1, 2012

Received: January 10, 2012

Reimbursement Category:

Annual Report Due: One Year From the **Stamped Date** of this Letter

Format for IND Progress Report

- Individual Study Information

1. Study Title
    1. Protocol number
    2. Protocol purpose
    3. Patient population
    4. Statement as to whether study has been completed
2. Original number of patients to be enrolled
    1. Patient number entered to date
    2. All applicable information relating to patients
3. Study completed/interim results known/description of results

Format for IND Progress Report

1. Study Progress/Summary Information
    1. Summary of most frequent and most serious AE's by body system
    2. Summary of all IND safety reports
    3. Any subject deaths
        a. Include cause of death
    4. Subjects who dropped out
        a. Due to AE?
        b. Drug related?
    5. New information on
        a. Drug interactions
        b. Dose response
        c. Controlled trial information
    6. List of preclinical studies
    7. Summary of any manufacturing changes
    8. Description of investigational plan for the upcoming year

Format for IND Progress Report

1. Study Progress/Summary Information (contd.)
    1. Investigator brochure updates
    2. Protocol modifications
    3. Significant protocol changes not reported as an amendment*
    4. Foreign market updates

Submission Timeframe: Can an IND Fall into Expiration??

Unlike an IRB approval, and IND Application cannot fall into Expiration if the report is not submitted and reviewed before the annual renewal date

However, to maintain compliance, an IND sponsor is REQUIRED to submit at least an annual progress report.

- Gold Standard: Begin the annual progress report 60 days prior to its due date
- Submit in triplicate form to the agency

Maintaining the IND Between Annual Renewal

IND Amendments

Maintaining the IND Between Annual Renewal

Understanding What Should be Submitted in an Amendment

Understanding when to submit an “amendment” is vital for an investigator

Several differences have been identified by the agency to help investigators understand when the correct time to submit an amendment

Maintaining the IND Between Annual Renewal

Understanding What Should be Submitted in an Amendment

New Clinical Protocol: Items associated must be reported to the FDA in the form of a supplemental application BEFORE implementing the change

- Brief description of most significant differences between protocols
- References to support changes
- Cover letter
  - Form 1571
- Request for comments
  - Any questions relating to the new version you'd like FDA to address

Maintaining the IND Between Annual Renewal

Understanding What Should be Submitted in an Amendment

Changes to the Clinical Protocol: Any change that significantly affects the safety of subjects (Phase 1), scope of investigation, or scientific quality of study (Phase II and III)

- Refer (date and number) to previous submission that contains protocol being revised
- Description of Change
- Cover letter
  - Form 1571
- References to help support changes
- Request for comments

** Immediate Hazard to Subjects= Immediate Implementation

Maintaining the IND Between Annual Renewal

Understanding What Should be Submitted in an Amendment

New Investigators: New study investigator is added to ongoing IND

- Submit within 30 days of adding investigator
- Grouping of several investigators in one submission is permitted

Content

- Cover letter
  - Form 1571
- Name and Qualifications
  - Why add them to protocol?
- Name and Address of research facilities/IRB
  - Where will new investigator conduct protocol?
- Reference to previously submitted protocol

Information Gathered and Report or Amendment has been Submitted

What Happens When the FDA has a Question?????

Responding to FDA Inquiries

Investigators must be aware that it is not uncommon for the FDA to respond with questions/inquiries

Investigators must be prepared to systematically respond to each inquiry in an organized manner.

FDA gives no specific requirements or suggestions on how to respond

Responding to FDA Inquiries
An Organized Approach

1. Cover Letter
    1. *IND Number*
    2. *Type of Supplement Response*
    3. *Submitted in Triplicate Form*
    4. *List of materials being submitted with the Response*
2. Point by Point Response
    1. *Header/Footer*
    2. *Rephrase FDA Question/Inquiry verbatim*
    3. *Response to inquiry*
3. Additional Items Requested by FDA

Responding to FDA Inquiries
An Organized Approach

- The FDA generally gives investigators a 45 day response window to provide additional information

Inquiries MUST be Taken Seriously

- If no attempt is made by an investigator to respond to an inquiry from the FDA, the agency will proceed with steps to withdraw the approval of an IND.

Safety Reporting

How to Complete the Process of Serious Adverse Event Submission to the FDA

Med Watch Reporting Form 3500

The Med Watch process is intended to report serious adverse events for human medical associated with the use of:

- FDA-regulated drugs,
- Biologics (including human cells, tissues, and cellular and tissue-based products)
- Medical devices (including in vitro diagnostics)

Med Watch Reporting Form 3500 Timeframes

Med Watch forms can be submitted via fax, facsimile, or online.

Written Safety Reports: Serious and Unexpected

- *No later than 15 days after discovery of event*

Telephone/Fax Safety Reports: Fatal or Life Threatening

- *No later than 7 days after discovery of event*

Med Watch Reporting Form 3500 Reporting Differences

- **Form FDA 3500 - Voluntary Reporting**

For use by healthcare professionals, consumers, and patients.

- **Form FDA 3500A - Mandatory Reporting**

For use by IND reporters, manufacturers, distributors, importers

FDA Guidance Documents

How to Navigate the Documents to Retrieve Useful Information

FDA Guidance Documents
Using Their Content to the Advantage of the Sponsor

Good Guidance Practice (GCP) documents are prepared for industry and the public that relate to:

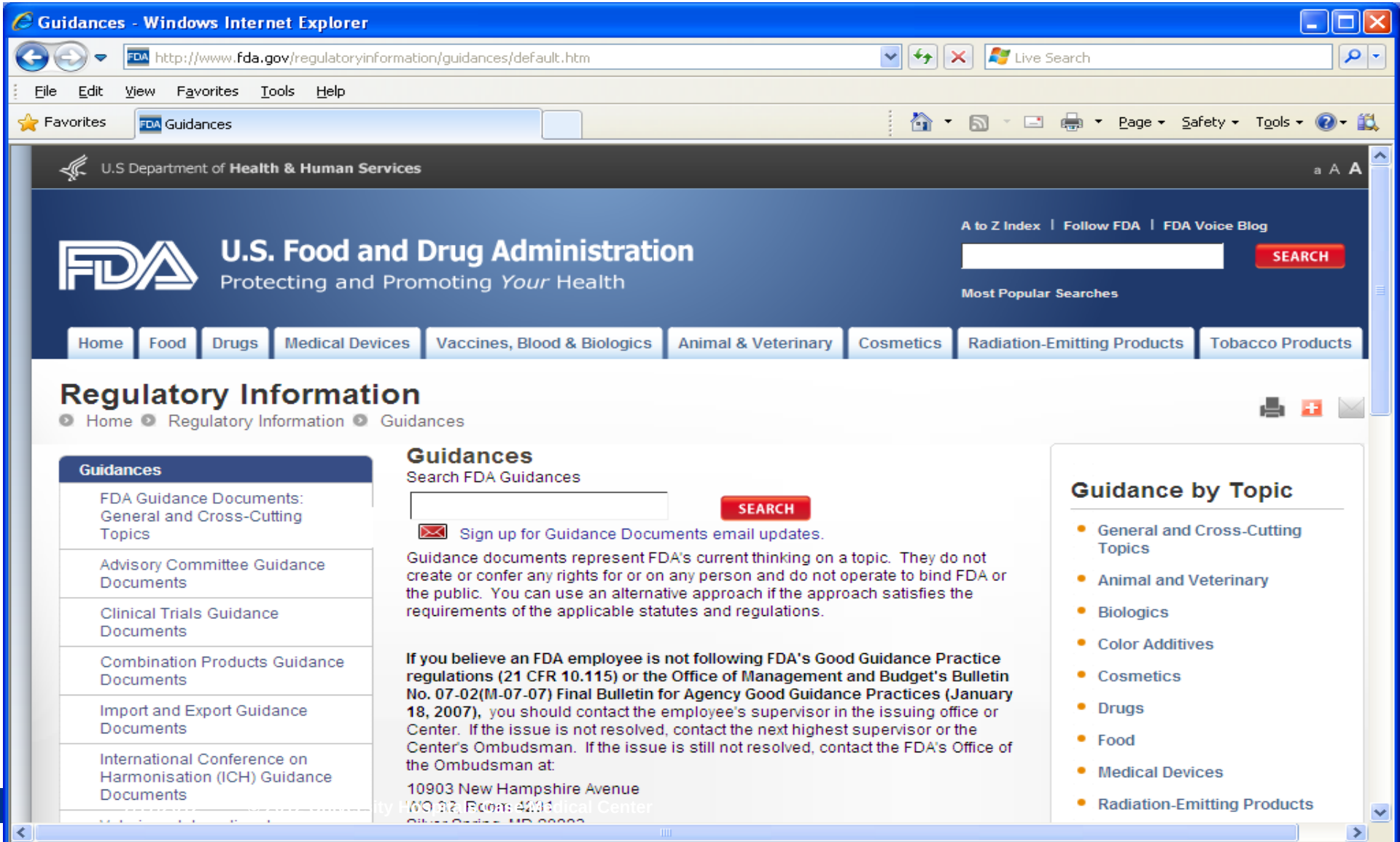
1) Processing, content, and evaluation of regulatory submissions
2) Design, production, manufacturing, and testing of products
3) Inspection and enforcement of polices and procedures

FDA Guidance Documents
Using Their Content to the Advantage of the Sponsor

Always Remember: Guidance Documents to NOT exist to bind the FDA to a particular thought or suggestion.

They are merely tools to help the investigator/sponsor/research staff to better interpret particular sections of the Code of Federal Regulations

FDA Guidance Documents
Using Their Content to the Advantage of the Sponsor



IDE Guidance
Some of the Most Helpful

- Determining if an IND is Required
  - Issued on: October 2010
- Financial Disclosure by Clinical Investigators
  - Issued on: March 20, 2001
- Considerations When Transferring Clinical Investigation Oversight to Another IRB
  - Issued on: June 2012
- IRB Review in Multicenter Research Study
  - Issued on: March 2006

Maintaining FDA and IRB Approvals

How to Ensure that Documents Submitted to Both Reviewing Bodies are Identical

Maintaining FDA and IRB Approvals
Tips and Helpful Hints

It is mandatory that both the FDA and IRB are provided and are reviewing the exact same version of research related documents.

Document Differences=Problem

- Obtaining FDA and IRB approval
  - In what order should the submissions be provided??

Thank you for Attending the Lecture

Questions….Comments