Free research paper on drug development

Technology, Development

Drug Development Slides

What are some of the major responsibilities of the US Food and Drug Administration?

The FDA is responsible for protecting public security by ensuring all foods sold meet hygiene and safety standards.

How long does the drug patent usually last? Can you gain an extension?

The drug patent lasts for 17 years and one can get a patent if they apply.

What are the basic sections of a US IND?

- Toxicology and effectiveness during pre-clinic trials
- Clinical work that will be carried out in Phase 1 and 2
- Manufacturing and chemistry procedures
- Reports from previous experiments that involved human subjects

How many major divisions review and IND?

Two

What are the important goals of a Phase 2 trial?

May a Sponsor start Phase 2 studies without long-term animal tox studies completed?

Yes

When should you meet with the FDA regarding the development of your drug?

Before Phase 3 begins

How efficient is the drug development process?

It is efficient in ensuring that only safe and effective drugs are sold in the market.

What are the basic sections included in the NDA?

- Results from preclinical and clinical studies

- All procedures and methods of manufacturing

Can drugs be approved if they may have potential, very serious side effects (death or inducing cancer)? Explain.

No, in such a case the FDA rules that the risks outweigh the benefits.

Using the Fosamax example, are delays in drug development costly? How much money was lost in every day that the NDA was delayed for Fosamax?

Delays in drug development are costly since expenses are incurred each extra day. Fosomaz lost about USD 4. 5m each day the NDA was delayed.

Why are surrogate endpoints important in drug development?

How did PDUFA speed up drug development?

Rheumatoid Arthritis Trial Guidance

What is a DMARD? an NSAID?

DMARD- antirheumatic drugs that modify a disease

NSAID- Anti-inflammatory drugs that are non-steroidal

What are 6 possible measurement classes of efficacy, which, if successful in one or more, might lead to approval of your DMARD?

- Reducing symptoms and signs of RA

- Major response in clinical studies

- Complete response in clinical studies

- Remission

- Preventing disability

- Structural damage prevention

What are 2 animal models that might be helpful in your development of your DMARD?

- Autoimmune response

- Transgenic animals

Why do most phase 2 trials in RA enter predominantly female subjects?

Because females enroll more for RA trials

What might be three useful efficacy endpoints for a phase 2 or 3 RA trial?

- Global consideration

- Trial design

- Analytical issues

What are the four important inclusion criteria for entry into an RA phase 2 trial?

- Disease activity

- Longer follow-up periods

- Sub-group of disease

- Gender

What should the primary efficacy endpoint be in an RA phase 2 trial? Can you use a VAS also, for primary endpoint?

Pediatric Trials

What are four reasons for proceeding with a drug development program for a product using in pediatric medicine?

- How serious the condition being treated is

- Suitability and availability of alternative treatments

- Whether endpoints specific to pediatrics have been developed

- Age of pediatric patients that will receive the treatment

How might patient compliance with dosing be enhanced in a peds population?

- Flavoring the drugs

- Coloring the drugs to attract the patients' attention

- Chewable tablets

- Alternative delivery systems

Can pediatric potential subjects give free and informed consent?

Yes

What is an " emancipated" pediatric potential subject?

This is one who can make decisions like an adult.

Accelerated Drug Approval

In contrast to the " regular marketing approval", how might " accelerated approval" be granted to an oncology drug?

If the surrogate endpoint is likely to lead to a better life even though it is not well established.

Are there usually restrictions following Accelerated Approvals?

Yes

In 1991, which oncology endpoints were determined to be most useful in oncology trials?

- Development in ensuring survival when disease-free

- Complete responses

Regarding imatinib, it’s first approval was for which indication? . was regular or accelerated? what were the endpoints? what type of trial design?

Indication: Failing interferon, CML, accelerated phase and blast phase

Approval Type: Accelerated

Endpoints: Cytogenetic and hematologic response.

Trial Design: SAT

SAME questions for pamidronate. Answers: .

Indication: Myeloma metastases, the osteolytic bone’s skeletal morbidity

Approval Type: Regular

Endpoints: SRE

Trial Design: Placebo RCT

Are accelerated approvals likely to be based on survival as an endpoint? Explain.

Yes, as the authorities try to speed up processing of drugs that have a high possibility of ensuring survival through improved effectiveness.

For Nelarabine and Sunatib:

Brief description of trial(s) design (disease, dose, treatment length) leading to accelerated approval:

Nelarabine

Trial design: Two phased trial

Disease: lymphoblastic lymphoma

Dose: 650mg/m2

Treatment length: 21 days

Sunatib

Trial design: Placebo

Disease: Advanced Renal Cell Carcinoma and Gastrointestinal Stromal Tumor and

Dose: 400mg/m2

Treatment length: 6. 4 weeks

Size of total populations studied: 133 patients

Describe results (primary endpoint(s) yielding successful data leading to accelerated approval: Indicated resistance of patients to imatinib

Indication achieved: Ability to treat gastrointestinal stromal tumor previously resistant to imatinib

Any restrictions on approval: No

What successful trials (design, patients, outcomes) moved imatinib from accelerated approval to full approval? It’s ability to ensure disease-free survival

What was the most striking efficacy endpoint reached? Complete clinical responses

Statistical Analysis Plan

What is the purpose (objective) of the study discussed in the SAP?

How did the study overcome the fact that the drugs were packaged differently, eliminating the ability to have a double-blind study?

All study procedures were conducted by a study coordinator.

Briefly, how was the sample size determined for the study?

Based on a standard deviation from the pilot study

How many primary endpoints? Why so many?

11, due to the number of variables under study

In order to prove non-inferiority, which three statistical steps MUST be met simultaneously?

Descriptive statistics

Inferential statistics

Individual subjects' listing

What is useful regarding the use of LOCF? What assumption may not be true, however?

Last Observation Carried Forward. It is not true to assume that the value from a previous visit is still the same at the beginning of a later visit.

The titles, headers, footers, formats, footnotes, layouts, fonts of every listing, figure, and table are VERY clearly described. What is the purpose or reason for attention to these details?

Data Management Plan

Is the DMP needed? Why?

It is essential in determining the safety of the drugs

Why type of data may need to be imported into a trial database containing only the CRFs data?

When might the data need to be exported somewhere?

What is " SAE reconciliation"? Why is it necessary?

Comparison of data from laboratory results with that from a safety database.

It is essential to ensure consistency.

What is an “ annotated” CRF?

A blank CRF with annotations or markings that link data points with the corresponding name of the data set.

What is an “ IVRS” utilized for?

For patient randomization

In this study, why was a DSMB convened? How often did it meet?

The DSMB met twice during the research and was convened to ensure all data collected was consistent.

What are “ front-end edit checks”?” back-end edit checks”

“ Front-end edit checks” are utilized to question or restrict various data entries.

“ Back-end edit checks” are programmed data checks to ensure synchrony of data during exporting.

Would you guess that data queries were generated mostly electronically or on paper during the course of this trial? Can hard copy DCFs be generated?

Electronically. Hard copy DCFs cannot be generated.

In this draft document, there is a single, one-way arrow missing from Figure 1. Where should it go in the figure?

Why were the “ Pentabs” (laptops) required to synch every week?

Are data listings for every data entry point created prior to database lock or post database lock? Explain.

Prior to database lock to ensure accuracy in data entry.

Which 8 items must be complete prior to “ final database lock”?

- Query resolution
- IVRS reconciliation
- Edit checks
- Failure review of the drug company’s treatment
- Safety reconciliation of the drug company
- Lab reconciliation
- Clinical review of Drug Company
- Document verification

Safety Reporting

Why do we report safety in a clinical trial?

It is a statutory requirement to ensure reduced risks to humans.

A patient gives informed, written consent and enters a clinical trial. His screening is not completed in one day. That evening he has severe vomiting and he reports it the next day when screening continues. Is this an AE? Explain. If it’s an AE, where does it become recorded? If not an AE where does it become recorded?

It is an AE which is recorded in eCRF page

Upon approval of the drug, where does all of the safety reporting become published?

As part of the publication that come with the drug

Are the 26 “ SOCs” of MedDRA set in stone or can you add new ones?

New ones cannot be added

How are ankle and peripheral swelling differently coded?

LLT

What is the job of the monitor in the field, or the data reviewer in the Sponsor regarding the accurate reporting of AEs?

- Raise queries regarding any inconsistency

- Ensure that data entered is consistent with the data in the source documents

- Follow-up on resolution of queries

Sample AE Database

Which columns in the database contain the MedDRA interpretation of the AE term reported by the clinic?

SOC, LLTC, PTC, LLTN, PTN

There are nearly 1500 AEs reported in this trial. How can you separate the SAEs from the AEs in a matter of seconds? (Is data manipulation neat or what!!!!)

Check for consistent figures which represent the SAEs

Approximately how many SAEs were reported?

200

Sample SAE Form

Notice: no space for the PI to select “ expected” or “ unexpected”. Why?

This is to ensure that all factors are taken into consideration without bias.

The SAE Report is often a data-conflicting-disaster. Why?

It details data that goes against other findings in the study.

SAE Report Completion Guidelines

What’s the “ upside” of getting a report within 24 hours of the event?

Downside?

Initial effects of the drug are easily detected. Downside:- some effects take longer to manifest and hence will not be recorded.

What is the current thinking from the FDA regarding PI opinion of drug causality or relationship to SAE?

That PIs should be impartial

I truly hate the misuse of the word " Severity" (one of the most misused words in the dictionary!!!!)? What word should we be using?

Intensity

Database Oncology Study Summary Review

No matter the trial AEs, Med Surg, and Con Meds are the data errors/queries that always lead the class. WHY???????

Incorrect indication on drugs

Note: the " good sites" and the " bad sites" (in terms of queries need to correct data). How do we get the " bad sites" to become better data entry sites?

Through encouraging the public to visit verified data sites.

Why is drug dosing compliance so great in this study?

It determines the effectiveness of the drug in treating the condition

CRF and CRF Guideline Document

What is the importance of " General Guideline" # 4?

Why is an " approver" needed for an entry criterion exemption?

What is the " HPA Axis function test"?

A test to determine the interaction various interactions and influences

Why is the GI GVHD assessment so important for this trial?

Because the drug is for a gastro-intestinal condition

What is the MDASI?

MD Anderson System Inventory

In this day and age of electronics, is the manual counting of tablets still important?

No

Upon completing Day 1 and answering ‘ Yes’, subject is continuing in the study, both Day 10 and End of Treatment (End RX) visits become available to enter data at anytime during the study. Why are both visits available?

Because the study uses LOCF

Why is this study especially focused on “ infectious adverse events”?

Because they represent a significant threat in clinical studies

FDA Inspections

Did Dr. Patrick Ma have an FDA inspection? If yes, what were the results?

(type, classification, any deficiencies)

Yes

How about Dr. Richard Macchia? (same questions)

No

Warning Letters

- Use this & Sample Warning Letter Files: The Clinical Investigator Inspection List:

http://www. accessdata. fda. gov/scripts/cder/cliil/index. cfm

Clinical Investigator Inspection List Data Codes:

http://www. fda. gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/ucm073059. htm

Warning Letters Database

http://www. fda. gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/default. htm

What three issues was the FDA Inspector highly concerned about with respect to Dr. Amato?

- Lapse of IRB approval
- No records were kept regarding dosage, patient information etc
- Study did not follow investigational plan

Dr Amstutz hit the " quadfecta"! Which four issues did the FDA Inspector cite?

- He did not conduct study according to the agreement signed with the sponsor
- Dr. Amstutz did not provide the IRB and sponsor with periodic reports on the progress of the study.
- Lack of adequate documentation for informed consent
- Lack of adequate documentation regarding the investigator's involvement in the study

Drug development proceeds slowly (it can take 10 years to gain approval). Why does it proceed so slowly?

Drug development is the process of acquiring a new drug. This process involves many tests. Tests involved include clinical and laboratory tests. The drug developers collect huge amounts of data. Observation of this data is undertaken. Once the results achieved are satisfactory, the new drug gets in the market. Testing involves many stages. Every stage consumes a lot of time. Some stages may take years before they are completed as accuracy and safety is emphasized more than merely finishing a stage in the process. Therefore, drug development is a long process, which may take a decade or more to complete.

How do you help clinics make few data entry errors and have fewer data discrepancy forms completed?

I will encourage the management to employ highly qualified records staff. In addition, I will encourage them to consider in-service training for the staff members. Patients can create portals from which they access their information when the need arises; this is through the use of electronic health records. I will establish data entry rules and procedures when dealing with computer data entry. I will achieve this by advising the clerical officers not to alter anything when entering data