Benefit-Risk Considerations in Drug Development

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Presentation Outline

- Key considerations in regulatory decision making
- Application during drug development
- Case studies
  - Partial Clinical Hold: Clinical safety concerns
  - Full Clinical Hold: Animal toxicology finding

Benefit-risk considerations

Regulatory decision making process

- Complex, can involve several aspects
- Decision based on benefits, risk, and the disease the drug is intended to treat
- Should not be arbitrary
- Consistent, systematic approach is critical

- Benefit-risk assessment terminology is typically referred to in the context of drug approval
  - Evidence of benefit or effectiveness
  - Evidence of product-related risk
- Similar general principles are applicable to decision making during drug development
  - During IND phase
  - And even, post-approval

Basis for regulatory decision making includes consideration of the following:

- Benefit: product effectiveness, proof of activity
- Safety: includes human safety data, toxicology study data, other nonclinical data, class-related toxicity concern
  - Consideration of risk minimizing strategies
- Nature and severity of the condition the drug is intended to treat or prevent

Basis for regulatory decision making generally includes consideration of the following (contd.),

- Medical need and attributes of alternative available therapy
  - Unmet medical need for a serious and life-threatening condition (e.g., Ebola infection) versus non-serious condition for which multiple therapies are approved

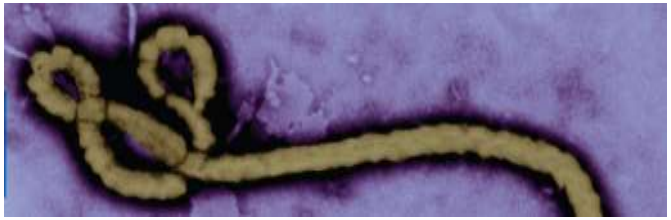
- Areas of data gap or uncertainty
  - Obtain additional information to respond to data gap?
  - Weighing the level of uncertainty in the overall equation

- And other considerations which may be specific to the drug or intended indication

Case studies - Antiviral drugs

Division of Antiviral Products

What do we review?



Treatment of HIV, chronic hepatitis C, influenza, Hepatitis B, herpes

Emerging infections, Biodefense e.g., Ebola, small pox, MERS virus

Pediatric antiviral drug products e.g., respiratory syncytial virus

Drug products to prevent disease e.g., HIV pre-exposure prophylaxis, CMV prophylaxis, rabies prophylaxis

Antiviral-related issues in other Divisions or Centers at the FDA

Small molecules products, interferons, biologics such as monoclonal antibodies

Issues discussed in this presentation may not be applicable to programs reviewed by other Divisions in CDER

Case study 1

Case study 1 overview

Safety concern was identified in a phase 2 clinical trial

- Impact on the ongoing HIV clinical program → **Partial Hold**

- Decision took into consideration two distinct HIV populations which were enrolled in trials
  - Treatment naive HIV-infected patients: for whom safer alternative drugs are available
  - Treatment experienced HIV-infected patients: with fewer treatment options

Case study - HIV

Animal toxicology data

Single dose clinical trial data

Multiple dose clinical trial data (short term)

Proof-of-concept data in the target population

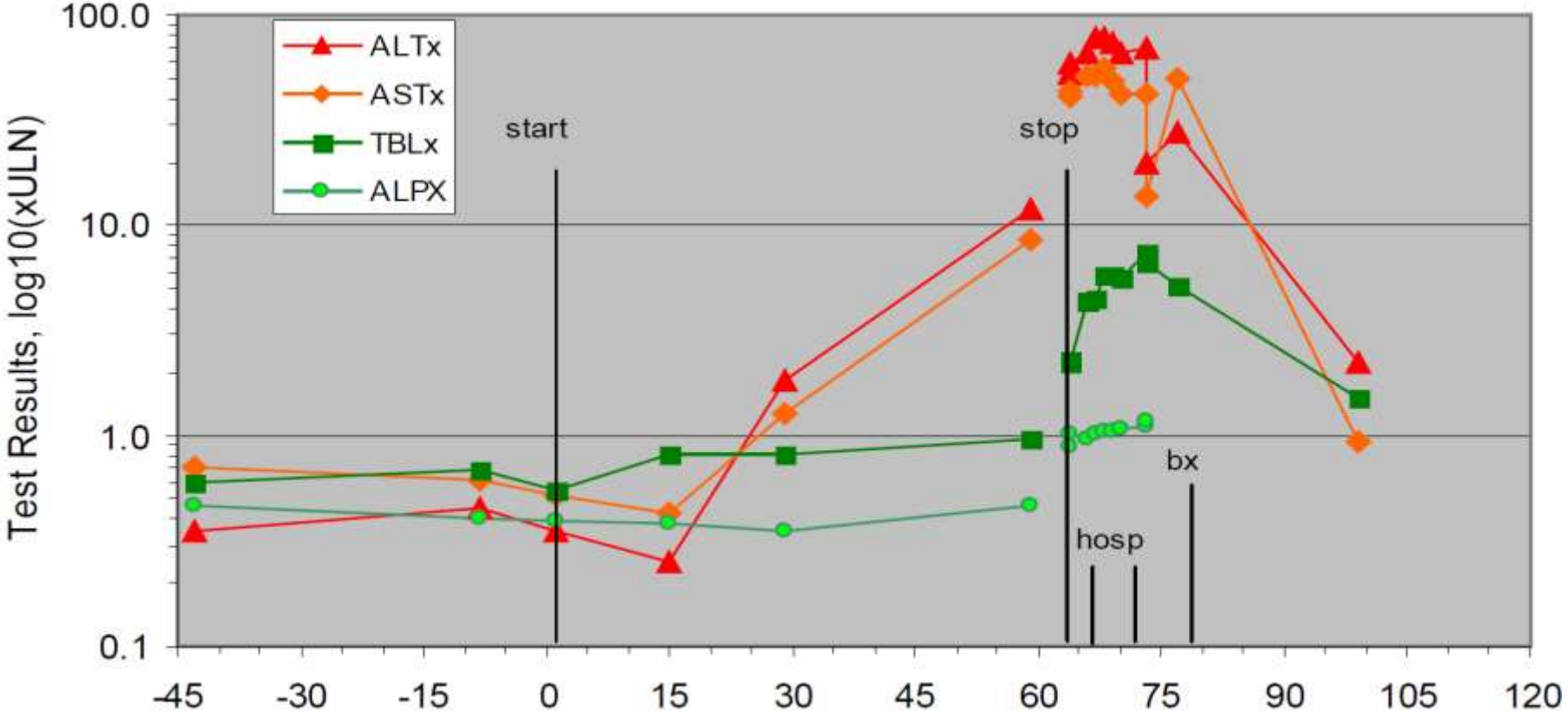
Six-month trial in target population ongoing

39 year-old male in HIV treatment naïve trial

- Experiences increase in ALT (2888 U/L), AST (1938 U/L), total bilirubin (2.7 mg/dL), nausea and vomiting on study day 59 leading to hospitalization
- Liver biopsy is compatible with drug-induced hepatitis

Case study

Sentinel case hepatic laboratory parameters



Question

- Does this case represent a safety concern for significant hepatotoxicity?

- Next steps…

Drug-Induced Liver Injury (DILI)

- May or may not be dose-related, may not be observed in animals
- Unpredictable for most drugs (except acetaminophen)
- Generally low incidence approximately $\leq$ 1/10,000
- Often discovered post-approval, primarily because of low incidence

Request for like-cases observed in clinical program

- 10 reports of treatment-emergent grade 3 or grade 4 increases in AST, ALT or total bilirubin
- Total 4 cases were identified and were considered clinically relevant
  - Included one dechallenge/rechallenge case
- Cases occurred at all doses

1. **Case # 1 sentinel case**
2. **Case # 2 at lower dose**
   - Symptomatic grade 4 bilirubin + grade 2 increase in ALT, AST
   - Co-infected with hepatitis B
3. **Case # 3 with dechallenge and rechallenge**
   - Increase in ALT at Weeks 8 and 16 of treatment, treatment was stopped
   - Treatment resumed followed by ALT increase to grade 3 severity
4. **Case # 4**
   - Subject discontinued treatment at Week 2 for GI toxicity
   - At withdrawal, grade 4 ALT and AST + grade 3 total bilirubin
   - History of fatty liver with hepatosplenomegaly, and suspected alcohol abuse

Approach to causality assessment

- Time to onset
- Rate of resolution or dechallenge
- Risk factors
- Exclusion of other causes (viral hepatitis, ischemia, biliary tract disease, alcoholic liver disease)
- Concomitant drugs
- Track record - prior information regarding the known hepatotoxic potential of the drug or drug class
- Rechallenge data

Reference: Drug induced liver disease edited by Kaplowitz and DeLeve 2003

Case study

- Enrollment in the ongoing and completed trials
  - About 300 treatment-naïve HIV-infected subjects had been exposed; median time on trial 10-12 weeks
  - About 50 treatment-experienced subjects had been exposed; median time on trial 30 days

- Incidence of grade 3-4 increases in ALT and/or total bilirubin by subpopulation
  - 3% in treatment-naïve patients
  - none in treatment-experienced patients

Considerations for regulatory decision

Intended indication	HIV infection is serious and life-threatening
Available treatments	Treatment naïve population: several safe alternative treatments. However, treatment experienced population: fewer treatment options due to development of resistance; medical need
Benefit	Investigational ARV; clinical proof-of-activity data available
Risks	Hepatotoxicity
Risk management	• Exclude subjects at greater risk: those with HBV, HCV, history of liver disease, ALT/AST exceeding grade 1 severity and total bilirubin value exceeding upper limit of normal • Include hepatic safety monitoring at frequent intervals: every two weeks • Scheduled interim safety analyses : monthly safety summaries for all increases in ALT/AST and bilirubin • Re-consent for participation
Regulatory Decision: Partial clinical hold to allow dosing in treatment experienced HIV infected patients	

Case Study 2

Case study 2 overview

Toxicity was identified in the 39-week chronic toxicology study while the clinical program was ongoing

- Impact on the ongoing program → **Full Clinical Hold** which prohibits all clinical studies under an IND until hold issues are resolved

- Subsequently, the development program was revised by the sponsor to focus on a specific population with medical need → **Full Clinical Hold was converted to Partial Clinical Hold** which allows limited evaluation under an IND

Intended Indication: Treatment of genital herpes in immunocompetent individuals

- Sexually transmitted viral infection
- Common clinical manifestations
  - Localized painful sores which may recur, usually self-limited
  - Bothersome condition - not viewed as a life-threatening condition

- Clinical disease varies depending on host's immune status
  - Immunocompromised patients
    - Severe ulcerative skin lesions, relatively prolonged duration
    - Post-transplant patients on immunosuppressive therapy, HIV

Available treatments for the intended indication

- Several approved antiviral agents for genital herpes
  - Includes acyclovir, valacyclovir, famciclovir
    - Nucleoside analogs; target HSV DNA polymerase enzyme
    - Reasonably well-tolerated; renal safety concern

- Fewer options for immunocompromised patients with severe or resistant herpes simplex virus (HSV)
  - Significant toxicity e.g., boxed warning

Case study - Herpes Antiviral

- Investigational agent being developed for the treatment of genital herpes in immunocompetent adults
- Novel mechanism of action exerts antiviral activity at site different from currently approved drugs

- Toxicology package for the initial IND not concerning - new IND was allowed to proceed

- During phase 2 clinical development
  - FDA was notified of animal toxicities which had not been identified previously
    - Severe drug-related toxicities in the chronic toxicology study resulting in unscheduled animal sacrifice

Considerations for toxicity observed in animal studies

- What are the target human concentrations in relation to the concentrations at which toxicity or adverse effect occurred in animals?
  - NOAEL or no observed effect dose/exposure
  - Safety factor for projected exposure in humans at the proposed clinical dose

- Toxicity in one species or more than one species
- Target organ/tissues involved, extent of severity
- Is the toxicity dose-related?
- Is the toxicity easily monitored in humans?

Risk Mitigation Strategies for First-In-Human Trial

- Start with small number of subjects
  - Dose 1-2 subjects
  - Stagger dosing between subjects for specified interval
  - Sufficient monitoring after dose administration
- Stringent stopping rules for individual subjects, cohorts and the trial

Risk Mitigation Strategies for First-In-Human Trial

- Stringent enrollment criteria
- For some products, need to monitor for infusion-related events in the immediate time frame after dosing
- Consideration for an independent unblinded medical monitor or data monitoring committee to oversee safety

Considerations for regulatory decision

Intended indication	Genital herpes in immunocompetent individuals • Self-limited condition; not life threatening
Available treatment	Yes, several alternatives for the intended indication
Benefit	Investigational agent with promise of clinical benefit based on nonclinical activity
Risks	• Severe toxicities in animal study resulting in early unscheduled animal sacrifice • Insufficient safety margin with the clinical dose • Drug-related toxicity
Regulatory decision: Because human subjects would be exposed to an unreasonable and significant risk of illness or injury [21 CFR 312.42 (b)(2)(i)], IND placed on full clinical hold	

Case study

- Advise to consider revising development program
  - Identify a patient population for which the benefit-risk assessment would be viewed as favorable - *likely the only feasible approach*

- Other approaches were considered
  - Toxicity not specific to one animal species
  - Study-specific issue not identified

Program revised to target patients who are immunocompromised and with resistant virus

- Greater disease severity in immunocompromised adults relative to immunocompetent adults
- Few treatment options, agent with considerable toxicity including boxed warning
- An investigational agent of new class and mechanism of action has the potential to circumvent common resistance pathway

- However, important to carefully decide the acceptable dose – limit to dose/duration based on support from clinical trials conducted to-date

Consider the dosing for the revised population

- Limit exposure to defined dose/duration
- Safety findings in immunocompetent adults may not be representative
- Therefore, clinical dosing needs to proceed carefully:
  - Stringent toxicity monitoring criteria
  - Conservative toxicity management plan
  - Conservative stopping criteria
  - Frequent periodic assessments of safety

Considerations for regulatory decision

Revised intended indication	Mucocutaneous HSV in immunocompromised patients can be severe, difficult to treat, resistant to acyclovir and related agents
Available treatment	Agent with significant toxicities including boxed warning in label
Benefit	Investigational agent has promise of benefit; in vitro activity shown against wild type and acyclovir-resistant viruses
Risks	Severe toxicities in the longer duration chronic toxicology study; insufficient safety margin. Clinical safety data obtained to-date allowed identification of an acceptable dose and duration for patients with severe disease and limited treatment options
Risk management	Clinical trial in patients with severe disease and limited treatment options requires conservative criteria: frequent monitoring, individual stopping criteria, toxicity management plan etc.
Regulatory Decision: Full hold converted to partial clinical hold to allow 1) dosing only in patients with severe disease with very limited treatment options, and 2) limit dosing to not exceed the acceptable dose and duration	

Summary

- Context matters – safety concerns are not assessed in isolation
- Totality of data
  - Disease condition, severity of illness, patient population
  - Available therapies, need for treatment options
  - How well the product works or treatment effect
  - Side effects or adverse event profile
  - Other considerations e.g., drug interactions
- Benefit-risk considerations in regulatory decision making throughout product life cycle, pre-approval and post-approval

Questions?

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Thank you!