



Dealing with the FDA - What's Hot?

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FDA FOCUS



SAFETY

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Presentation Outline



Many FDA initiatives have a common theme of **SAFETY**:

- Assess early safety signals
- Pharmacogenomics
- Biosimilars
- Suicidality in clinical trials
- Risk Evaluation and Mitigation Strategy



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Early Safety Signals

Early Clinical Holds: Safety Signals from Animal Studies

- GLP toxicology studies and basic safety pharmacology (SP) may not be sufficient
 - Perform dedicated SP studies (GI, renal, etc.)
- Animal studies are not waived by presence of early human data
 - Human data do NOT trump animal data
- Conduct basic panel prior to pre-IND

Following the Safety Signal



- Ensure toxicology studies include high enough doses to:
 - Identify potential target organs of toxicity
 - Identify gender-specific toxicities
- Fully disclose any safety findings to FDA
- DATA are required to demonstrate that a toxic effect in animals is species-specific

Later Clinical Holds: Safety Signals from Human Studies

- Placebo control in Phase 1?
- Careful AE documentation critical
 - Even in ex-US studies conducted prior to IND submission (likely increased scrutiny per Office of the Inspector General June 2010 report)
 - Create contemporaneous study reports from study 1; do not rely on journal publications



Prediction of Safety Risks through Pharmacogenomics

Predictable Risks Due to Increased Drug Exposure

■ Supra-therapeutic exposure from:

- ↓ metabolism of the active form or ↑ metabolism of a prodrug

■ Examples:

- antidepressant and antipsychotic drug levels can vary by 5-20 fold in actual clinical use
- 9-fold higher risk of suicide with CYP2D6 ultrarapid metabolizers

Dedicated PGX/PK P1 studies



■ Required

- Preclinical work indicates a polymorphic DME or transporter could significantly alter systemic or target organ exposure

■ Recommended

- Unknown significance of polymorphic DME
- Highly variable clinical PK (divergent outliers, or among ethnic groups)

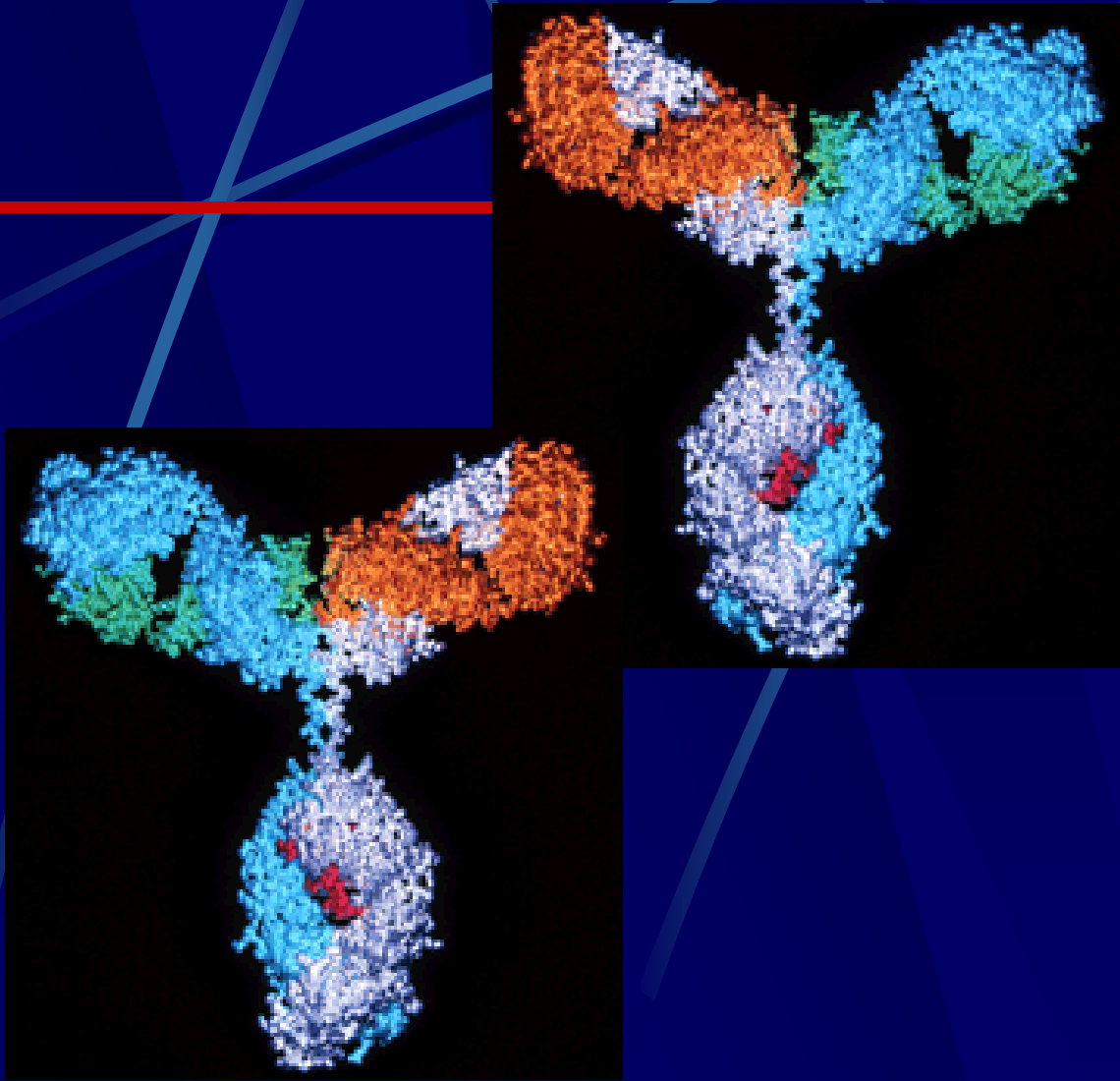
Planning for Unpredictable Risks

- FDA and EMA suggest banking DNA samples from the **first subject** dosed
 - Allows possible investigation of rare toxic effects
 - Can result in a drug approval with special labeling requirement, rather than drug failure
 - The FDA will be increasingly suggesting or requiring additional data

Labeling Implications



- Exclusion of certain genotypes from treatment for safety
 - Abacavir and HLA-B 5701
- Dose reduction for certain genotypes
 - Irinotecan and UGT1A1
- Pre-selection of certain genotypes for efficacy
 - Trastuzumab and HER2/neu overexpression



Biosimilars

Why is Patient Safety A Concern in the Biosimilars Debate?



- Living cells are inherently variable; slight changes in their environment that can significantly alter produced proteins
 - Immunogenicity
- The changes can be undetectable by lab analysis
 - E.g., J&J manufacturing change of EPREX (new neutralizing antibody killed RBC production)

Latest BioSimilarars Legislation

- Biologics Price Competition and Innovation Act of 2009 signed by Obama in March 2010
- New CDER Biosimilars Review Committee (BRC)
- FDA holding “stakeholder” meetings
- “There will not be a ‘one-size-fits-all’ approach. There will, rather, be a science-driven, case-by-case decision-making process” - *FDA Commissioner Hamburg, Feb 2010*
 - Developers must prove no increased patient risk when alternating or switching between use of the biosimilar product and the reference product

Guidance for Industry Suicidality: Prospective Assessment of Occurrence in Clinical Trials

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Thomas Laughren at 301-796-2260.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Medical

**Suicidality in
Clinical Trials**

Purpose of Guidance

- Acknowledge a signal for treatment-induced suicidality in patients **without** known risk factors
- Direct **prospective** suicidality assessment
 - Even in single-dose, healthy volunteer studies
 - Use standard assessment tool
 - Special consideration for patients with cognitive disorders

Current “At Risk” Drug Classes

- All drugs under the review by the FDA Division of Psychiatry Products
- Non-psychiatric drugs with CNS activity (e.g. epileptic)
- Drugs related to those suspected of an elevated suicide risk:
 - tretinoins, beta blockers that cross the BBB, reserpine, smoking cessation and weight loss

BIZARRO



Risk Evaluation and Mitigation Strategy (REMS)

Risk Evaluation and Mitigation Strategies (REMS)

- FDAAA granted FDA authority to require REMS in 2007
- Variable requirements
 - Ranges from medication guide to limited distribution
 - May require periodic assessments
- Risk to be mitigated can include risk to a nonpatient third party

REMS, in the beginning



- In March 2008, CDER Deputy Director Throckmorton said that FDA would use its new REMS authority “judiciously,” by “targeted use.”
 - “[too many [REMS] would increase confusion in the system [and] could increase errors and decrease [product] availability.”

REMS, Today

- FDA required a REMS in 1/3 of the new molecular entities and biological products approved by FDA during the first half of 2010
- Between Jan-Sep 2010 alone, 67 new or revised REMS were approved (60% had a MedGuide only)
- A total of >144 approved products now have REMS

Class Effect REMS

- REMS were initially drug product specific
- FDA is moving to more class-effect REMS
 - E.g., opioids, testosterone gels, TNF α blockers, botulinum toxin-based products
- Develop REMS early for new agents in these classes

Summary

- Recent drug withdrawals have made FDA extremely risk-averse
- Attentiveness to safety signals is critical
- Even when conducting ex-US studies, be aware of class concerns and collect extra data early

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