One FDA Reviewer’s Perspective on the Agency’s View of the Need for DIT Testing

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May 4, 2010
Disclaimer

• The views disseminated in this talk are my own views and do not necessarily represent the views of the FDA.
Risk/Benefit Paradigm in Assessing New Drugs

Severity of Disease

Benefit: Freedom from Disease, Alleviation of Symptoms, Improved Quality of Life

Risk: Drug Related Toxicity

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Severity of Disease
Like to Know vs. Need to Know

• As scientists we’d like to know everything about how the drug product works, but as regulators we need to know how it impacts safety.
Guidances

21 C.F.R. 314.50(d), CFR 601.2

- ICH M3
- ICH S8
- CDER Guidance on Immunotoxicity
- CDER Guidance on Nonclinical Safety Evaluation of Pediatric Drug Products
- ICH S6
- ICH S9
- ICH S5A
ICH M3

- ICH M3 refers to the ICH S8 guidance on immunotoxicity

- all new human pharmaceuticals should be evaluated for the potential to produce immunotoxicity using standard toxicity studies and additional immunotoxicity studies conducted as appropriate based on a weight-of-evidence review, including immune-related signals from standard toxicity studies. If additional immunotoxicity studies are indicated, these should be completed before exposure of a large population of patients (phase 3)
• For most anticancer pharmaceuticals, the design components of the general toxicology studies are considered sufficient to evaluate immunotoxic potential and support marketing. For immunomodulatory pharmaceuticals, additional endpoints (such as immunophenotyping by flow cytometry) might be included in the study design.
ICH S8

- **Standard Toxicity Studies**
  - Hematological changes
  - Immune system organ weights and histology
  - Changes in serum globulins
  - Increased infections
  - Increased tumors

- “If the pharmacological properties of a test compound indicate it has the potential to affect immune function (e.g., anti-inflammatory drugs), additional immunotoxicity testing should be considered.”

- ICH S8 is silent on the specific need for developmental immunotoxicity testing

- However, DIT could be interpreted as additional testing
ICH S8: Factors to Consider in Evaluation of Potential Immunotoxicity

- Statistical and biological significance of changes
- Severity of effects
- Dose/exposure relationship
- Treatment duration
- Number of species and endpoints affected
- Secondary changes to other factors (e.g. stress)
- Cellular targets and mechanism of action
ICH S8: Factors to Consider in Evaluation of Potential Immunotoxicity (cont.)

- Safety factor above anticipated clinical dose
- Doses that produce immunotox changes in relation to doses that produce other toxicities
- Reversibility of effects
- Pharmacological Properties
- Intended Patient Population
- Structural Similarity
- Disposition of the Drug
- Signs Observed in Clinical Use

Weight-of-Evidence Review
ICH S8 (cont.)

- If a specific target is not identified in standard toxicity studies, TDAR and immunophenotyping may be best.

- Generally accepted study design for immunotoxicology assessment is the same as the study design for the study in which the flag was seen.

- If additional testing shows no risk of immunotoxicity, no further studies needed.

- If additional studies are inconclusive, use a weight-of-evidence approach to determine if additional studies are needed.
CDER Immunotoxicology Guidance

CDER ITOX guidance states:

- If a drug has been shown to have immunosuppressive potential in adult animal studies, determination of potential developmental immunosuppression should be incorporated into an ICH Stage C to F reproductive toxicology study (ICH, 1994). At a minimum, this would include determination of clinical and anatomical pathology parameters indicative of immunosuppression (e.g. effect of maternal drug exposure on lymphoid system histology and hematology in the F1 generation offspring).

- Although methods have been proposed for assessing functional parameters of immunosuppression in neonatal animals (Ladics et al., 2000), no recommendation is made concerning appropriate studies to determine the effect of fetal and/or perinatal drug exposure on immune function.

- No statement about assessing toxicity in juvenile animals
Suggested Assays from CDER ITOX Guidance

T-cell dependent antibody response
  Antisheep red blood cell primary IgM response
    (plaque assay)
  KLH
ELISA/ELISPOT
NK Cell Function
CTL Response
Cytokine/Chemokine Production
DTH Response
Host Resistance Assays
Immunophenotyping
ATTACHMENT 1: FLOWCHART FOR DETERMINING WHEN TO CONDUCT IMMUNOTOXICITY TESTING

1. **Start**

2. Topical administration? → Yes → Determine dermal sensitizing potential: GPMT, BA, LLNA, or other test method as appropriate (V.C)

3. Yes → Inhalation administration?

   Yes → Determine respiratory sensitizing potential: Inhalation induction/challenge or other test method as appropriate (V.A)

   Yes → Conduct follow-up immune function study (studies) as appropriate (II.A)

4. Yes → Evidence of immunosuppression in nonclinical (or clinical) studies?

   Yes → Conduct immune function study (studies) (III.B)

5. Yes → Drug to be used to treat HIV infection?

6. Yes → Drug likely to be used in pregnant women and evidence of immunosuppression?

   Yes → Determine effect of drug on immune system in F₁ offspring in reproductive toxicology study (III.B)

   Yes → Drug/drug metabolite accumulation in immune system tissues?

   Yes → Conduct immune function study as appropriate (III.B)

7. If none of the above applies, no further immunotoxicity testing needed
Reproductive Toxicity

- Generally, by Phase 3, Fertility and Embryofetal Development Studies should be completed.
- Pre- and postnatal development studies should be submitted before marketing approval.
- The aim of the prenatal and postnatal development studies described in ICH S5A (Detection of Toxicity to Reproduction for Medicinal Products) is to “detect adverse effects on the pregnant/lactating female and on development of the conceptus and the offspring following exposure of the female from implantation through weaning. Since manifestations of effect induced during this period may be delayed, observations should be continued through sexual maturity [i.e., stages 3 to 6 (C to F)]."
ICH S5A, 1994

Females are exposed to the test substance from implantation to the end of lactation [i.e., stages 3 to 5 (C to E) listed in I.B. (1.2)].

Adverse Effects To Be Assessed

- Enhanced toxicity relative to that in nonpregnant females;
- Prenatal and postnatal death of offspring;
- Altered growth and development; and
- Functional deficits in offspring, including behavior, maturation (puberty), and reproduction (F1).

- Developmental Immunotoxicology is not specifically addressed
Reproductive Toxicology in ICHS9

• A study of fertility and early embryonic development is not warranted to support clinical trials or for marketing of pharmaceuticals intended for the treatment of patients with advanced cancer. Information available from general toxicology studies on the pharmaceutical’s effect on reproductive organs should be used as the basis of the assessment of impairment of fertility.

• In cases where an embryofetal developmental toxicity study is positive for embryofetal lethality or teratogenicity, a confirmatory study in a second species is usually not warranted.

• A pre- and postnatal toxicology study is generally not warranted to support clinical trials or for marketing of pharmaceuticals for the treatment of patients with advanced cancer.
Reproductive toxicity studies should be conducted in accordance with the principles outlined in ICH S5(R2); however, the specific study design and dosing schedule can be modified based on:

- an understanding of species specificity
- the nature of the product and mechanism of action,
- immunogenicity and/or pharmacokinetic behavior and embryo-fetal exposure

The evaluation of toxicity to reproduction should be conducted only in pharmacologically relevant species. When the clinical candidate is pharmacologically active in rodents and rabbits, these species should be used unless there is a scientific reason to use a NHP.
ICH S6 Reproductive Toxicology cont.

- For products pharmacologically active only in NHPs, one well-designed study in NHPs (stage C to E ICH S5a) which includes dosing from day 20 of gestation to birth can be considered. For the single NHP study design addressing ICH S5a stages C to E, no caesarian section group is warranted, but assessment of pregnancy outcome at natural delivery should be performed:
  - Offspring viability/survival
  - External malformations/skeletal effects
  - Visceral morphology at necropsy

- Other endpoints in the offspring can also be evaluated if relevant for the pharmacological activity (e.g. immune function or neurobehavioural assessment).
ICH S6 Reproductive Toxicology cont.

• The specific study design and dosing schedule may be modified based on issues related to species specificity, immunogenicity, biological activity, and/or a long elimination half-life.

• For example, concerns regarding potential developmental immunotoxicity, which may apply particularly to certain monoclonal antibodies with prolonged immunological effects, could be addressed in a study design modified to assess immune function of the neonate.
PeRC

- Pediatric Review Committee established with the responsibility of assuring quality and consistency for pediatric studies required by PREA (Pediatric Research Equity Act) or requested under BPCA (Best Pharmaceuticals for Children Act)
- Written Requests may include preclinical studies
ICH M3

- The conduct of any juvenile animal toxicity studies should be considered only when previous animal data and human safety data, including effects from other drugs of the pharmacological class, are judged to be insufficient to support pediatric studies. If a study is warranted, one relevant species, preferably rodent, is generally considered adequate. A study in a nonrodent species can be appropriate when scientifically justified.
Juvenile Animal Studies

• Nonclinical developmental toxicity studies have traditionally focused on prenatal development, with only limited assessment of postnatal developmental effects.

• Animals used in multiple-dose toxicity studies are usually peripubertal. In some circumstances, data generated from these studies may provide sufficient information to support pediatric clinical trials without additional animal studies.

• Juvenile animal studies are especially relevant when a known target organ toxicity occurs in adults in tissues that undergo significant postnatal development.
Juvenile Studies cont.

- Brain, where neural development continues through adolescence
- Kidneys, where adult levels of function are first reached at approximately 1 year of age
- Lungs, where most alveolar maturation occurs in the first 2 years of life
- Reproductive system, where maturation is not completed until adolescence
- Skeletal system, where maturation continues well into adulthood for 25-30 years
- Gastrointestinal systems, which may have direct consequences on bioavailability, clearance, and biotransformation of drugs are functionally mature by about 1 year of age
  
- Immune system, where adult levels of IgG and IgA antibody responses are not achieved until about 5 and 12 years of age, respectively
Labeling Evolution

Developmental Immunotoxicology findings can be important from a regulatory perspective; these studies can impact labeling

Original Rituxan Label, 1997

**Indications and Usage**
RITUXAN is indicated for the treatment of patients with relapsed or refractory low grade or follicular, CD20 positive, B-cell non-Hodgkin’s lymphoma

**Immunization:** The safety of immunization with any vaccine, particularly live viral vaccines, following RITUXAN therapy has not been studied. The ability to generate a primary or anamnestic humoral response to any vaccine has also not been studied
Pregnancy Category C: Animal reproduction studies have not been conducted with RITUXAN. It is not known whether RITUXAN can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Human IgG is known to pass the placental barrier, and thus may potentially cause fetal B-cell depletion; therefore, RITUXAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether RITUXAN is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infants is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable. (See CLINICAL PHARMACOLOGY.)

Pediatric Use: The safety and effectiveness of RITUXAN in children have not been established.
Rituxan is a CD20-directed cytolytic antibody indicated for the treatment of:

• Non-Hodgkin’s Lymphoma (NHL) (1.1)
• Chronic Lymphocytic Leukemia (CLL) (1.2)
• Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to-severely-active RA who have inadequate response to one or more TNF antagonist therapies (1.3)

Limitations of Use: Rituxan is not recommended for use in patients with severe, active infections (1.4)

USE IN SPECIFIC POPULATIONS:

• Pregnancy: Limited human data; B-cell lymphocytopenia occurred in infants exposed in utero (8.1)
• Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3)

WARNINGS AND PRECAUTIONS:

• Do not administer live virus vaccines prior to or during Rituxan (5.10)
• Monitor CBC at regular intervals for severe cytopenias (5.11, 6.1)
8.1 Pregnancy

Category C: There are no adequate and well-controlled studies of rituximab in pregnant women. Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed to rituximab in-utero.

Non-Hodgkin’s lymphoma and moderate-sever rheumatoid arthritis are serious conditions that require treatment. Rituximab should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Reproduction studies in cynomolgus monkeys at maternal exposures similar to human therapeutic exposures showed no evidence of teratogenic effects. However, B-cell lymphoid tissue was reduced in the offspring of treated dams. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months of birth.
8.3 Nursing Mothers

It is not known whether Rituxan is secreted into human milk. However, Rituxan is secreted in the milk of lactating cynomolgus monkeys, and IgG is excreted in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. The unknown risks to the infant from oral ingestion of Rituxan should be weighed against the known benefits of breastfeeding.

8.4 Pediatric Use

FDA has not required pediatric studies in polyarticular juvenile idiopathic arthritis (PJLA) patients ages 0 to 16 due to concerns regarding the potential for prolonged immunosuppression as a result of B cell depletion in the developing juvenile immune system.

The safety and effectiveness of Rituxan in pediatric patients have not been established.
Conclusions

• Science should drive the testing
  – Triggers, including immune targets, pharmacology, and findings seen from clinical experience in adult populations (increased infection etc.) should all be considered

• The need for testing may be a review issue determined by the division
  – Talk to the division
Acknowledgments

- Carmen Booker, PhD
- Kim Benson, PhD
- Lisa Mathis, MD
- Elizabeth Bolan, PhD
- Melissa Tassinari, PhD
- Adam Wasserman, PhD
- Karen Davis Bruno, PhD
- Leigh Verbois, PhD