

Clinical Trials Transformation Initiative

Developing Rational Guidance for Pregnancy Testing in Clinical Trials

July 15-16, 2013

Pharmaceutical industry process for selecting a pregnancy testing protocol for a clinical trial

Sheila Ronkin, MD, MBA

Vice President, Clinical Affairs

Specialty Care



The views expressed in this presentation are those of the speaker and do not necessarily represent Pfizer, Inc.

Agenda

Goal:

Minimize the risk of unintentional exposure of the embryo or fetus when including females of child-bearing potential in clinical trials

Continuous improvement will benefit clinical trial participants, investigators, regulatory agencies AND industry.

CTTI's guidance for pregnancy testing in clinical trials is welcome and anticipated.

Today's Agenda:

Background

Considerations and Risks

Current Status – Pregnancy Testing in Pfizer Clinical Trials

Wish List



Background: Responsibility

ICH M3(R2) Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

June 2009

CHMP CPMP/ICH/286/95; Approved June 2009, effective Dec 2009

MHLW #0219-4; Adopted on 19 Feb 2010

FDA Published in Federal Register, vol. 75, # 13, docket FDA/2008/D/0470, p.3471; 21 Jan 2010

It is important to **characterize and minimize the risk of unintentional exposure of the embryo or fetus when including WOCBP in clinical trials**. One approach to achieve this objective is to conduct reproduction toxicity studies to characterize the inherent risk of a drug and take appropriate precautions during exposure of WOCBP in clinical trials. A second approach is to limit the risk by taking precautions to prevent pregnancy during clinical trials. Precautions to prevent pregnancy include **pregnancy testing** (eg, based on the β -subunit of HCG), use of highly effective methods of birth control, and study entry only after a confirmed menstrual period. Testing for pregnancy during the trial and subject education should be sufficient to ensure compliance with the measures designed to prevent pregnancy during the period of drug exposure (which could exceed the length of study).

WOCBP: Women of Childbearing Potential

ICH: International Conference on Harmonisation of Technical Requirements for Registrations of Pharmaceuticals for Human Use



Background

Despite pregnancy testing and contraception requirements, WOCBP continue to experience pregnancy during the conduct of clinical trials.

M3 (R2) Guidance for Industry, Endnote 5

Pregnancy rates estimated from PH 3 studies conducted in WOCBP were observed to be <0.1 percent per menstrual cycle. During these studies, subjects were encouraged to avoid pregnancy and measures were instituted to prevent pregnancy.



Considerations and Risks

The background risk of congenital anomalies is substantial and may not be well understood by clinical trial participants.

- **Major congenital anomalies are observed in ~3% of all births.**
- **It is believed that 5% of these (~1 in 670 live births) result from maternal exposure to drugs or environmental chemicals.**
- **Only 1% of teratogen-related anomalies can be attributed to the use of pharmaceutical agents; the bulk result from maternal ethanol use.**
- **The most important determinants of the developmental toxicity of an agent are timing, dose and fetal susceptibility. Many agents have teratogenic effects only if taken while the susceptible fetal organ system is forming.**

SOURCE:

American College of Obstetricians and Gynecologists. *Précis IV: An Update in Obstetrics and Gynecology*. Amer College of Obstetricians & Gynecologists, 2010.



Considerations and Risks

- **In the US, ~50% of all pregnancies and ~37% of live births were unintended at the time of conception. ***
- **Reducing the percentage of unintended pregnancies has been an objective of the Healthy People national health initiative since its beginning in 1980. #**
- **Women and couples have a complex mix of traits, desires and intentions resulting in a spectrum of behaviors aimed at preventing or achieving pregnancy that go beyond simply practicing or not practicing contraception. ^**

SOURCES:

* National Health Statistics Reports, Number 55, Jul 2012

Based on the 2006 – 2010 National Survey of Family Growth (NSFG) conducted by the CDC National Center for Health Statistics (NCHS). 80-minute interviews were conducted with 12,279 women selected from a nationally-representative, multistage, area probability sample drawn from 110 primary sampling areas across the US. The response rate was ~78%.

Mosher DW, Jones J, Abma JC. Intended and Unintended Births in the United States: 1982 – 2010.

^ Trussell J, Vaughan B, Stanford J. Are all Contraceptive Failures Unintended Pregnancies? Evidence from the 1995 National Survey of Family Growth. Family Planning Perspectives, 1999, 31(5):246-247 & 260.



Considerations and Risks

- **Pregnancy tests are intended for use in the context of pregnancy signs/symptoms; their sensitivity, specificity and accuracy has been determined within this context.**
- **In clinical trials, we commonly test for pregnancy in the absence of signs/symptoms; pregnancy is expected to be a rare event.**
- **Increase in indeterminate, false positive and false negative results are not unexpected; confirmatory testing is needed.**
 - Subject burden (interrupted treatment, unnecessary alarm, more tests)**
 - Investigator burden (associated management)**
 - Sponsor burden (resolution oversight, cost of additional testing)**



Pregnancy Testing for Clinical Trials

Who selects the pregnancy testing scheme in pharma clinical trials?

- **Trials are designed by clinicians, statisticians and clinical pharmacologists**
- **Protocols undergo multiple levels of review in advance of issue**
 - External opinion leaders
 - Internal reviews and governance
 - Internal quality assurance
 - All Pfizer phase 1 through 4 interventional clinical protocols (and substantial amendments) undergo mandated review by an AAHRPP-accredited IRB/IEC in advance of issue/distribution to investigators
- **After issue, protocols undergo IRB/IEC review/approval at the site level (and country level, if required by local laws and/or regulations)**

IRB: Institutional Review Board

IEC: Independent Ethics Committee

AAHRPP: Association for the Accreditation of Human Research Protection Programs



Pregnancy Testing for Clinical Trials

What factors may be considered when selecting the pregnancy testing scheme?

- Trial design (Interventional?)
- Subject population (WOCBP?)
- Compound class and characteristics
- Existing data on compound's reproductive and embryo-fetal risk
- Co-medication(s) and their reproductive and embryo-fetal risks

Which Pfizer studies include pregnancy testing?

Interventional clinical studies enrolling females of childbearing potential



Pregnancy Testing for Clinical Trials

All interventional clinical trials enrolling WOCBP include testing prior to first dose; a negative result is required before the subject may receive the first dose of test article.

- **Exception: studies intending to enroll pregnant females**

Most also include periodic testing

- **Exceptions include but are not limited to:**

Studies of non-live vaccines with no novel adjuvants or excipients

Studies of nutritional products involving only the consumption of food or food ingredients considered safe for intended use AND safe for use during pregnancy

Studies of consumer health products that meet certain criteria

Studies intending to enroll pregnant females

Most include testing at end of treatment or at early withdrawal to confirm the subject has not become pregnant during conduct of the study.



Pregnancy Testing for Clinical Trials

Pregnancy testing minimizes potential exposure to the embryo/fetus when conducted in accord with protocol, and test result correctly triggers process controls

- Serum or urine test with sensitivity of at least 25 mIU/mL.
- Pregnancy testing is repeated whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected).
- Test article is withheld for all indeterminate or positive results, pending confirmatory testing

When a compound of known teratogenic potential to the human fetus must be administered to females of childbearing potential enrolled in a clinical trial:

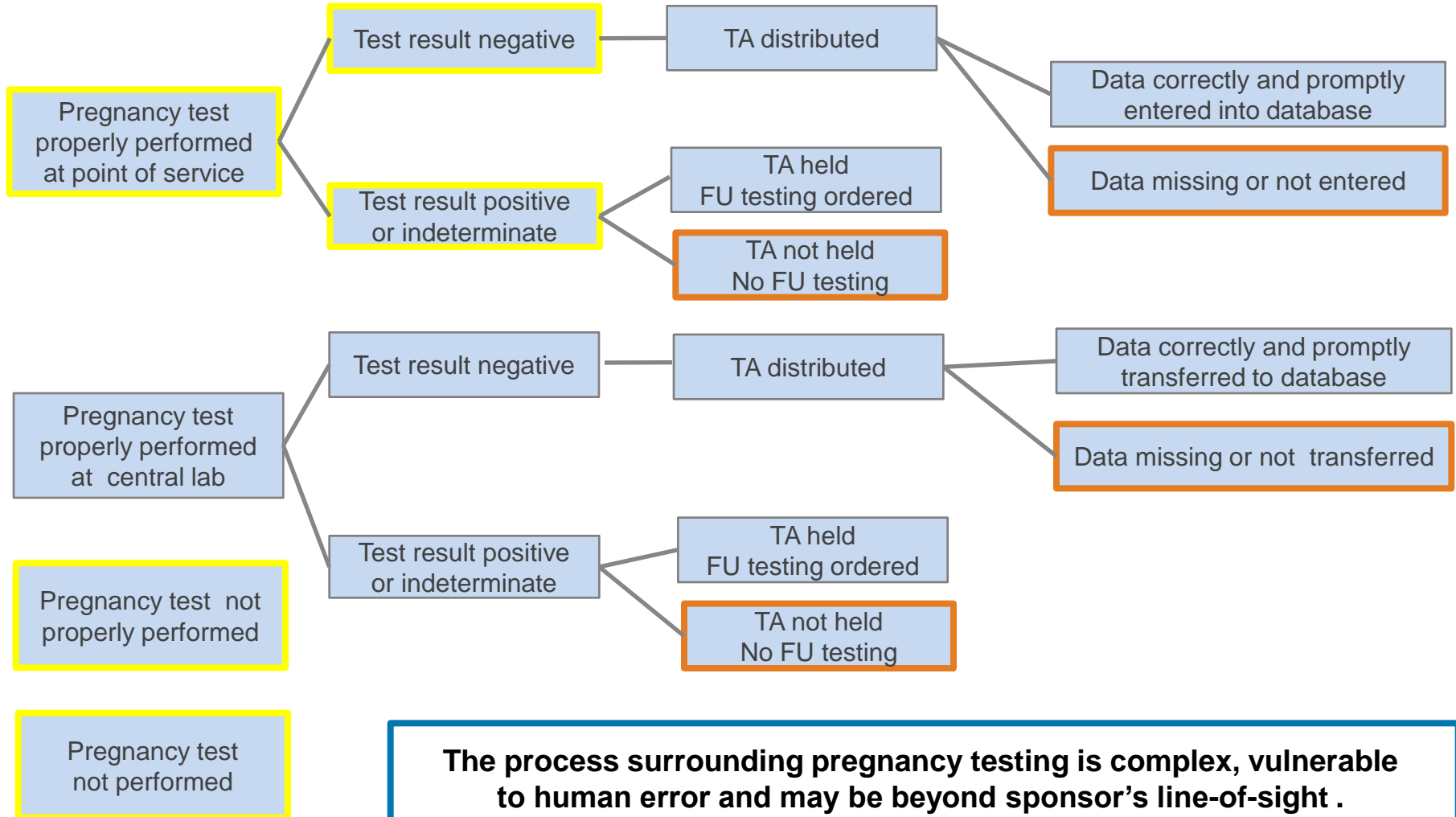
- All pregnancy tests are performed by a certified laboratory
- Two (2) negative tests are required before dispensing test article

The second negative test should be at least 19 days after the first and during the first 5 days of the menstrual period immediately preceding first dose.

- Pregnancy testing is repeated at all visits, a negative result is required to dispense test article



Pregnancy Testing for Clinical Trials



The process surrounding pregnancy testing is complex, vulnerable to human error and may be beyond sponsor's line-of-sight .

TA = Test article

= Breach of process and may be invisible to sponsor at time of activity

= Breach of process and visible to sponsor at time of activity



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Wish List:

- **Evidence-based proposals**
- **Standards, Recommendations, Best Practices should be differentiated and paired with rationale**
- **Proposals should be operationally-feasible (possible to implement and apply oversight)**

