FDA Regulations and Birth Defect Prevention: It's More Than Labeling

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Disclaimer

Opinions expressed in this presentation are those of the speaker and do not necessarily reflect official positions or policy of the FDA.

The following presentation is for educational purposes only. Questions regarding specific products should be referred to the Center/Division responsible for regulation of that product.

The speaker has nothing to disclose.

Overview

- **Introduction**
- **Review of Risk Management Programs**
- **Summary**

INTRODUCTION

What is the Risk?

- Of the 6 million pregnancies in the U.S. each year, ~50% are unplanned or unintended (CDC)
- Up to 70% of pregnant women take at least 1 prescription drug, with about ~50% taking ≥1 prescription drug during the first trimester (Mitchell, Gilboa, et al. 2011).
- The risk is unintended embryofetal exposure to a drug with teratogenic potential

Who is at Risk?

- Pregnant women
- Females of Reproductive Potential (FRP)
  - Girls who have entered puberty (menarche) and
  - all women who have a uterus and ovaries and have not passed through menopause
- May include female partners of male patients

Agency Approaches to Manage the Risk (1)

- Drugs and biologic products that are known or strongly suspected to be teratogenic should include a risk management plan if they are likely to be used by females of reproductive potential.
- Goal: To reduce exposure of the embryo or fetus to a drug with teratogenic potential

1. Approved Product Labeling
   - Includes Warning with description of teratogenic risk
   - Recommends pregnancy testing
   - Recommends contraception use
2. Risk Evaluation and Mitigation Programs (REMS)

Labeling Example - Vismodegib

5.1 Embryo-Fetal Toxicity

Based on its mechanism of action, Vismodegib can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. In animal reproduction studies, vismodegib was embryotoxic, fetotoxic, and teratogenic at maternal exposures lower than the human exposures at the recommended dose.

Verify the pregnancy status of females of reproductive potential within 7 days prior to initiating Vismodegib therapy. Advise females of reproductive potential to use effective contraception during therapy with Vismodegib and for 24 months after the final dose. Advise male patients to use condoms, even after a vasectomy, to avoid potential drug exposure in pregnant partners and female partners of reproductive potential during therapy and for 3 months after the final dose of Vismodegib. Advise pregnant women of the potential risk to a fetus *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

Labeling Example - Vismodegib

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential within 7 days prior to initiating Vismodegib therapy.

Contraception

Females

Based on its mechanism of action and animal data, Vismodegib can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].* Advise females of reproductive potential to use effective contraception during treatment with Vismodegib and for 24 months after the final dose.

Males

Vismodegib is present in semen *[see Clinical Pharmacology (12.3)]*. It is not known if the amount of vismodegib in semen can cause embryo-fetal harm. Advise male patients to use condoms, even after a vasectomy, to avoid potential drug exposure to pregnant partners and female partners of reproductive potential during therapy with and for 3 months after the final dose of Vismodegib. Advise males not to donate semen during therapy with and for 3 months after the final dose of Vismodegib.

History of Risk Management

- 2002 – FDA may recommend a risk management plan (RiskMAP) for higher risk drugs that carry substantial risk not sufficiently controlled with labeling
  - No authority to require labeling changes, risk communication, or postmarketing study
  - Often led to lack of commitment to conduct study
- 2006 – IOM report with recommendations for improvement of current system, included:
  - Clarify/strengthen existing postapproval authority
  - Enhance enforcement tools for postmarketing fulfillment of commitment

Risk Evaluation and Mitigation Strategy (REMS)

- 2007 - Food and Drug Administration Amendments Act (FDAAA) authorizes FDA to require a REMS:
  - Before approval if FDA determines a REMS is necessary to ensure the benefits of the drug outweigh the risks
  - After approval if FDA becomes aware of new safety information and determines that a REMS is necessary to ensure the benefits of the drug outweigh the risks

What is Considered in Determining Need for a REMS ?

- Size of the population likely to use the drug involved.
- Seriousness of the disease or condition to be treated with the drug.
- Expected benefit of the drug with respect to such disease or condition.
- Expected or actual duration of treatment with the drug.
- Seriousness of any known or potential adverse events that may be related to the drug.
- Whether the drug is a new molecular entity.

REMS Elements

- Patient Education (e.g., Patient Guide)
- Communication Plan (e.g., Dear Healthcare Provider (HCP) letter, professional medical societies)
- Elements to Assure Safe Use (ETASU)
- Implementation System
- Timetable for submission of assessments

Elements to Assure Safe Use (ETASU)

May include any or all of the following:

- Prescribers have specific training/experience or special certifications
- Pharmacists or other dispensers be specially certified
- Drug be dispensed only in certain healthcare settings (e.g., infusion settings, hospitals)
- Drug be dispensed with evidence of safe-use conditions such as laboratory test results
- Each patient using the drug be subject to monitoring
- Each patient using the drug be enrolled in a registry

REVIEW OF RISK MANAGEMENT PROGRAMS

REMS Example: Thalidomide

- Indicated for treatment of newly diagnosed multiple myeloma; acute cutaneous manifestations of erythema nodosum leprosum, approved in 2006, 1998
- Known human teratogen with very public history
- Risk management information in product labeling, had a prior Risk MAP, and currently has a REMS program with restricted distribution
- Prescribed by specialists
- Small percentage of females of reproductive potential population for labeled indication

REMS Thalidomide: Goal

1. To prevent the risk of embryo-fetal exposure to Thalidomide.
2. To inform prescribers, patients, and pharmacists on the serious risks and safe-use conditions for Thalidomide.

REMS Thalidomide: ETASU

- Healthcare provider certification
- Pharmacy certification
- Drug dispensed to patients enrolled in program with evidence or documentation of safe use conditions (i.e., pregnancy testing, contraception use)
- Pregnancy Exposure Registry to monitor outcomes

Thalidomide Analogues

Lenalidomide (approved 2005)

- Structurally related to thalidomide
- Thalidomide-like limb defects in offspring of pregnant monkeys
- RiskMAP (converted to REMS in 2010) similar to that for thalidomide

Pomalidomide (approved with REMS in 2013)

- Structurally related to thalidomide
- Malformations in offspring of rats and rabbits
- REMS similar to that for thalidomide and lenalidomide

Patient Survey on Thalidomide and Lenalidomide REMS

- Conducted between June 2012-2013
- 3.8% (n=2,780/73,645) of total patients enrolled in REMS completed survey
  - Most with being treated for multiple myeloma
  - 8.4% females of reproductive potential
  - >90% compliance with contraception requirements
  - 98% understood drugs can cause birth defects
- Survey does not necessarily report patient behavior
- No reported births with drug-associated congenital malformations

Brandenburg NA, Bwire R, Freeman J, Houn F, Sheehan P, Zeldis JB. Effectiveness of Risk Evaluation and Mitigation Strategies (REMS) for Lenalidomide and Thalidomide: Patient Comprehension and Knowledge Retention. Drug Safety. 2017;40(4):333-341.

REMS Example: Isotretinoin

- Indicated for treatment of severe recalcitrant nodular acne, approved in 1982
- Based on human experience, increased risk of major congenital malformations (i.e., craniofacial, cardiac, CNS, thymus and parathyroid), miscarriage and premature birth
- No “safe” window in pregnancy
- Mostly prescribed by dermatology or dermatologic surgery
- Significant number of females of reproductive potential at risk

History of Isotretinoin Risk Management Programs

- 1982 - Approved Labeling
- 1988 - Pregnancy Prevention Program
- 2002 - System to Manage Accutane Related Teratogenicity
- 2005 - RiskMAP
- 2006 - iPLEDGE with restricted distribution
- 2010 - Converted to REMS
  - single shared system ETASU REMS

REMS Isotretinoin: Goal

1. To prevent fetal exposure to isotretinoin
2. To inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions

REMS Isotretinoin: ETASU

- Healthcare provider certification
- Pharmacy certification
- Drug dispensed to patients enrolled in program with evidence or documentation of safe use conditions (i.e., pregnancy testing, contraception use)
- Pregnancy Exposure Registry to monitor outcomes

Compliance with Contraception Recommendations in iPLEDGE

- Pharmacy database study, analyses restricted to females of reproductive potential 13-45 years of age
- After iPLEDGE implementation,
  - Prescriptions to females dropped 33%
  - Median proportion of contraceptive use 32%, up from 29%
  - Contraceptive use increased by 1.3%, mostly in 13-18 year age group
- Surgical contraceptive methods and abstinence not captured
- Contraception use inadequate

Pinheiro SP, Kang EM, Kim CY, et al. Concomitant use of isotretinoin and contraceptives before and after iPledge in the United States. Pharmacoepidemiol Drug Saf 2013; 22: 1251–1257.

Ongoing Challenges with REMS

- Customization vs. Standardization
- Difficult to determine the appropriate trade off between enhanced safety and additional burden to the health care system
- Difficult to change human behavior; behavior is influenced by multiple factors and is difficult to observe and assess – so we rely on proxies
- Knowing where the failure in the healthcare system could occur and targeting best interventions to prevent or mitigate the failure
- Can track and measure system inputs but associating particular interventions with outcomes will continue to be difficult

Stakeholder Input

- Agency holds annual meetings to evaluate REMS of a specific drug at the Drug Safety and Risk Mitigation Advisory Committee.
- Regular Public Meetings and workshops to gain input on issues and challenges with REMS (i.e., 2010, 2013, 2015)
- REMS Integration Initiative
  - Develop guidance to provide more information on how to apply statutory criteria
  - Reduce variation, develop standardization and rigorous design of programs
  - Develop evidence-based approach for evaluating effectiveness and burden on healthcare system

SUMMARY

Summary

- FDA has authority to issue REMS as it deems necessary before or after drug product approval
- Ongoing program assessments and review
- Challenges remain
- Modifications as needed to improve program, while minimizing burden to prescriber/patient

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Thank You
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