

Review

An overview of upcoming changes in pregnancy and lactation labeling information

Juan F. MOSLEY II, Lillian L. SMITH, Megan D. DEZAN.

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ABSTRACT*

Background: Many medications can be used safely and effectively to provide health benefits for disease state management during pregnancy with minimal risk to the fetus or mother. Today nine out of ten women take at least one medication during pregnancy, and the number of women taking four or more medications has more than doubled over the past 30 years. However, the lack of safety data combined with the generalizations of the current risk category system (A, B, C, D, X) makes risk versus benefit assessment difficult.

Discussion: In response to these concerns, the U.S. Food and Drug Administration (FDA) has decided to implement a new pregnancy and lactation labeling rule designed to improve risk versus benefit assessment of drugs used in pregnant and nursing mothers; this rule is set to take effect in June of 2015. This change is designed to provide clear and detailed information for both patients and healthcare providers pertaining to three main categories: pregnancy, lactation, and females and males of reproductive potential. The new labeling rule also removes the previous letter risk categorization system.

Conclusion: The upcoming changes regarding pregnancy and lactation safety labeling are going to have a vast impact on drug safety interpretation and prescribing practices. While this rule will provide practitioners with more detailed information pertaining to pregnancy, lactation, and reproduction, it will also place more responsibility on the practitioners to ensure the safety of their patients. This review will summarize these changes and discuss their potential effect on clinical practice.

Keywords: Drug Labeling; Pregnancy; Lactation; United States Food and Drug Administration; United States

INTRODUCTION

On December 4, 2014 the U.S. Food and Drug Administration (FDA) passed a new rule to implement new labeling requirements for pregnancy and lactation to take effect June 2015.¹ This new rule was designed to address several of the concerns regarding the old labeling system and the need for better information regarding pregnancy and lactation. In today's society medication is vital to disease state management, even in pregnancy when additional precautions regarding the fetus have to be taken into the consideration of care. The number of pregnant women taking medications has more than doubled over the past 30 years, and now nine out of ten women take at least one medication while pregnant.¹ According to the Centers for Disease Control, 65% of women reported using acetaminophen while pregnant and 29.7% reported using antibiotics.² The drastic increase in use of prescription and non-prescription medications during pregnancy has highlighted the need for more information about the use of medications during pregnancy. This new rule standardizes the format for providing information about the risks and benefits of prescription drug use and biological agents, and was designed to facilitate the prescriber counseling for these populations. The new format will remove the old letter risk categorization system (A, B, C, D, X), and provide more complete information to providers and patients pertaining to three main categories: pregnancy, lactation, and females and males of reproductive potential. These changes have been designed to address former concerns regarding the old labeling information, and provide information to promote better prescribing practices in these patient populations.

BACKGROUND AND HISTORY OF CURRENT PREGNANCY CATEGORIES

The first regulations regarding drug labeling were introduced in the U.S. beginning in 1962 in response to the thalidomide disaster that occurred during this time.³ During that time thalidomide was being used for nausea and vomiting during pregnancy, but caused tragic fetal abnormalities including the underdevelopment of extremities. This medication was set to be approved in 1960, but was denied due to lack of safety data. Although it was not approved, thalidomide was sent to several physicians throughout the country and caused 17 confirmed cases of phocomelia.³ This tragic incidence brought to light the imminent need to assess all medications for safety of use during pregnancy. This resulted in the Kefauver-Harris Amendments passed by congress in 1962.³ These

* **Juan F. MOSLEY II.** Pharm. D., AAHIVP. Assistant Professor of Pharmacy Practice. Florida Agricultural & Mechanical University. Tallahassee, FL (United States). juan.mosley@famou.edu

Lillian L. SMITH. Pharm.D., MBA. Assistant Professor of Pharmacy Practice. Florida Agricultural & Mechanical University. Tallahassee, FL (United States). lillian.smith@famou.edu

Megan D. DEZAN. Pharm.D. Florida Agricultural & Mechanical University. Tallahassee, FL (United States). Megan1.dady@famou.edu

amendments to the Federal Food, Drug, and Cosmetic Act (F, D, & C) established framework for manufacturers to prove that medications were both safe and effective. The amendment addressed several of the shortcomings of the F, D, & C act and prevented medications from being sold on the market without proven safety and efficacy. Some of the requirements put into place by this act include: effectiveness proven by well-designed clinical trials, allows the FDA 180 days to approve a new drug application before it can be released to market, demanded post-marketing evaluation of drugs, and allowed the FDA to control marketing of drugs to consumers.⁴ Overall, all of these changes required manufacturers to go to greater lengths to prove their drug to be safe and effective before hitting the market, and allowed the FDA to become the ultimate controlling force of drugs manufactured in the United States.

In 1979, the FDA introduced the 1979 Labeling for Prescription Drugs Used In Man that included pregnancy labeling the ranking system still in use today for the purpose of classifying drug products according to the risks posed to the fetus and the benefits posed to the pregnant woman.³ This proved to be a crucial turning point for the improvement safety and efficacy of medications. This rule proposed the first system to assess risk of medications to the fetus during pregnancy. The labeling system based its criteria on the amount and quality of research done on a medication pertaining to pregnancy and findings of that research. When assigning a drug to a category many variables would be considered such as if the research was based on human studies or animal studies, what the outcomes of the studies done were, and benefits vs. risk for the mother and fetus. Unfortunately, many drugs did not have adequate research performed to thoroughly assess risk and consequently all were placed in similar categories despite what actual risk they may pose. This system has received an abundance of criticism over the years. Some of the main concerns emphasized have included that the categories imply that the degree of risk increased with each letter (not based on research available), all drugs within a category do not pose equal risk of fetal toxicity, and that fetal development toxicities are not clearly distinguished by severity, incidence or type. The upcoming changes attempt to remedy these concerns by providing narrative summaries of risk posed by drugs during pregnancy, lactation, and reproductive potential.

In 2006, the final rule on “Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products” mandated the subsections of pregnancy, labor and delivery, and nursing mothers be moved to a “special populations” section rather than “precautions” within the prescribing information in an attempt to make the information more easily identified by practitioners.¹ Subsequently, after years of research and expert input from several advisory meetings, the FDA proposed a rule to reformat the subsections and altogether remove the pregnancy categories from prescribing information. After several years of revisions, this rule was passed in

December of 2014 and set to take effect in June of 2015.

UPCOMING CHANGES IN LABELING

The new ruling attempts to address present concerns by providing narrative summaries of risk posed by drugs during pregnancy, lactation, and reproductive potential.⁵ The new format will include three sections: pregnancy, lactation, and a new section on females and males of reproductive potential.¹ This is in contrast to the previous sections that included information on pregnancy, labor and delivery, and nursing mothers. In addition, each section will include a detailed risk summary, clinical considerations section, and relevant data section. The biggest upcoming change; however, will be the phasing out of the category system. New medications approved after June 2015 will no longer be assigned a safety category, and in addition all drugs previously approved after June 30, 2001 will have a minimum of 3 years to submit updated labeling requirement information.¹

Pregnancy

This section will give an overview of fetal development abnormalities from drug exposure and provide any information regarding use of the medication during labor and delivery. The likelihood of these abnormalities will be discussed in a “fetal risk” subheading as well as if this data came from human or animal studies.¹ If outcomes are based on human data this section will provide information on the incidence, severity, and reversibility of the developmental abnormalities. Information for practitioners regarding prescribing and patient education will be included as part of “clinical considerations” subheading.¹ In addition, recommendations on advisability of treatment and effects of disease for mother and fetus if left untreated will be discussed. Any dosing adjustments will be highlighted, and alternative treatment possibilities will be presented if appropriate. In addition, a “data” subheading will provide a detailed analysis of clinical trial data and post-marketing data to support the fetal risk summary and clinical considerations.¹ Using the information provided in this section, the provider will then perform a benefit vs. risk assessment and use sound clinical judgment to make prescribing decisions.

Lactation

This section will replace the former “breastfeeding mothers” section under the old labeling system. All medications will be required to have a “Lactation” section to provide practitioners valuable information about whether this medication is safe in breastfeeding women.¹ It will include information on how much of a drug is secreted in breast milk, and how this amount compares to blood concentrations at steady state under the “Risk Summary” heading.¹ Using this information, the consumption of the drug consumed by the infant will be estimated. Any study information that is available assessing the infant’s absorption and exposure will be summarized, as well as the effects seen in the infant. Based on this

information, recommendations to the provider on how to reduce or avoid exposure to the infant, if deemed necessary, can be found under the "Clinical Considerations" subheading.¹ All available safety data supporting the recommendations for use will be summarized under the "Data" subheading for the practitioner to consider when weighing risk vs. benefit and prescribing the medication.¹

Females and males of reproductive potential

This section will allow providers to easily and quickly find information regarding contraception recommendations, pregnancy testing, and information about infertility before, during, and after drug therapy. This section will give an overview of any precautions that should be made when patients are using this medication, and will provide any clinical trial or post marketing data to support recommendations that are made.¹ Other information, such as safety registries patients must enroll in, may be included in this section based on the medication's profile. Providers can use this section to identify whether or not a patient is a good candidate for the medication, and to understand what counseling points should be discussed with the patient regarding potential reproduction.

PHASING OUT OF PREGNANCY CATEGORIES

The new rule has also set up guidelines to phase out the old letter risk category system (A, B, C, D, and X). Over the years the FDA has learned that pregnancy categories were heavily relied upon by clinicians to make prescribing decisions but were often mis-interpreted and misused. Decisions were made based on the pregnancy category rather than the understanding of underlying information that placed a particular medication in that category.¹ The goal of this change is to aid in eliminating the confusion and ambiguity associated with medication use and fetal risk. The new rule provides guidelines on standard language that will be used to describe risk for drugs in which only animal studies are available (e.g. unknown, none, low, moderate, or high).⁵ Once the rule takes effect, it will require all new drugs to adhere to the new labeling requirements. In addition, it requires that all previous pregnancy risk categories be removed within 3 years.¹ The 3-year transitional period may lead to some confusion for practitioners, and raise some safety and effectiveness concerns for providers attempting to optimally treat their patients during the transition. Providers will have to use both the new and old systems to determine safety and effectiveness of treatments during this time, and will rely heavily on their clinical judgment to make decisions. With these new changes it is also emphasized that treatment should include making patient specific education health care decisions rather than a one size fits all approach. It will be prudent for health care providers to be very knowledgeable about both category systems when making clinical judgments.

EFFECT OF CHANGES IN PRACTICE

These various changes will undoubtedly make a huge impact on healthcare practice. With these changes a huge amount of responsibility will be placed in the provider's hands to be educated on the risks associated with medications. While developing this new rule the FDA received a significant amount of feedback from advocacy groups, medical associations, pharmacists, and drug manufacturers supporting the changes stating that the previous system was "confusing and misleading".¹ Some concern was also expressed about the narrative format not facilitating a consistent decision-making process for prescribers.¹ The FDA feels that the previous system oversimplified the decision making process, and that the new system is designed to better facilitate prescribing.¹ It is designed to help practitioners consider not only fetal risk, but a variety of factors including severity of maternal disease, impact of disease on the fetus, co-existing conditions, and alternative therapies to treatment. Providers will need to make clinical decisions based on each patient and the new information provided rather than just depending on the category it falls within for treatment decisions. This will require providers to become more educated about the potential risks and benefits of the medications for the safety of their patients. This change has many benefits, but also poses some risks. The benefits of these changes are due to more detailed information provided to help guide practitioners when prescribing medications. However, these changes also have the potential to put both the patient and prescriber at more risk of negative outcomes if recommendations are unclear or the practitioner does not do proper research to gain complete understanding of the risks and benefits of treatment. Practitioners should use caution and sound clinical judgment when assessing the safety data provided to support the use of medications when weighing potential benefits to the risk they may propose.

CONCLUSIONS

Today's drug and research industry is rapidly growing and changing. This requires the ongoing revision of current policies and procedures to ensure maximum patient safety supported by clinical data, when available. The upcoming changes regarding pregnancy and lactation safety labeling are going to have a vast impact on drug safety interpretation and prescribing practices. With this new rule, more detailed information will be available to help guide providers when making clinical decisions in patients who are pregnant and breastfeeding. However, this new system also implies more responsibility on the practitioners to ensure the safety of their patients. Practitioners must make every effort to be educated and well-informed about the risks associated with medications they prescribe. Overall, the hopes of this new rule are to improve safety and reduce risk in patients who are of childbearing age, pregnant, and/or breastfeeding.

CONFLICT OF INTEREST

The authors of this manuscript report no conflicts of interest including, but not limited to, consulting fees, paid expert testimony, employment, grants, honoraria, patents, royalties, stocks, or other financial or material gain that may involve the subject matter of the manuscript.

REVISIÓN DE LOS PRÓXIMOS CAMBIOS EN LA INFORMACIÓN SOBRE MEDICAMENTOS EN EMBARAZO Y LACTACIÓN

RESUMEN

Antecedentes: Muchos medicamentos pueden ser utilizados con seguridad y efectividad para mejorar la salud en la gestión de enfermedades durante el embarazo con mínimo riesgo para la madre o el feto. Hoy, 9 de cada 10 mujeres toman al menos un medicamento durante el embarazo, y el número de ellas que toma 4 o más medicamentos se ha más que doblado en los últimos 30 años. Sin embargo, la falta de datos de seguridad, combinada con las generalizaciones de la actual categoría de riesgos (A, B, C, D, X) hace difícil la evaluación riesgo contra beneficio.

Discusión: En respuesta a estas preocupaciones, la U.S. Food and Drug Administration (FDA) ha decidido

implantar una nueva regla de información en embarazo y lactación diseñada para mejorar la evaluación riesgo contra beneficio de los medicamentos usados en madres embarazadas o lactando; esta regla entrará en vigor en junio de 2015. Este cambio está diseñado para proporcionar una información clara y detallada tanto para pacientes como para profesionales de la salud comprendiendo 3 apartados principales: embarazo, lactación, y potencial reproductivo masculino y femenino. La nueva información elimina el anterior sistema de categorización por letras.

Conclusión: Los próximos cambios en la información de seguridad de embarazo y lactación van a producir un gran impacto en la interpretación de la seguridad en las prácticas de prescripción. Mientras esta regla proporcionará a los facultativos una información más detallada sobre embarazo, lactación y reproducción, también les dará más responsabilidad para asegurar la seguridad de sus pacientes. Esta revisión resume estos cambios y discute sus efectos potenciales sobre la práctica clínica.

Palabras clave: Etiquetado de Medicamentos; Embarazo; Lactación; United States Food and Drug Administration; Estados Unidos

References

1. Department of Health and Human Services. Food and Drug Administration. 21 CFR Part 201. Content and Format of Labeling Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling. Published 12/04/2014. Available at: <http://www.fda.gov/OHRMS/DOCKETS/98fr/06-545.pdf> (accessed March 20, 2015).
2. Centers for Disease Control and Prevention. Treating for Two: Data and Statistics. Updated: February 19, 2014. Available at: <http://www.cdc.gov/pregnancy/meds/treatingfortwo/data.html> (accessed March 20, 2015).
3. Ramoz LL, Patel-Shori NM. Recent Changes in Pregnancy and Lactation Labeling: Retirement of Risk Categories. *Pharmacotherapy*. 2014;34(4):389-395. doi: 10.1002/phar.1385
4. Food and Drug Administration. Kefauver-Harris Amendments Revolutionized Drug Development. Published October 2012. Available at: <http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM322886.pdf> (accessed March 20, 2015).
5. Aschenbrenner DS. Drug Watch: The FDA Proposes Revisions to Pregnancy Information in Drug Labeling. *Am J Nurs*. 2008;108 (11):32-34.
6. U.S. Food and Drug Administration. Promoting your health. Pregnancy and Lactation Labeling Final Rule. Published 12/3/2014. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm425317.htm> (accessed: March 20, 2015).