FDA Actions to Improve Prescription Drug Labelling for Pregnancy

When healthcare providers look to prescribe a medication, ideally their decision is clear cut because ample clinical data exist in the relevant study populations. In reality, however, it is not uncommon that certain patient populations are not yet well captured, if at all, in prescription drug labelling. This is the case for pregnant women, who usually are actively excluded from clinical trials. Actions by the US Food and Drug Administration (FDA) in recent years, including the issuance of new regulations and guidance documents, aim to remedy this shortcoming.

In April 2018, the FDA released the draft guidance for industry, *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials*, to support an informed and balanced approach to gathering data on the use of drugs and biological products (hereafter referred to as "drugs") during pregnancy. The guidance is intended to serve as a focus for continued discussions among various entities (e.g., the FDA, pharmaceutical manufacturers, academia, institutional review boards) that are involved with the conduct of clinical trials in pregnant women.

The FDA explained in the Federal Register notice[1] announcing the availability of the guidance that safety data collection on prescription drugs used during pregnancy usually occurs after approval, and clinicians and patients must undertake a risk-benefit analysis for the use of such products in pregnant women with limited human safety information. Historically, pregnant women have been an understudied population and there have been barriers to obtaining data from pregnant women in clinical trials (e.g., concerns about protecting women and their foetuses from research-related risks). However, data are needed to inform safe and effective treatment during pregnancy. Further, in certain situations it is ethically and scientifically appropriate to collect data in pregnant women in clinical trials conducted during drug development.

The draft guidance notes that there are more than 60 million women in the US between the ages of 15 and 44 years, and nearly four million births per year. As with women who are not pregnant, some expectant women need to use drugs to manage chronic disease conditions or treat acute medical problems. There are numerous reasons to consider the inclusion of pregnant women in clinical trials, the FDA states, including the following:

- Women need safe and effective treatment during pregnancy.
- Failure to establish the dose/dosing regimen, safety, and efficacy of treatments during pregnancy may compromise the health of women and their foetuses.
- In some settings, enrolment of pregnant women in clinical trials may offer the possibility of direct benefit to the woman and/or foetus that is unavailable outside the research setting.
- Development of accessible treatment options for the pregnant population is a significant public health issue.

Another reason to conduct dedicated clinical evaluation of pregnant women is that extensive physiologic changes associated with pregnancy may alter drug pharmacokinetics (PK) and pharmacodynamics (PD). Altered PK and PD directly affect the safety and efficacy of a drug administered to a pregnant woman through changes in drug absorption, distribution, metabolism, and excretion.

As detailed in the October 2004 draft guidance for industry, *Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling*, generally the safety and efficacy of a drug are established for a particular dosage regimen or range of dosage regimens in late-phase (Phase 3) clinical trials involving relatively typical representatives from the target patient population. Pregnant women are actively excluded from these trials and, if pregnancy does occur, the usual procedure is to discontinue treatment and drop the subject from the study.

The 2004 guidance explains that extrapolation of PK data from studies performed in non-pregnant adults fails to account for the impact of the many physiologic changes that occur during pregnancy. These changes are not fixed throughout pregnancy and instead reflect a continuum of change as pregnancy progresses, with return to baseline at various rates in the postpartum period. As noted earlier, physiologic changes have the potential to alter the PK and/or PD of drugs. Some of these changes include:

- Changes in total body weight and body fat composition.
- Delayed gastric emptying and prolonged gastrointestinal transit time.
- Increased extracellular fluid and total body water.
- Increased cardiac output, increased stroke volume, and elevated maternal heart rate.
- Decreased albumin concentration with reduced protein binding.
- Increased blood flow to the various organs (e.g., kidneys, uterus).
- Increased glomerular filtration rate.
- Changed hepatic enzyme activity.

Guidelines for Including Pregnant Women in Clinical Trials

The April 2018 guidance provides general guidelines for including pregnant women in clinical trials with the recognition that every drug development situation is unique, and individualised approaches to clinical trial design may be required to facilitate inclusion of pregnant women in specific drug development plans. In the guidelines, the agency notes that "adequate non-clinical studies," as covered below, refers to recommendations for the design and conduct of reproductive toxicology and other non-clinical studies described in the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (2010) and *S5(R2) Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility* (1996).

According to the FDA, it is ethically justifiable to include pregnant women with a disease or medical condition requiring treatment in clinical trials under these circumstances: post-market (i.e., FDA-approved drugs), pre-market (i.e., investigational drugs), and in women who become pregnant while enrolled in a clinical trial. Requirements for each category are as follows:

- **Post-market –** The FDA requires that: 1) adequate non-clinical studies (including studies on pregnant animals) have been completed; 2) there is an established safety database in non-pregnant women from clinical trials or preliminary safety data from the medical literature and/or other sources regarding use in pregnant women; and 3) efficacy cannot be extrapolated and/or safety cannot be assessed by other study methods.
- **Pre-market –** The FDA requires that: 1) adequate non-clinical studies (including studies on pregnant animals) have been completed; and 2) the clinical trial holds out the prospect of direct benefit to the pregnant woman and/or foetus that is not otherwise available outside the research setting or cannot be obtained by any other means (e.g., the woman may not have responded to other approved treatments or treatment options may not exist).
- **Pregnancy onset during a clinical trial –** The FDA stipulates that unblinding should occur so that counselling may be offered based on whether the foetus has been exposed to the investigational drug, placebo, or control. The risks and benefits of continuing versus stopping investigational treatment can be reviewed with the pregnant woman. Pregnant women who choose to continue in the clinical trial should undergo a second informed consent process that reflects these additional risk-benefit considerations.

If foetal exposure has already occurred, the FDA advises that a woman who becomes pregnant while enrolled in a clinical trial should be allowed to continue on the investigational drug if the potential benefits of continued treatment for the woman outweigh the risks of ongoing foetal exposure to the investigational drug, of discontinuing maternal therapy, and/or of exposing the foetus to additional drugs if placed on an alternative therapy. Regardless of whether the woman continues in the trial, it is important to collect and report the pregnancy outcome, the FDA states.

Among the concluding sections in the April 2018 guidance, sponsors are advised to consider the following issues when designing a clinical trial that will include pregnant women: disease type and availability of therapeutic options in the pregnant population, timing of enrolment, PK data, safety data collection and monitoring, and stopping a clinical trial that enrolls pregnant women. Public comments on the guidance were due to the FDA by June 8, 2018 (Docket No. FDA-2018-D-1201).

New Pregnancy Final Rule

Regulations are another avenue through which the FDA is working to address pregnancy-related deficiencies in prescription drug labelling. In December 2014, the FDA published a final rule – the Pregnancy and Lactation Labeling Rule (PLLR) – to enhance the safe and effective use of prescription drugs in pregnant women, lactating women, and females and males of reproductive potential[2,3]. The PLLR, which took effect June 30, 2015, amended the FDA's regulations governing the content and format of the "Pregnancy," "Labor and Delivery," and "Nursing Mothers" subsections of the USE IN SPECIFIC POPULATIONS section (section 8) of labelling for human prescription drugs (Figure 1). Also unique to the PLLR is the requirement of a "Risk Summary" subheading under the "Pregnancy" and "Lactation" subsections.

Source: FDA

Figure 1

The PLLR applies to holders of applications – new drug applications (NDAs), biologics license applications (BLAs), and efficacy supplements – that are required to comply with the Physician Labeling Rule (PLR)[4], a final rule that governs the content and format of labelling for human prescription drugs. Applications approved on or after June 30, 2001, are subject to the PLR, which took effect June 30, 2006.

The goal of the PLR requirements, as described in 21 Code of Federal Regulations (CFR) 201.56 and 201.57, is to enhance the safe and effective use of prescription drugs by giving healthcare providers clear and concise prescribing information that is easier to access, read, and use. The PLR format also makes prescribing information more accessible for use with electronic prescribing tools and other electronic information resources.

Applications subject to the PLR must have the content and format of their pregnancy and lactation sections in labelling revised according to the implementation plan published in the PLLR (Table 1). The final rule also requires the removal of the pregnancy categories A, B, C, D, and X from *all* drug product labelling, which includes applications approved before June 30, 2001 (i.e., those not subject to the PLR).

In its rationale for the PLLR provisions, the FDA explained that the pregnancy categories are often viewed as confusing and overly simplistic and do not accurately and consistently communicate differences in degrees of foetal risk. According to the FDA, a narrative structure for pregnancy labelling, rather than a category system, is best able to capture and convey the potential risks of drug exposure based on animal or human data, or both.

Issued concurrently with the PLLR was a draft guidance for industry, *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*, intended to assist applicants in complying with the new content and format requirements. In June 2015, the FDA released a final guidance for industry, *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format, Small Entity Compliance Guide*, intended to help small businesses better understand and comply with the new requirements.

PLLR Implementation

Progress updates and lessons learned with implementation of the PLLR have been shared by the FDA at public meetings over the last year. At the Prescription Drug Labeling Conference 2017, hosted by the FDA's Center for Drug Evaluation and Research and Small Business and Industry Assistance (CDER SBIA) Regulatory Education for Industry (REdI) in November, presentations included members of the Maternal Health Team (MHT) in the Division of Pediatric and Maternal Health, Office of New Drugs, CDER.

Tamara Johnson, MD, MS, lead medical officer, MHT, presented data on the tracking of drug product labelling compliance with the PLLR. Since June 30, 2015, more than 500 product labels have been converted to comply with the PLLR format. Future PLLR

submissions anticipated via prior approval supplement (PAS) are approximately 400, 800, and 300, respectively, for the 2018, 2019, and 2020 cohorts (Table 1). Johnson noted that, at the time, the FDA was still working through public comments received on the PLLR guidance (Docket No. FDA-2014-D-1551 closed on February 2, 2015). She added that the FDA plans to expand subsection 8.3 ("Females and Males of Reproductive Potential"), which currently is slim.

Applications requried to conform to new pregnancy/lactation content requirements	Time by which labeling with new pregnancy/ lactation content must be submitted to the FDA for approval
New or Pending Applications	
Submitted on or after the effective date of the final rule	Time of submission
Pending on the effective date of the final rule	4 years after the effective date of the final rule or at time of approval, whichever is later
Approved Applications Subject to the PLR	
Approved any time from June 30, 2001, up to and including June 29, 2002, and from June 30, 2005, up to and including June 29, 2007	3 years after the effective date of the final rule (2018 cohort)
Approved any time from June 30, 2007, up to and including the effective date of the final rule	4 years after the effective date of the final rule (2019 cohort)
Approved from June 30, 2002, up to and including June 29, 2005	5 years after the effective date of the final rule (2020 cohort)

Table 1: PLLR Implementation Plan

Another speaker with the MHT, Jane Liedtka, MD, medical officer, covered considerations and emerging best practices for PLLR labelling conversion. She outlined that the submitted labelling should comply with the PLLR format; reflect an integrated assessment of known risks relevant to pregnancy, lactation, and infertility based on available information/data; and be accompanied by a summary and review of the available relevant information/data that supports labelling content. If a submission lacks information/data to support PLLR-compliant labelling content, this would not be grounds for a refuse-to-file letter, Liedtka said. Instead, the review division may issue an information request (IR), the response to which could be considered by the FDA to be a major amendment to the submission.

Updates on the PLLR were shared more recently at a meeting of the FDA's Risk Communication Advisory Committee (RCAC) on March 5–6, 2018. This public session was convened by the agency to discuss the impact of pregnancy and lactation labelling information in prescription drugs as modified under the PLLR. In a background packet issued ahead of the meeting, the FDA provided a revised prediction for the number of PLLR labeling conversions anticipated for 2018 (approximately 450). Of the more than 500 product labels that have been converted in the past two years to comply with the PLLR, the agency noted that fewer than 25% include human data. To demonstrate the limitations of available data, and challenges with providing a clear conclusion based on available human data, labelling examples complying with the PLLR were shared (Table 2).

Among the discussion questions, the RCAC was asked to consider how effective the PLLR has been in conveying safety evidence in pregnancy that is useful to benefit-risk decision-making. While there was agreement that use of the pregnancy categories A, B, C, D, and X was problematic, panellists in their discussion repeatedly returned to the possibility of incorporating a new type of heuristic (e.g., a star/grading system). A drawback of the current PLLR format, it was noted, is that the required risk summaries largely rely on the healthcare providers to deduce the quality of the evidence.

Example	Human Data	Animal Data
Solosec (secnidazole)	Limited data from cases reported in pharmaco-vigilance database	No adverse developmental outcomes
Xenazine (tetrabenazine)	Limited data from published case report	Adverse develop-mental outcomes
Segluromet (ertugliflozin, metformin hydrochloride)	Human data with metformin hydrochloride component from observational studies	Adverse develop-mental outcomes due to ertugliflozin component
Zofran (ondansetron)	Data from observational studies; inconsistent findings	No adverse developmental outcomes
Enbrel (etanercept)	Data from pregnancy registry and an observational study	
Trizivir (abacavir/lami-vudine/zidovudine)	Data from pregnancy registry	Inconsistent findings between animal species
Menactra [meningo-coccal (groups A, C, Y and W-135) polysaccha-ride diphtheria toxoid conjugate vaccine]	Limited data from pregnancy registry	No adverse developmental outcomes

Table 2: Examples of PLLR Labeling

Panellists agreed that an improved system would provide the necessary, consistent structure to help summarise the information and permit the healthcare provider to access and interpret it efficiently at the point of care. They advocated that the approach should also communicate the strength and quality of the evidence, such as through the use of confidence intervals and forest plots. Members acknowledged that risk summarisation becomes complicated when there are multiple risks to consider.

One of the challenges is the tendency to oversimplify information, said RCAC member Andrew Pleasant, PhD, senior director for health literacy and research, Canyon Ranch Institute. "The job is not to simplify," Pleasant said. "The job is to explain complexity in a clear and usable fashion, and that means you have to embrace the complexity and not be afraid of it."

REFERENCES

1. Federal Register: April 9, 2018 (Volume 83, Number 68) (Pages 15161 – 15162)
2. Federal Register: December 4, 2014 (Volume 79, Number 233) (Pages 72064 – 72103)
3. Komlos, D. New Pregnancy Labelling for Risk Communication. Journal for Clinical Studies. 2015; Volume 7 Issue 1, Watch Pages 8-9
4. Federal Register: January 24, 2006 (Volume 71, Number 15) (Pages 3922 – 3997)

Deborah A. Komlos

Deborah A. Komlos, MS, is the Senior Medical & Regulatory Writer for the Cortellis Regulatory Intelligence US module at Clarivate Analytics. In this role, her coverage centres on FDA advisory committee meetings, workshops, and product approvals. Her previous positions have included writing and editing for magazines, newspapers, online venues, and scientific journals, as well as publication layout and graphic design work.

Email: deborah.komlos@clarivate.com