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Roche

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: *Docket No. 02D-0388: Guidance for Industry on Establishing Pregnancy Exposure Registries; 67 Fed. Reg. 59528 (September 23, 2002).*

Dear Sir or Madam:

Thank you for the opportunity to comment on FDA's final guidance, "Establishing Pregnancy Exposure Registries." The document is intended to provide sponsors with guidance on how to establish pregnancy exposure registries to monitor the outcomes of pregnancies exposed to specific medical products. The guidance provides sponsors with recommendations on how to establish registries, how to help ensure the quality and integrity of registry data, and how to help ensure the adequacy of document registry research methods. 67 *Fed. Reg.* 59528 (September 23, 2002).

As you know, Hoffmann-La Roche (Roche) has significant experience with pregnancy exposure concerns through the development of risk management programs for the drug Accutane® (isotretinoin). As a result of Accutane's teratogenic effects, Roche places the utmost importance on risk management mechanisms to prevent pregnancies in women taking Accutane. We also participate in the anti-retroviral registry and we are working to design a ribavirin registry.

As a general matter, the guidance states that the ultimate goal of pregnancy exposure registries is "to provide clinically relevant human data that can be used in a product's labeling to provide medical care providers with useful information for treating or counseling patients who are pregnant or anticipating pregnancy." However, the guidance does not provide significant guidance regarding what should be done with the information that is obtained from a registry. For example, the guidance would provide additional benefit if it discussed how the data obtained from the registry can be used to determine if a label change is needed. In establishing a registry, it is important to consider how the information ultimately might be used.

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Roche has the following additional comments:

Section II, Background. The guidance states that the limitations of spontaneous reporting data include, among other limitations, a "lack of controls." However, Roche notes that it is possible to utilize controls with spontaneous reporting data. Roche often analyzes spontaneous adverse event reports using Proportional Reporting Ratios (PRRs) and compares the drug at issue to a background of other drugs; the background could include all drugs or a class of drugs known to cause problems in pregnancy (or a control group that have taken a non-teratogen to see what the underlying base-rate is). Therefore, while spontaneous reports obviously have implicit limitations, they still can provide useful data. Roche agrees however, that many of the limitations associated with spontaneous reporting can be overcome through the use of prospective pregnancy exposure registries.

Section III, What is a Pregnancy Exposure Registry. The guidance describes a pregnancy exposure registry as a "prospective observational study." Roche disagrees with this characterization of pregnancy exposure registries. Registries are not set up like formal epidemiologic studies, with a well-defined null hypothesis upon which is based the sample size calculation. Most registries look for multiple endpoints and are often hypothesis-generating, as opposed to hypothesis-testing. Therefore, pregnancy exposure registries should not solely be characterized as prospective observational studies.

The Guidance states that a single registry can collect data on many pregnancy outcomes. Registries also potentially can collect data on more than one drug, such as an antiretroviral registry. Thus, the issue is raised as to how to handle data on an individual who has been on multiple drugs. It would be helpful if the guidance included information about how the registries can be designed to collect information on multiple drugs.

The guidance states that pregnancy exposure registries "provide margins of reassurance regarding the lack of risk when a precise measure is impossible. . .". In reality, providing reassurance regarding "lack of risk" is proving a negative, which is not possible. Therefore, a more accurate description of pregnancy registries is that they "provide some margin of reassurance regarding absolute risk when a precise measure is impossible."

This section concludes by stating that "A pregnancy exposure registry ***is not*** a pregnancy prevention program." While Roche recognizes that the two are not equivalent, Roche believes that it is important to include risk management considerations when designing a pregnancy exposure registry. A pregnancy exposure registry involves collecting data on potential teratogens, and thus it is important that a company include consideration of a pregnancy prevention component as part of the overall effort.

Section IV, What Medical Products Make Good Registry Candidates? The guidance states that the "positive and negative predictive values of [animal reproductive toxicology studies] for humans are often uncertain" (*citing* Mitchell 2000). Therefore, FDA recommends that,

regardless of findings from animal studies, pregnancy exposure registries be considered when the product likely will be used during pregnancy. Roche notes that this potential problem is not unique to animal toxicology studies. Rather, registries can present a similar problem because they may have high false positive or negative rates and thus, the predictive value of a registry may be uncertain as well. Furthermore, Roche believes that the guidance should recognize the potential benefits of animal toxicology studies as well as the potential drawbacks, and explain the role of such studies in pregnancy exposure registries.

In addition, the guidance recommends that a pregnancy exposure registry be "seriously considered when it is likely that the medical product will be used during pregnancy as therapy for a new or chronic condition." First, such a broad category might include most marketed drugs. Second, this situation presents quite differently from when a teratogenic drug is being used and a pregnancy exposure registry is intended to track unintended pregnancies while undergoing treatment. Therefore, the guidance should distinguish between these situations and should point out differences in sections of the Guidance where the information might differ depending on the purpose of the registry. The Guidance should also distinguish a registry from the normal collection of data on pregnancies by manufacturers as part of safety reporting activities.

Section VI, What Should One Consider When Designing a Registry? The guidance states that one of the potential objectives when designing a registry may be to test a single specific hypothesis. It is unclear why a pregnancy exposure registry would be designed for this purpose. For example, a pregnancy exposure registry would not be set up to test if a drug is a teratogen. As discussed earlier, a pregnancy registry should not be considered akin to a prospective observational study.

This guidance, and in particular this section, does not reference the Health Insurance Portability and Accountability Act (HIPAA) and related privacy regulations. When designing a registry, Roche believes it is important that these requirements be considered to preserve the privacy interests of individual subjects of the registry. This also is particularly relevant under Section VI.B.4. on privacy and informed consent issues.

Roche is uncertain of the relevance of using an institutional review board (IRB) as stated in section VI.B.4. While, as stated above, privacy issues must be considered in establishing the registry, it is unclear why an IRB must be employed for this purpose in that a pregnancy registry is more akin to collecting adverse event reports than to conducting a study.

Section VI.B.5. discussed eligibility requirements. Roche believes that in many cases, the guidance's statement that women should be enrolled in the registry prospectively is unrealistic. For example, in the case of a woman taking a suspected or known teratogen, the physician likely would conduct testing on the fetus. If the woman entered the registry after the testing, the data would be retrospective and would not be considered as valuable. Furthermore, if testing is performed, whether the woman is included in the registry should be independent of the test results. Therefore, in this case, Roche does not agree that the

prospective versus retrospective nature of the data is an important factor for determining inclusion in the registry or segregation of the data for analysis.

Section VI.B.9. discusses sample sizes for the registries. One of the guidance's recommendations is for a sample size that is sufficient to show no difference based on an acceptable limit for the confidence interval of the difference between the exposed and comparison group. In fact, this determination, which is equivalence testing, requires very large sample sizes that might not be practical for the registry, particularly if a drug is a suspect or known teratogen..

This discussion also implies a single calculation of sample size to determine a difference in rates. However, the absolute value of the rates as the difference that is being looked for affects the sample size, and on the following page of the guidance there is a list of rates for various conditions that clearly differ from one another. Therefore, it is difficult to determine how one can calculate a single sample size, as there is no single null hypothesis being tested.

Finally, under the five variables that need to be specified in calculating samples sizes, the guidance lists "minimum relative risk." However, the risk difference may be of interest – not just the relative risk, which implies a different sample size calculation. Therefore, we believe that this "one size fits all approach" is inappropriate. Moreover, it may not be possible to calculate a sample size at all in certain cases. For example, it would appear to be unethical to calculate a sample size if a known teratogen is at issue.

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Roche appreciates this opportunity to comment on the above-referenced guidance and looks forward to working with the agency on the issues presented by pregnancy exposure registries.

Sincerely,

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