JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 4, No. 7, July 2008 "Can You Handle the Truth?"

What's New in GCP?

FDA Final Rule on Acceptance of Non-IND Foreign Clinical Studies Makes Few Changes from Draft

Reprinted from the Guide to Good Clinical Practice with permission of Thompson Publishing Group, 805 15th. St., Washington, D.C. 20005; www.thompson.com. To learn more about the Guide to Good Clinical Practice, visit: www.firstclinical.com/gcpguide.

The FDA's final rule, issued April 28 and effective Oct. 27, on the acceptance of foreign clinical studies not conducted under an investigational new drug application (IND) as support for an application for marketing approval of a drug or biological product makes only a few changes from the proposed rule released in June 2004 (see "FDA Proposes Using GCP Standards for Non-IND Foreign Studies," Guide to Good Clinical Practice, August 2004, p. 1).

The agency changed the rule "to make it clear that the regulation also applies to foreign clinical studies supporting abbreviated new drug applications," as well as INDs, new drug applications and biologics license applications.

The final rule also includes a specific requirement that applicants must retain records required by 21 C.F.R. §312.20 for two years after the agency's decision on the application or for two years after the submission of the IND, if the study is submitted in support of an IND but not an application for marketing approval.

The agency noted it needed "source documents, such as hospital records, to verify data," and the records must be available during onsite inspections or provided upon request. "If the necessary records are not available, we might not accept the study as support for an IND or application for marketing approval," the agency warned. And if foreign laws prohibit records disclosure, the applicant and the FDA "need to agree upon an alternative validating procedure if the agency is to rely on the data."

Circumstances for Consent Waiver

The final rule clarifies the "limited" circumstances in which informed consent would not be required. The proposed rule said informed consent was not required in life-threatening situations when the independent ethics committee (IEC) reviewing the study found the conditions present were consistent with those described in 21 C.F.R. §50.23 or 21 C.F.R. §50.24(a) or when measures in the study protocol or elsewhere protected the rights, safety and well-being of subjects and "ensured compliance with applicable regulatory requirements."

The proposed rule preamble noted that the provision was consistent with good clinical practice (GCP) guidance, which recommends that a legally authorized representative provide informed consent or that the requirement of informed consent be waived under such circumstances. The final rule adds two "explicit" conditions that were "implicit" in the proposed rule: The IEC review must occur before initiation of the study, and the IEC must find that informed consent is not feasible.

The final rule also deletes a provision referring to the IEC ensuring compliance with "applicable regulatory requirements," because the term "was not clear."

We had not described the requirements we considered to be applicable, and without additional clarity, the phrase did not provide additional protections for subjects."

The agency revised the rule at 21 C.F.R. §312.120(b) "to make clear that a sponsor or applicant is not required to duplicate information already submitted in the IND or application for marketing

approval. Instead, the sponsor or applicant may either submit the supporting information or provide a cross reference to another section of the submission where the information is located."

Two Information Requirements Changed

The final rule also changes two of the information requirements.

The FDA noted several comments that voiced privacy concerns about requiring the names of specific IEC members, so rather than requiring the names and qualifications of IEC members who reviewed the study, the final rule requires the name and address of the IEC that reviewed the study and a statement that the committee meets the definition of an IEC found in 21 C.F.R. §312.3. In addition, applicants must maintain records supporting the statement, including records of the names and qualifications of IEC members, and make these records available for agency review upon request.

In addition, under investigator training, the final rule requires a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained. The proposed rule had required sponsors to submit copies of the written commitments to the agency. However, the FDA notes "any signed commitments must be maintained and available for agency review."

One comment contended that the agency was imposing an additional regulatory burden by requiring a description of investigator qualifications and the research facilities. The FDA said the requirement was unchanged from the original regulation, "so there is no greater or lesser regulatory burden compared to what was previously required." The agency noted it is "less likely to be familiar with [foreign] research facilities. Therefore, we believe that it is appropriate to require a description of the research facilities to help us determine the adequacy of the facilities and to prioritize the need for an onsite inspection."

Why Move from Declaration of Helsinki?

The old regulation required that foreign studies be conducted in accordance with the ethical principles of the 1989 version of the Declaration of Helsinki. The agency proposed moving away from using the declaration "because it was not the most recent version approved [and] had the potential to cause confusion about the requirements for non-IND foreign clinical studies." The FDA had not adopted the 2000 version of the declaration because of prohibitions on placebo-controlled trials.

In addition, the agency did not want to tie its regulations to either the Declaration of Helsinki or the International Conference on Harmonisation's (ICH) GCP guidance because those documents are "subject to change independent of FDA authority and, therefore, could be modified to contain provisions that are inconsistent with U.S. laws and regulations."

The agency noted the final rule was consistent with the ICH guidance (ICH E6) and "was sufficiently flexible to accommodate differences in how countries regulate the conduct of clinical research and obtain informed consent, while helping to ensure adequate and comparable human subject protection." In addition, "there are other international documents that provide acceptable standards for GCP."

Will Stricter Rules Be in Effect?

Some comments on the proposed rule contended the new rule would delete a requirement that foreign clinical research be conducted according to the laws and regulations of that country when those laws provide greater protection for human subjects than the Declaration of Helsinki.

"We do not agree," the FDA said. "Sponsors, IECs, investigators and research sites and/or institutions are all responsible for complying with the local requirements for conducting research,

including any requirements that may be more stringent than the requirements in 21 C.F.R. §312.2120."

The agency noted that a host nation can deny a research request if the sponsor does not comply with local requirements or stop a study in progress if it violates the host country's laws.

Must Host Nation Approve IEC?

Asked whether an IEC used for a study must be approved by the host country, the FDA said that "if a host country requires by law that the host country approve the IEC, the sponsor would need to comply with that requirement. However, we will not specifically require in 21 C.F.R. §312.120 that an adequately constituted IEC be approved by the host country. This is a matter left to the discretion of the host country."

The FDA also noted that one comment requested the GCP requirements be waived for any study conducted in European Union member states or in Japan under its GCP regulations. The FDA said the information required must be submitted "for the agency to evaluate a study. It would not be adequate to simply submit a statement" that EU or Japanese GCP were followed.

The agency also noted that applicants "must submit all studies, including 'noncompliant' studies. We would review information from 'noncompliant' studies because they might have bearing on the safe use of the product." Applicants need to identify the studies that do not meet the regulatory requirements for foreign studies.

Waiver of Requirements Discussed

The rule provides a procedure through which applicants can request a waiver of the requirements, if the agency finds that "doing so would be in the interest of the public health." One comment said this could be "construed as placing the interest of public health ahead of the need to protect trial participants in foreign countries." The commenter wanted the agency to clarify that a waiver would not be granted if it would compromise the sponsor's obligation to show that trial participants had been protected at all times, even if the waiver was in the interest of public health. The FDA said the waiver was an opportunity to give "the agency a measure of discretion to avoid inappropriate results." The regulation allows the FDA "to decide whether to grant or deny waivers on a case-by-case basis, taking into account all appropriate circumstances."

To Find Out More

The final rule is available at http://www.regulations.gov/fdmspublic/component/main?main=DocumentDetail&o=0900006480537f08 and in the update to App. II in this month's issue of the Guide to Good Clinical Practice.

Other Recent GCP Developments in the Guide to Good Clinical Practice

FDA bioresearch monitoring inspections continue to decline.

OHRP grapples with foreign equivalence to common rule.