

FDA Developing Guidance on Exploratory INDs; Lilly Endorses Concept

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FDA is developing guidance on “exploratory” investigational new drug applications that will simplify toxicology requirements for “pre-Phase I” human trials, Clinical Pharmacology Lab Director Jerry Collins, PhD, Said during an FDA workshop on Nov. 16.

“Our agency has committed to publishing a guidance document on Exploratory INDs within the next two months,” Collins said.

The upcoming guidance will allow sponsors to test “microdoses” of drugs in humans to help identify pharmacokinetic properties before beginning formal *Phase I* studies.

The guidance will distinguish an “Exploratory” IND from a conventional IND program by setting limitations on the scope of research in terms of dosing and numbers of patients exposed.

The Nov. 16 workshop focused on FDA’s regulation of radioactive drugs used for research purposes; the Exploratory IND concept, however, will apply to any drug.

Collins noted that the agency is drafting two other guidance documents related to INDs, one on the chemistry and good manufacturing practices standards for all investigational drugs, and another on the specific rules governing the radioactive drugs research committee process (*see following story*).

All three guidances are moving toward release relatively quickly since they have been prioritized as supporting FDA’s Critical Path initiative.

The Exploratory IND guidance “has a lot overlap with” a position paper issued by the European Medicines Agency, Collins said.

The EMEA position paper, entitled “Non-Clinical Safety Studies to Support Clinical Trials with a Single Microdose,” was published in June. The paper defines abbreviated animal toxicology requirements to allow studies of miniscule doses of drugs in humans.

Using an accelerator mass spectrometer, researchers can analyze microdoses to learn more about a drug’s bioavailability, pharmacokinetics profile or metabolites before initiating a full *Phase I* program.

The contract research organization Accium BioSciences told the FDA it supports the Exploratory IND concept.

The proposal is important for small companies because it “will allow them to get into clinical trials quicker with good medication,” VP-Business Development Michael Chansler said.

University of Pittsburgh Research Compliance Office Director Dennis Swanson suggested that the U.S. is missing out on some research opportunities already because it lacks an appropriate microdosing model.

“If you look at Sweden, we actually had a situation where a compound was developed at the University of Pittsburgh [and] was taken to Sweden to do initial human studies because their regulations do permit first in humans under a very limited set of animal toxicity studies.”

He suggested that FDA follow an International Conference on Harmonization recommendation

that the estimation of safe human dosing be based on certain animal toxicity data.

ICH “basically proposes an extended single dose toxicity study which includes a control group [and] sufficient number of treatment groups to allow estimation of the dose inducing a minimal toxic effect,” Swanson said.

The Exploratory IND guidance will also address concerns among researchers that the extensive animal toxicology studies required for a conventional IND are prohibitively expensive.

“If we’re hearing from people that the IND process is a huge barrier, then we need a dialogue on how to make that barrier lower while maintaining safety,” Collins said.

The Exploratory IND was presented as an alternative to the current Radioactive Drug Research Committee regulations. The RDR process is defined in a 1975 regulation (Sec. 361.1) that exempts clinical trials of radioactive tracer drugs from the conventional IND process.

The advantage of the Exploratory IND process “is that our staff or the EMEA staff will be able to look at each one on a case by case basis” rather than leave the decision entirely in the hands of independent RDRs, Collins said.

FDA has very little flexibility to change the RDR process because it is written in regulations, Collins noted.

“For the IND process, we have the ability to be much more flexible in providing a guidance. All the IND regulations require is that we assume” it will be safe to proceed, Collins said.

Lilly Medical Fellow David Mozley, MD, offered his support for the Exploratory IND concept.

“We’d like to endorse the concept of the simplified or mini-IND. We’re confident that it’s what we need to pursue our goals of using radiopharmaceuticals in research,” Mozley said.

Mozley and several other meeting participants are hoping for greater clarity in the regulations regarding RDRs and radioactive drug INDs.

“As you revise your regulations for the RDR, and for radiopharmaceutical specific INDs, we would like to encourage you to become more explicit with respect to your definitions on specifications, policies and procedures,” he said.

The Lilly exec explained that his company does not use the RDR process because of concerns about variability in approaches.

“We have a lot of trouble working with RDRs or a variety of reasons. Standards don’t seem uniform to us and as a consequence the risks that we engender using...different RDRs becomes prohibitive,” Mozley said.

Mozley advocated moving toward greater federal oversight of RDRs.

“So given that the RDR in its current concept is closed off to us, what we need is a process for using a centralized mechanism that is a federal mechanism, one where there is standard definition.”**U U**