ICH Updates: What's Coming in 2019 and Beyond

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US Food and Drug Administration (FDA) officials on Monday morning held a meeting to offer a rundown of what needs to be done and what to expect from more than a dozen different International Council for Harmonisation (ICH) guidelines.

Kicking off the three-hour meeting, hosted alongside Health Canada, three FDA experts and Lisa LaVange, professor of biostatistics at the University of North Carolina, discussed topics that recently reached Step 3 of the ICH process. The ICH Assembly's next two meetings are in Amsterdam in June and Singapore in November.

E8(R1)

LaVange discussed E8(R1), which is a revised guideline on general considerations for clinical trials and part of a broader good clinical practice (GCP) renovation, which includes adopting a quality-by-design framework for clinical studies, and expanding the guideline's scope to include a broader range of study designs and data sources.

She said the expert working group (EWG), which has met three times in person and held multiple conference calls, wanted to make sure the guideline is pertinent in today's world, where there are a variety of clinical trial designs and the ability to use more real-world data sources, including electronic health records. She also noted that the EWG joked about renaming this guideline E0 "because it should come before all the other guidelines."

The guideline is expected to reach Step 2b in early May 2019 and be issued for public

consultation. A public meeting on the topic at FDA is slated for November, and finalization as a Step 4 document is planned for June 2020.

E19

Mary Thanh Hai, director of the Office of Drug Evaluation II at FDA, next discussed E19, which deals with the optimization of safety data collection. More specifically, the 10-page guideline deals with when it's appropriate to use a selective approach to safety data collection in some late-stage pre-marketing or post-marketing studies.

And although E19 does not alter local/regional safety reporting requirements and sponsors and investigators should still ensure that routine patient care is not compromised, Hai explained how selective safety data collection might be able to occur in some subsets of patients in a trial or when a drug is already approved by one regulator, and a company wants to submit for the same indication to a new regulator. She also stressed that such a selective approach should be done with early consultation with regulators.

Currently, E19 is at Step 3, with the EU setting comments due by 29 September. Hai said the EWG plans to meet next fall to review public comments, and in June 2021, the plan is slated to reach Step 4.

S11

Karen Davis Bruno of FDA's Office of New Drugs presented on S11, which deals with the nonclinical safety testing in support of pediatric medicines, and which is currently in Step 3 of the ICH process.

She said the guideline will be discussed at a face-to-face meeting in Amsterdam in June to go over the public comments, which were due earlier this month for several regulators. Industry groups recently called for changes to be made to S11 and to reduce the need for juvenile animal studies.

M10

Brian Booth, deputy director of FDA's division of clinical pharmacology, discussed M10, which deals with bioanalytical method validation.

The 57-page guidance, which has been in the works since late 2016, provides recommendations for the validation of bioanalytical assays for chemical and biological

drug quantification and their application in the analysis of study samples for non-clinical and clinical studies.

Booth said he expects that the experts will have a face-to-face in November on the guideline and bring it to Steps 3 and then 4 by November 2020. Japan's PMDA, which is working on a translation of the guideline, and FDA, have yet to begin consultation, but all other major regulators have begun a consultation on M10.

Update on Electronic Standards Topics and MedDRA

Mary Ann Slack, director of FDA's Office of Strategic Programs, also offered updates on E2B(R3), which deals with the electronic submission of individual case safety reports, M2 on the electronic standards for the transfer of regulatory information and M1, which deals with the Medical Dictionary for Regulatory Activities (MedDRA).

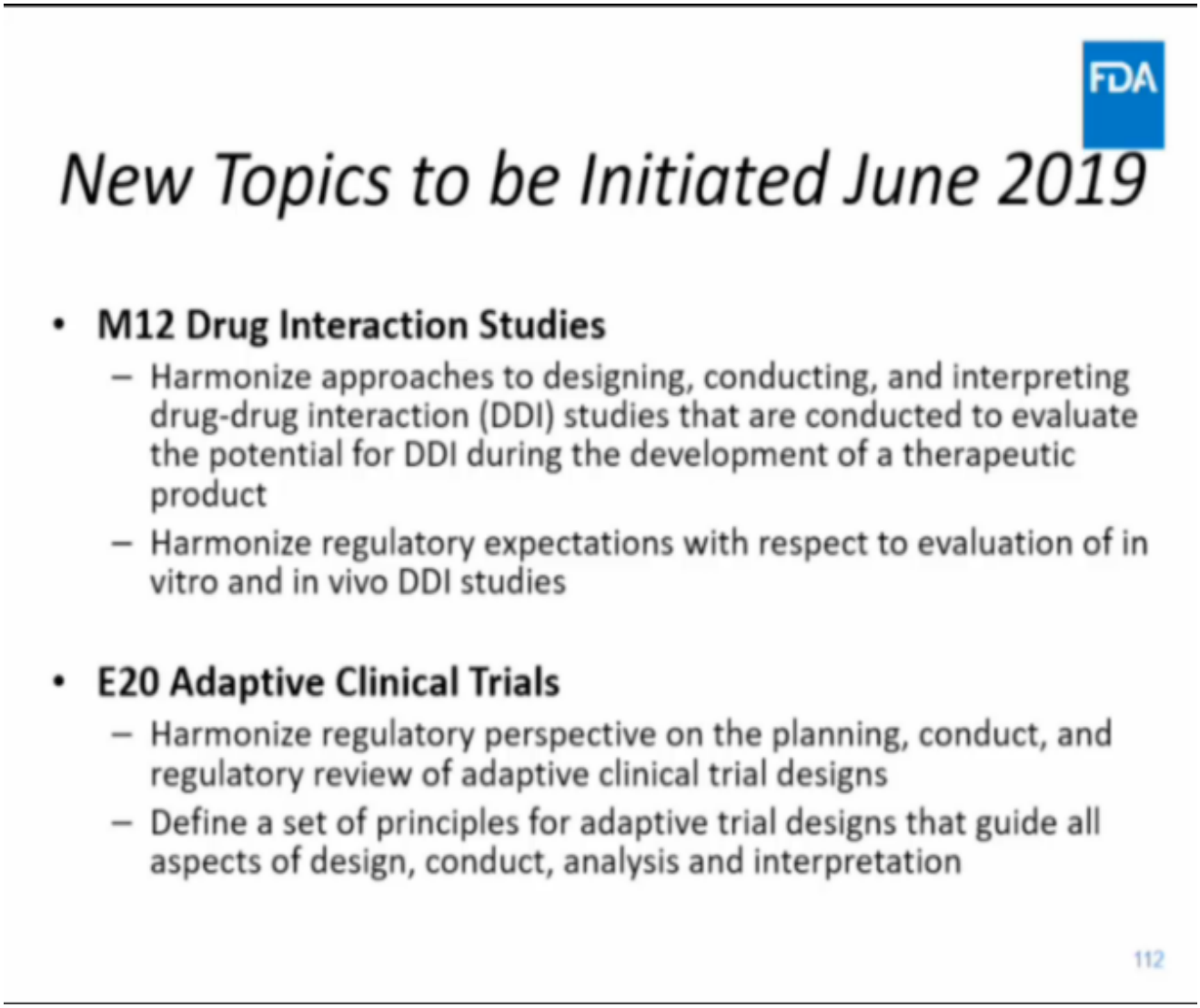
On E2B(R3), Slack said that they are working on training materials and preparing to map routes of administration between E2B and the European Directorate for the Quality of Medicines' (EDQM) terms. She noted that they are also planning to work with FDA's FAERS II, which is under development now, and in the first half of 2020 they will implement and test with industry to roll out E2B(R3).

The working group for M2, alongside Apple, Google and other tech companies, is crafting a white paper on HL7's Fast Healthcare Interoperability Resources, and work on related considerations for ICH is underway. She also noted that M2's charge includes monitoring technology and regulatory trends for impact on ICH areas of interest, such as managing relations with standards development organizations, including HL7, ISO/TC215 and EDQM.

And as far as MedDRA, she said it's now subscribed to by over 5,000 organizations in 110 countries, noting that further local support is expected in several new areas, including Central America, Korea, China and India. In addition, the Russian MedDRA translation has been completed and the Korean translation is underway. And the MedDRA Points to Consider companion document, with a focus on data quality and medication errors, is intended to be updated this year.

Lots More

Amanda Roache, operations research analyst in FDA's Office of the Center Director, also touched on a series of guidelines coming either this year or in the near future, although she noted that the timelines are subject to change.



E9(R1) Addendum to Defining the Appropriate Estimand for a Clinical Trial/Sensitivity Analyses

Roache said that for this addendum, the working group is seeking to establish a framework for translating trial objectives into a precise definition of the treatment effect that is being estimated. In addition to clarifying the existing E9, regulators will expand upon it and revisit issues on missing data and analyses. A final guideline is expected by the end of this year.

E11A Pediatric Extrapolation

This guideline was developed to reduce the sizable gap (7-10 years) between an initial adult approval and the inclusion of pediatric-specific information in product labeling, she said. In addition, the guideline will harmonize methodologies and strategies to

incorporate pediatric extrapolation into overall drug development plans. A draft guideline is anticipated by November 2020.

E14/S7B The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

This Q&A document is meant to streamline the clinical development for drugs that prolong the QT interval but are found to have low proarrhythmic risk and which could result in fewer products being dropped from development.

The document was initiated in 2018, and the first stage of the final document by June 2020.

M9 Biopharmaceutics Classification System-based Biowaivers

A final guideline is expected this year (draft guideline issued in 2018). She said the guideline will look to provide for the biopharmaceutics classification of medicinal products and reduce the cost and time for pharmaceutical development when in vivo studies to prove the biopharmaceutical quality of the medicinal product are unnecessary.

**M7(R2): Addendum to Assessment and Control of DNA Reactive (Mutagenic) Impurities in
Pharmaceuticals To Limit Potential Carcinogenic Risk**

Roache said experts working on this revision are working on two different projects — an addendum and a question and answer document. The Q&A document is anticipated this year. According to ICH, the Q&A will be developed to clarify and address quality and safety issues and concerns that have been identified following implementation of M7 in 2014.

M11 Clinical electronic Structured Harmonized Protocol (CeSHarP)

This guideline is part of an effort to establish an internationally harmonized standard template for the format and content of the clinical protocol document to support consistency across sponsors and the exchange of protocol information. A draft version is expected in June 2020.

S1(R1) Revision on Rodent Carcinogenicity Studies for Human Pharmaceuticals Guideline

The outcome of a study begun in August 2013 will inform whether the revision is needed, Roache said. She noted that a determination needs to be made on whether a weight of evidence approach can be used to characterize carcinogenicity risks without conducting a two-year rat carcinogenicity study.

S5(R3) Revision on Detection of Toxicity to Reproduction for Human Pharmaceuticals

This guideline is being revised based on comments received, with a final guideline expected in November.

Q3C(R8) Maintenance of the Guideline for Residual Solvents

This guideline will develop PDE levels for three solvents: 2-methyltetrahydrofuran, cyclopentylmethylether and tert-butanol. A draft guideline expected by the end of 2019.

Q3D(R2) Maintenance of the Guideline for Elemental Impurities

Work is ongoing to include PDEs for subcutaneous and transdermal routes of administration. A draft is coming later this year, Roache said.

Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

This guideline will provide guidance on a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner across the product lifecycle. It will also allow regulators to better understand a firm's pharmaceutical quality systems for the management of post-approval CMC changes, she said.

A draft version was issued in November 2017, and the goal is to have a final version by November of this year.

Q13 Continuous Manufacturing

As part of efforts to reduce the barriers to implementing continuous manufacturing, Roache said this topic was initiated at ICH in June 2018. A draft guideline is anticipated in June 2020.

Two new informal ICH discussion groups have been established in 2019 on quality (looking at issues relevant to the quality portfolio to harmonize the quality management

system across a product's lifecycle, and for generics, to identify opportunities for additional guidance, such as bioequivalence or other areas for harmonization. ICH published a reflection paper on generic drugs in September 2018.

FDA Public Meeting

ICH Guidelines

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