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ICH Publishes Reflection Paper on GCP Renovation

On 12 Jan 2017, the International Council for Harmonisation (ICH) published a reflection paper titled 'ICH Reflection on "GCP Renovation": Modernization of ICH E8 and Subsequent Renovation of E6". Comments from stakeholders on this revised 'modernisation' of ICH E6 and E8 are being sought with the deadline for comments being 13 Mar 2017. The reflection paper outlines an approach to potential renovation of the ICH guidelines relating to the design, planning, management and conduct of clinical trials, namely *E8 General Considerations for Clinical Trials* and *E6 Good Clinical Practice*s. The goal is to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of clinical trial designs and data sources that are being employed to support regulatory and other health policy decisions. ICH believes that the proposal outlined in this reflection paper would largely address concerns that have recently been raised by Stakeholders (research organisations and an international consortium of health researchers). These include concerns that the current ICH E6 guideline fails to sufficiently recognize variations in the level of risk for participants in different types of trials and allow corresponding flexibility in managing the risks. Another major concern was related to E6's limited scope. The proposed renovation would address these concerns through targeted revisions made to the two current ICH guidelines. ICH proposes to firstly address the broader concerns about the principles of study design and planning for an appropriate level of data quality through revision to the current *E8 General Considerations for Clinical Trials*. Subsequently, ICH proposes to address the flexibility concern via further renovation of *E6 Good Clinical Practices.* ICH E8 was first published in 1997 and has not been revised since. It is a high-level guidance that serves as a general roadmap to other ICH Guidelines concerning clinical trials. ICH proposes to revise and modernize E8 to address the critically important aspects of study quality. This would include the need to identify aspects of the trial that are critical to generating reliable data and the strategies and actions that could effectively and efficiently support quality in these critical areas (e.g. relevant critical-to-quality factors). Proposed revisions to E6 include the following: 1) recognizing that the most important tool for ensuring human subject protection and high-quality data is a well-designed and well-articulated protocol, the renovated E6 would refer to the *proposed-to-be-revised* E8 guideline for a more comprehensive discussion of study quality considerations and relevant discussions and guidance in other ICH E guidelines; 2) the main body of the E6 guideline would be revised to focus on overarching principles including key elements of human subject protection and data quality, using a risk-based approach to study oversight and monitoring. A number of available reference documents could be used to inform the development of these basic principles and list of candidate 'critical-to-quality' factors including, for example, *FDA Guidance to Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring,* the *EMA reflection paper on risk based quality management in clinical trials;* and MHLW administrative notice on Basic Principles of Risk-based Monitoring. A set of annexes would be developed to be attached to the new E6 guideline. The proposed annexes are as follows:

Annex 1 – traditional interventional trials of investigational unapproved or approved drugs; Annex 2 – Non-traditional interventional trials and/or data sources; Annex 3 – Non-traditional trial designs.

http://www.ich.org/ichnews/newsroom/read/article/ich-reflection-on-gcp-renovation-modernization-of-ich-e8-and-subsequent-renovation-of-ich-e6.html

MHRA Inspectorate Blog on Reference Safety Information

Part II of the MHRA Inspectorate blog on Reference Safety Information (RSI) was published this month. This post follows-up on queries received following publication of the first blog on RSI and provides guidance on areas of confusion identified during last years' MHRA GCP Symposium. The reason for the current focus on RSI is that MHRA inspectors are seeing critical and major findings relating to pharmacovigilance at the majority of inspections and the root cause for these findings is linked to the management of the RSI. The blog clarifies the definition of RSI, who is responsible for approving it, and gives examples of ways of communicating new safety information to investigators. It highlights the fact that it is the MHRA that is responsible for approving the RSI and if RSI is implemented without regulatory approval then the MHRA has not had the opportunity to: 1) assess new information that may impact on the risk benefit ratio of your trial, and 2) determine if as a result of the information your IMP and its dosing regime are still appropriate for your trial population.

https://mhrainspectorate.blog.gov.uk/2017/01/18/reference-safety-information-ii/

FDA Issue Final Rule on Clinical Trials Registration and Results Information Submission

The Food and Drug Administration (FDA) has issued its Final Rule detailing the requirements for submitting registration and summary results information to ClinicalTrials.gov (the clinical trial registry and results database operated by the National Library of Medicine (NLM) of the National Institutes of Health (NIH)). The requirements apply to the responsible party (meaning the sponsor or designated principal investigator) for certain clinical trials of drug products and device products that are regulated by the FDA and for paediatric postmarket surveillances of a device product that are ordered by the FDA. The final rule is effective from 18 January 2017. As of that date, the ClinicalTrials.gov system will allow responsible parties to comply with the rule. Responsible parties will have 90 calendar days after the effective date to come into compliance with the requirements of this rule. The final rule clarifies and expands requirements for the submission of clinical trial registration and results information to the ClinicalTrials.gov database. It specifies how the data that were collected and analysed in accordance with a clinical trial's protocol are submitted to ClinicalTrials.gov.

https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission

FDA Publishes Inspectional Observations Summaries for FY 2016

Listings of 483s from each product area (e.g. Drugs, Devices, Biologics, Bioresearch Monitoring etc.) issued by the FDA during the fiscal year 2016 (01 Oct 2015 to 30 Sep 2016) are now available on the FDA website. The table doesn't represent the complete set of 483s issued during the fiscal year since some 483s were manually prepared. Additionally, the sum of 483s from all product areas is greater than the actual total 483s issued during the fiscal year since a 483 may include citations related to multiple product areas, and counted more than once, under each relevant product centre. The FDA Form 483 is used to notify a company's management of objectional conditions observed during an

FDA inspection. At the conclusion of an FDA inspection, the FDA Form 483 is presented and discussed with the company's senior management. Companies are encouraged to respond to the 483 in writing with their corrective action plan and then implement that corrective action plan expeditiously.

http://www.fda.gov/ICECI/EnforcementActions/ucm531890.htm

FDA Issues Draft Guidance on Multiple Endpoints in Clinical Trials

The FDA issued a new draft Guidance for Industry this month, titled "Multiple Endpoints in Clinical Trials". Most clinical trials of investigational medicinal products contain multiple endpoints to assess the effect of the drug and to document the ability of the drug to favourably affect one or more disease characteristics. As the number of endpoints analysed in a single trial increases, the likelihood about making false accusations about the drug's effects with respect to one or more of those endpoints becomes a concern if there is not appropriate adjustment for multiplicity. Hence, the purpose of this guidance is to describe various strategies for grouping and ordering endpoints for analysis and applying some well-recognised statistical methods for managing multiplicity within a trial in order to control the chance of making erroneous conclusions about a drugs effects. Although ICH E9 *Statistical Principles for Clinical Trials* includes discussion on multiple endpoints, this draft FDA guidance provides greater detail on the topic.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536750.pdf