ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

July 15, 2022

Lauren K. Roth
Associate Commissioner for Policy
Food and Drug Administration, Dockets Management Staff
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: ACRO comment submission to the FDA on the International Council for Harmonisation (ICH) Draft Guidance for Industry: Q9(R1) Quality Risk Management [Docket No. FDA–2022–D–0705]

Dear Ms. Roth,

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics, and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval and pharmacovigilance research. ACRO member companies manage or otherwise support the majority of FDA-regulated clinical investigations worldwide. The member companies of ACRO advance clinical outsourcing to improve the quality, efficiency, and safety of biomedical research.

ACRO thanks ICH for releasing this draft guidance on *Q9(R1) Quality Risk Management.* ACRO is pleased to provide the following comments.

I. General comments:

ACRO is encouraged by and supportive of this draft guidance. It provides a much-needed perspective in order to support the industry in adopting quality risk management practices. The draft guidance does an excellent job of highlighting the core expectations and key operational process components of quality risk management.

ACRO suggests that ICH make a strong statement to emphasize the scope of the guidance. There is general consensus within the industry that this guidance mostly applies to manufacturing, but the scope section clearly indicates that it also applies to the development process as well (Line 68). We believe that this point should be strengthened and reiterated, that the guidance applies and supports the *entire* research and development process of pharmaceutical products.

II. Line-Specific Comments

Lines 40-43:
The current text states*:*
"The application of digitalization and emerging technologies in the manufacture and control of medicinal products can present certain challenges. The application of quality risk management to the design, validation and technology transfer of advanced production processes and analytical methods, advanced data analysis methods and computerized systems is important."

ACRO recommends a connection be made with ICH's (E8) R1 guidance on technology and where it is applied. Traditionally, studies have used study-specific data collection processes. Data such as that obtained from electronic medical records (EMRs) or digital health technologies (DHTs) may be leveraged to increase the efficiency of studies or the generalizability of study results.

Lines 75-80:
The current text states*:*
"Two primary principles of quality risk management are:

- *The evaluations of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient. (Note: Risk to quality includes situations where product availability may be impacted, leading to potential patient harm.)*
- *The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk."*

ACRO suggests that you consider including quality, either data and/or product quality as a key principle *in addition* to patient protection. The connection between patient and quality is key.

Suggested addition is underlined below:

Two primary principles of quality risk management are:

- The evaluations of the risk to quality, based on:
    - Scientific knowledge and ultimately link to the protection of the patient. (Note: Risk to quality includes situations where product availability may be impacted, leading to potential patient harm.)
    - Quality of data as fitness for purpose. The quality of the information generated should therefore be sufficient to support good decision-making to ultimately support decision-making while protecting study participants
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

Lines 89-90:
This comment is regarding the figure on page 4:
"Figure 1: Overview of a typical quality risk management process"

ACRO recommends that Critical-to-Quality (CtQ) factors be added to Figure 1. There is an opportunity to make a connection to E8(R1) to support a basic set of factors relevant to ensuring study quality should be identified. Emphasis should be given to those factors that stand out as critical to study quality. These critical-to-quality factors are attributes whose integrity is fundamental to the protection of study participants, the reliability and interpretability of the study results, and the decisions made based on the study results. These quality factors are critical because, if their integrity were to be undermined by errors of design or conduct, the reliability or ethics of decision-making based on the results of the study would also be undermined.

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Lines 126-127:
The current text reads:
"Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;"

See comment directly above. ACRO recommends adding critical-to-quality factors in as a consideration here.

Lines 144-148:
The current text reads:
*"**Hazard identification** is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis,*

informed opinions, and the concerns of stakeholders. Hazard identification addresses the "What might go wrong?" question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process."

In addition to hazards referring to the risk question or problem description, the hazards should be impactful to the Critical to Quality (CtQ) factors. This supports a narrowing of hazards to those most impactful to quality endpoints.

Lines 372-373:
The current text reads:
*"**Risk communication** is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process (see Fig. 1: dashed arrows)."*

ACRO suggests that a connection be made with ICH's E8(R1) guidance supporting companies to go beyond reliance on tools and checklists. Emphasis should be made to support open dialogue to facilitate the development of innovative methods for ensuring quality.

Lines 344-366:
The section titled:
"6. INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS"

Suggestion to add diversity plans to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials. Inclusion of the role of quality management as a key component of supporting diversity and inclusion within-trial management and oversight. Diversity must be built into studies from the beginning, a sound quality management, and risk assessment process is the first step.

Lines 349-351:
The current text reads:
"However, effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight."

ACRO suggests that you include a reference here that quality risk management is a mechanism that demonstrates a company oversight practice, which then impacts the extent and level of direct regulatory oversight. The key inclusion of quality risk management is a method to demonstrate oversight.

Lines 353-355:
The current text reads:
"Training of both industry and regulatory personnel in quality risk management processes provides for greater understanding of decision-making processes and builds confidence in quality risk management outcomes."

ACRO suggests adding a connection to ICH's E8(R1) here. Creating a culture that values and rewards critical thinking and open, proactive dialogue about what is Critical-to-Quality (CtQ) for a particular study or development program, going beyond sole reliance on tools and checklists, is encouraged. Open dialogue can facilitate the development of innovative methods for ensuring quality.

Lines 357-360:
The current text reads:
"While manufacturing and supply chain diversity can be enablers of product availability, increasingly complex supply chains lead to interdependencies that can introduce systemic quality/manufacturing risks impacting supply chain robustness. Application of quality risk management can proactively mitigate these risks. Preventive measures supporting product availability may be identified through quality risk management activities."

ACRO suggests that you add an example for clinical development activities. For example, the use of biomarkers has the potential to facilitate the availability of safer and more effective drugs, to guide dose selection, and enhance a drug's benefit-risk profile (see the ICH guidance for industry E16 Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions (August 2011)) and can be considered throughout drug development. Quality risk management is paramount in the evaluation of biomarkers to better target patients more likely to benefit and less likely to experience adverse reactions, or as intermediate endpoints that could predict clinical response.

Thank you for this opportunity to provide feedback. Please do not hesitate to contact ACRO (aadelfio@acrohealth.org) if we can provide additional details or answer any questions.

Respectfully submitted,

The Association of Clinical Research Organizations