September 30, 2019

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket ID FDA-2019-D-3049: E8(R1) General Considerations for Clinical Studies; International Council for Harmonisation

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on E8(R1) General Considerations for Clinical Studies; International Council for Harmonization.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO welcomes this document on internationally accepted principles and practices for the design and conduct of clinical studies of drug and biologic products. The draft guidance provides an overview of the types of clinical studies that may be performed and data sources during the product's life cycle. Although we believe the guidance is well written, we have provided general comments below for FDA's consideration, as well as detailed comments in the annexed table.

- The draft guidance uses the traditional framework for the logical progression of drug development in phases (Phase 1-4). BIO recommends that this document resets the framework for how drug development is approached. Scientific methodologies have evolved. There are a multitude of methodologies (e.g., adaptive designs, master protocols, platform trials, observational research, pragmatic research) that can be used to provide evidentiality for drug development. For example, adaptive designs can be used in Phase 1, which is not reflected in the document. BIO recommends that the document lessen the focus on Phase 1-4, which provides appearance of operating in the old paradigm, and instead focus on answering the research questions using appropriate methods at the suitable time.

- There are a number of terms used which are new to ICH, as such, BIO recommends a glossary be added to clearly define the terms used in the document. For example, the draft guidance introduced new terminology into the ICH efficacy series, "critical to quality factors." This terminology appears to convey the same intent as the terminology in E6(R2), "critical data and processes." It is recommended that consistent language be used throughout the ICH efficacy documents to prevent confusion.

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200 P
202.488.6306 F
bio.org

- While we agree that we need to raise awareness and encourage seeking patient feedback in trial design, other stakeholders, such as health care professionals and care givers are still important and should be consider earlier in the draft document (i.e., these are not mentioned until line 190).

- Guidance should be provided how the application of a quality by design approach for clinical study planning and conduct should be documented for regulatory purposes. In particular as the document points to incorporation of patient perspective into the quality by design for clinical studies. As such, further guidance should be provided on how to include patient perspectives for individual studies and overall clinical development to be used for regulatory purposes

- It is highly appreciated that Quality will become an integral element of clinical trials. Although assessed as a significant step forward the document does not address or incorporate by reference to other documents (i) some definitions of Quality Measures (e.g., Key Performance Indicators, Key Quality Indicators) addressing performance and Key Quality Elements of a clinical trial and (ii) introduction of strategic audit planning and Quality Management System addressing clinical trial activities of a company.

- The critical to quality factors need to be explained in conjunction with the quality tolerance limits (QTLs) according to ICH GCP E6 (R2). Otherwise it is confusing to the audience where the differences are. In addition, the draft guidance should provide a linkage to E6 (R2) describing the risk-based approach in more detail.

- For consistency with international guidances 'Clinical Studies' should be replaced by 'Clinical Trials', whenever it is possible considering ICH E3 is still using clinical study.

- The intended use of Annex 3 is unclear. The table would benefit from explain the use of the critical to quality factors concept, as well as inclusion of other ICH guidelines such as E3, Structure and Content of Clinical Study Reports.

BIO appreciates this opportunity to submit comments on E8(R1) General Considerations for Clinical Studies; International Council for Harmonization. We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Sesquile Ramon, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

Lines	Issue and Proposed Change
I. General Principles	
II. Objectives of This Document	
2-5	On line 3, the objective of guideline is written as "Clinical studies of medical interventions are... ", which can be read that scope of the guidance scope is intervention trials. On the other hand, line 31 describes that the term "clinical study" in this document is meant to refer to a study of a medicinal product in humans, conducted at any point in a product's lifecycle; which can be read that the guidance scope is not limited to intervention trials. In addition, the subsequent content seems to describe guidance for clinical studies including observational research. If the "clinical study" referred to in this guideline includes not only intervention studies but also observational studies, we propose revision of the description of "objectives of this document" to "Clinical studies of medicinal products are... " (line 3). Suggested change: "Clinical studies of *medicinal products* are conducted to provide information that can ultimately improve access to safe and effective drugs with meaningful impact on patients, while protecting those participating in the studies."
32-33	Please kindly confirm whether the term "drug" or "medicinal product" in this guidance include not only vaccines and biological products, but also regenerative medical products including gene therapy products.
54-75	Some languages on promoting innovative designs under scientific approach (2.2) may be warranted.
58 - 61	Proposed change (if any): The purpose of a clinical study is to generate reliable *and accurate high-quality evidence to* ~~*information to*~~ answer key questions and support decision making while protecting study subjects.
72	It is unclear as to whether the inclusion of the statement about the logic behind serially conducted studies is intending to convey an endorsement or expectation of that serial conduct. It would be useful to also state the potential for seamless studies or other adaptive approaches.
74	As emerging data can arise from sources beyond the clinical development plan, add an example such as the following.

Lines	Issue and Proposed Change
	Proposed change: For example, results of a confirmatory study may suggest a need for additional human pharmacology studies~~.~~ *, or a safety concern that emerges within the drug class may prompt additional nonclinical studies or changes to data collection.*
72	Section 2.2 only refers to traditional clinical trial design- need to expand to include adaptive references.
81-84	Patients also provide their perspective of living with a condition, which contributes to the determination of endpoints that are meaningful to patients, selection of the right population, duration of the study, and use of the right comparators. Proposed change: "Consulting with patients and/or patient organisations in the design, planning and conduct of clinical studies helps to ensure that all perspectives are captured. Patients' views can be requested on all phases of drug development. *Patients* ~~*also*~~ *provide their* ~~*perspective*~~ *experience of living with a disease or condition and their preferences, which contribute to the determination of endpoints that are meaningful to patients, selection of the right population, duration of the study,* ~~*and*~~ *use of the right comparators, and acceptable benefit and risks of a treatment*. Involving patients at the early stage of study design is *also* likely to increase trust in the study, facilitate recruitment, and promote adherence, which should continue throughout the duration of the study. ~~*Patients also provide their perspective of living with a condition, which contributes to the determination of endpoints that are meaningful to patients, selection of the right population, duration of the study, and use of the right comparators.*~~ This ultimately supports the development of medicines that are better tailored to patients' needs *and study designs that are more manageable for participation.*"
85	This section should also recognize the input from healthcare practitioners, as such we propose adding: "*Other aspects for consideration are treatment guidelines with input from HCPs to help align the protocol with clinical care and direct patient input (e.g., patient and/or patient organizations and advocacy groups) as much as possible. This will allow protocols to be better integrated with a patients' care and a practitioner's delivery of care. Following this model may also result in more meaningful data, improved patient engagement and compliance and better managed trials by HCPs."*
III. Design quality into clinical studies	

Lines	Issue and Proposed Change
99-101	Suggest changing wording to: Quality should rely on good *planning and* design and its execution *in conjunction with quality control and quality assurance measures rather than overreliance on retrospective correction activities.* ~~rather than overreliance on retrospective document checking, monitoring, auditing or inspection. These activities are an important part of a quality assurance process but are not sufficient to ensure quality of a clinical study.~~"
113	We suggest adding the following language: "*reduction of complexity to the extent possible and elimination or minimization of redundant data collection*"
114-116	Section 3.1 should reference risk-based study execution as an operational consideration
114-115	The current draft does not specifically mention Critical to Quality (CTQ) factors that might be appropriate to consider when utilizing CROs, vendors or other third parties. This may be implied by reference to "other parties" and "external sources" within the document. Given the prevalence/use of third parties in the conduct of clinical trials it would be helpful to call this out. Suggested edit: "Operational criteria are also important, such as ensuring a clear understanding of the feasibility of the study, selection of suitable investigator sites, *suitability and qualification of third-party service vendors,* quality of specialised analytical and testing facilities and procedures, and processes that ensure data integrity."
115	Given that the definition of a "site" is evolving based on new approaches (e.g., virtual trials), we recommend this to be changed: "selection of suitable investigator*s* ~~sites~~…"
118	It is unclear what is meant by "A basic set of factors". ICH should consider adding some examples.
134-135	Proposed change: "The sponsor and other parties designing quality into a clinical study should identify the critical to quality factors *and associated outcome measure*."
137-139	Proposed change: Where it is decided that risks should be mitigated, the necessary control processes should be put in place and communicated *to study subjects, investigators and relevant site staff*, and the necessary action taken to mitigate the risks.

Lines	Issue and Proposed Change
143-144	Proposed change: "Proactive support (e.g., broad training to all relevant site staff *and description of critical to quality factors and potential mitigation measures* in the protocol or in the case report form) will enhance correct implementation of study protocol, procedures, and associated operational plans and process design. *Appropriate planning and description of mitigation measures could allow for adaptation of the study protocol or case report form without the need for approval by ECs or Health Authorities."*
161	Suggest adding: "Patient *and Investigator Site consultation* early in the study"
162-163	Proposed change: Protocols and ~~case report forms/~~data collection methods *(e.g. case report forms)* should enable the study to be conducted as designed.
166	In reference to "create a culture", it is unclear "where/who" this change needs to happen (e.g., within a company, at the hospitals/research sites, within the HCP). We suggest the document further specifies the stakeholders involved in this process and how to implement.
190-192	Suggest adding: "including patients and treating physicians" to health care professionals or add that phrase and the treating physician is not the only HCP involved
197	In addition to learning "whether scheduled study visits and procedures may be overly burdensome" it is valuable to learn how the scheduled visits and procedures compare to the care delivery for these patients; inclusive of any regional differences.
202-204	Proposed change: When a study has novel elements, *which will amend or replace existing elements and are* considered critical to quality (e.g., defining patient populations, procedures, or endpoints), early engagement with regulatory authorities should also be considered.
202-204	As noted in Section 4, early engagement with regulatory authorities should be considered for efficient drug development. Recommend revising statement to encourage early engagement with regulatory authorities to agree on study elements critical to quality, and not only when a study has novel elements.
209-211	Proposed change: "These will require proactive planning and ongoing review and adjustment of critical to quality factors, and risk management. *Well defined processes for adaptation of critical to quality factors*

Lines	Issue and Proposed Change
	based on accumulated experience and knowledge could allow for changes to study design without the need for approval by EC and health authorities.
IV. Drug development planning	
General	The use of real-world data (RWD) and real-world evidence (RWE) for regulatory decision-making is a fast-evolving area of clinical trials. To maintain pace with the growing use of RWD and RWE in this capacity by global HAs, we request that the Agency discuss and provide any recommendation or suggestions for best practices when utilizing RWD/RWE in clinical trials to support developing of designs or in support of regulatory decision-making.
272-406	Could acknowledge that phase 2 studies may also support initial approval for some indications in certain regions based on a surrogate endpoint, in which case they would not be purely exploratory as described.
282-286	We recommend adding language that allows for flexibility in scenarios in which a later stage clinical study (e.g., Phase 3 or 4) may enrol a narrower population than is the typical standard population in most late-stage studies. Without such flexibility, enrolment in certain clinical trials (such as those for establishing proof of efficacy in a population that expresses a biomarker linked to the disease/indication) may prove burdensome without additional value, possibly leading to delay in the development of potentially life-changing medicines. Proposed change: "…Later confirmatory studies are generally larger and longer and include a more diverse study population. *However, there may also be instances in which later studies may focus on a narrower population based on information from earlier studies (e.g. efficacy study in patients with a particular biomarker) that indicate the population with highest potential for a positive benefit-risk profile."*
329	Given that certain medicinal products (e.g., monoclonal antibodies, drug-device combinations) may have long half-life, consider revising "with a short duration of drug exposure" to "with limited dosing"
331	Comment: This description does not seem to take into consideration the potential for an adaptive Phase 2/3 design where the transition is seamless vs. serial.
332	Should not define that Exploratory studies are Phase 2 following new guideline concept. Exploratory studies or Exploratory studies (usually Phase 2)

Lines	Issue and Proposed Change
342	Should not define that Confirmatory studies are Phase 3 following new guideline concept. Confirmatory studies or Confirmatory studies (usually Phase 3)
358	Is there an intended message by focusing on randomised parallel design? If not, it could be more inclusive to indicated that "Confirmatory studies may include the use of randomised, parallel design; cross-over design; or other"
366	Suggested change: "Be conducted to demonstrate effects on clinical ~~endpoints~~ outcomes."
367	As elderly subjects are likely to be studied in Phase 3 or earlier, suggest the following edit: "Studies in special populations, such as paediatric ~~*and elderly*~~ populations, may be conducted"
378	For special population, it is often difficult to conduct regular clinical trials. Additional information should be included as to how to consider the various trial designs as described in Section 5
386	Although technically not a "special population", recommend that non-clinical (section 4.1) and clinical considerations for investigations in women of child-bearing potential are addressed in this guideline
408-429	Section 4.4 would be more appropriate to refer to a study's sample size justification as opposed to its "power analysis".
413-420	Further to the considerations in this section, we request that the Agency note that in certain instances, a clinical study design may not be adequately aligned with real-world practice, potentially resulting in generation of data that are not applicable to clinical practice—and potentially not valuable post approval in a clinical setting. As such, we propose the addition of the proposed statement to this section of the guidance. Proposed change: "Feasibility considerations include but are not limited to the availability of qualified investigators/site personnel with experience in conducting a clinical study; availability of equipment and facilities required to successfully conduct the clinical study; availability of the desired patient population; ability to enrol sufficient numbers of participants as determined by the study's power analysis; the ethical and regulatory considerations, which include informed consent, parental/caregiver consent and patient

Lines	Issue and Proposed Change
	assent for paediatric studies; and regional standards of care. *Trial feasibility may be indicative of the extent to which a clinical study design and real-world practice are aligned.*"
V. Design element for clinical studies	
444-626	We recommend a new subsection be added to Section 5.1 on sample size.
451	This will be under the current ICH-E6, but I think that the need for consent when using various data sources such as Real world data will be a future discussion. Suggested edit: "usually for whom consent is available"
480	Suggested edit: "An important distinction between studies is whether the choice of the *drug* and the health"
480-490	We recommend the document include that a device could also make a drug interventional.
487	Comment: The utility of observational studies to help understand disease progression, especially in rare disease deserves mention Proposed change: "Observational studies are usually conducted in the post-approval period*, however, they may also be of utility in other phases, such as disease natural history studies to facilitate endpoint selection and study design*."
Section 5.1.3	Many Sponsors develop innovative medicines with the intent of seeking global marketing approvals. However, when conducting active control trials, it is important to note that what is considered an appropriate active control may differ from one region to another, making for greater challenge in multi-regional trials for these Sponsors. The choice of active comparator is an important topic and should be discussed with global HAs for multi-regional clinical studies, and we ask that the Agency make note of the same in this section of the guideline.
506-511	We ask that the Agency expand upon its recommendations for external controls by reminding Sponsors to create and utilize an external control that most consistent with the trial population for a more robust dataset.

Lines	Issue and Proposed Change
	Proposed change: "In addition, external control subjects may differ from study subjects with respect to some demographic and background characteristics (e.g., medical history, concurrent diseases, etc.), possibly reflecting a somewhat different subject population, which should be taken into account in the design and analysis of the study. *However, Sponsors should consider appropriate factors/criteria when identifying external control groups that are most consistent with the comparator clinical trial populations."*
543-545	Proposed change: The choice of endpoints should be meaningful for the intended population and take into account the views of patients *and expectations of the regulators to facilitate acceptance of data for regulatory purposes.*
558	Suggested edit: "The extent of safety data collection may be tailored to the objectives of the study *(See ICH E19)*."
581	In the text "Maintaining confidentiality of the interim study results…" the use of confidentiality here is unexpected. Given that the section is focused on maintain the blind we suggest the following change: "Maintaining ~~confidentiality~~ *blinding* of the interim study results (…)"
598-600	The reason why the statistical analysis plan should be finalised before the unblinding of study data, or in the case of an open-label study, before the conduct of the study, is not only to "increase confidence that important aspects of analysis planning were not based on accumulating data in the study or inappropriate use of external data" but more to "avoid influence to the analysis planning by knowing unblinded data in the blinded study, and accumulating data in the open-label study". These steps will increase confidence that important aspects of analysis planning were not influenced by knowing unblinded group data in the blinded study, and accumulating data in the open-label study.
628-629	The definition of the word "Study Data" is ambiguous. It may mean the data that is obtained by sponsor such as CRF. If so, what does the sentence "necessary information to conduct the study" mean?" In addition, we suggest the following edit: "The study data should reliably contain the necessary information to ~~*conduct*~~, monitor, *review* and analyse the study.
637	It is unclear what "other mechanisms" means. We suggest ICH provide examples such as ePRO

Lines	Issue and Proposed Change
641-644	Proposed change: "Note that secondary data themselves may have had careful quality control processes implemented during their acquisition, but those processes were not *necessarily* designed with the objectives of the present study in mind."
653-658	It is not clear as to what the message is for this section. Is the guidance intending to make any recommendation about when or when not to use secondary data? Or a message that such data may be evaluated differently?
661-662	The guidance could be stronger with respect to the use (not just the existence) of data standards Proposed change (if any): "International data standards exist, *and should be used,* for many sources of study data."
662	Comment: An example to further elaborate on the statement: "Data standards should be developed for emerging sources of study data" would be helpful. Proposed change: Data standards should be developed for emerging sources of study data *such as wearable devices*.
VI. Conduct and reporting	
679-682	Proposed change (if any): "Study stakeholders, such as sponsors; investigators, coordinators, and other local site staff; site monitors; adjudicators and members of the data monitoring committee; and third-party service providers (e.g., central laboratory or reading centre personnel) should receive thorough training prior to enrolment of the first study subject *or for those joining during a clinical trial, prior to commencement of any activity related to a clinical trial."*
692-695	Suggested edit: "Inappropriate access to data during the conduct of the study may compromise study integrity. In studies with planned interim analyses, special attention should be given to which individuals have access to the data and results. Even in studies without planned interim analyses, special attention should be paid to any ongoing monitoring of data to avoid inappropriate access, *especially with adaptive designs, open-label studies*."

Lines	Issue and Proposed Change
725-726	Please provide specific examples of the "other reporting formats appropriate for the type of study and information being reported "such as for observational studies. Please consider adding such concrete description in ICH-E3 when it is revised.
722-732	We believe that it should be recommended that patients be accessible. It seems that this will promote patient participation/involvement in clinical trials.
VII. Considerations in identifying critical to quality factors	
777	Consideration to add human-factor studies to table, particularly to align with reference to drug-device combination products (line 238)
786	ICH E6 is expected to change a lot with GCP Renovation, but ICH E6 will be applicable to all except Accrual and Dissemination of Study Result.