BIOTECHNOLOGY
INDUSTRY ORGANIZATION
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September 28th, 2009

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2009-D-0324 ICH Topic E16: Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submission

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the draft guidance *ICH Topic E16: Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submission.*

BIO represents more than 1,200 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, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS

1. The Guideline speaks to instances when the biomarker qualification data would be included as part of a specific product-related application but does not provide the details/examples for such an application. It would be helpful to separate and clarify the guidelines for the stand alone biomarker qualification applications and the product-related applications incorporating biomarker data.

2. Reiteration of the following statement from the final ICH E16 concept paper entitled "Pharmacogenomic (PG) Biomarker Qualification: Format and Data Standards on 16 June 2008 EMEA/CHMP/190395/2008" (page 3) would be helpful if this statement still applies to the current guidance. BIO suggests this statement (without the word "proposed") be included in the guidance:

   "It is important to also stipulate what is not in the scope of this new proposal. Issues that will not be addressed in the ~~proposed~~ guideline include:

- The regulatory process to be applied to accept PG biomarkers (e.g., for use as diagnostic tests)
- Use of qualified PG biomarkers in Marketing Authorization regulatory decisions (e.g., use as surrogates for clinical efficacy)
- Qualification and content/format for submission of non-PG biomarkers."

3. Additionally, the concept paper states the new guideline should provide recommendations on the collection of data to support the qualification of PG biomarkers including how to define qualification context and the claims for intended use, standard methods for data collection, and formats for submission of data to regulatory authorities. However, the draft guideline does not address the claims for intended use. We recommend that the qualification submission state succinctly the specific performance claim(s) for intended use of the new biomarker that is/are supported by the qualification data provided. This could be stated in *Section 2: Summaries*, after *Context*, and before *Methodology and Results*.

4. Although the guideline describes in detail *"how"* a qualification for a genomic biomarker should be submitted it remains unclear *"when"* a submission should be done. We request that this submission not be prospectively required for clinical studies that make use of such biomarker, because in that case it might be very difficult to provide all requested information for a biomarker qualification (i.e., lines 222-269), and clinical studies could be unnecessarily delayed. Please clarify the timeline for submission.

5. We would appreciate clarification of the purpose and implications of preparing/submitting a genomic biomarker for qualification to a regulatory authority. For example, does submission or approval of a genomic biomarker qualification assure acceptance of the use of this biomarker in 'the broad context of utility' for which the genomic biomarker is qualified (e.g., a clinical drug development program, a therapeutic area)? Will submission of a biomarker qualification become a *requirement* for the use of a biomarker in a prospective clinical study?

6. We recommend that this guideline be fully aligned and complementary with the IVDMIA (In Vitro Diagnostic Multivariate Index Assays) guidance of FDA (currently a draft version).

7. We request FDA to clarify that in the situation that only pharmacogenetic information of well-established genomic biomarkers for pharmacokinetics **(**PK) (e.g., CYP2D6 genotype) is used in a regulatory Clinical Pharmacology Summary section 2.7.2., this does not automatically also result in the requirement for a separate Genomic Biomarker Qualification Summary, with all the necessary cross-links towards the Clinical Pharmacology Summary and potentially other summaries (e.g., clinical) and study results.

8. We request clarification of which FDA staff will be assigned as the primary reviewer of Genomic Biomarker Qualification Summaries. For example, what types of expertise will these staff have, and where will they be located within FDA's organizational structure?

9. Regulatory authorities may consider relabeling drugs that are already on the market based on newly evolving data on genomic biomarkers predictive for drug efficacy or

safety. Will the same principles for genomic biomarker qualification and its data submission as described in this guideline apply to and be required from all possible sources of such genomic biomarker data (i.e., pharmaceutical or biotech companies, academic laboratories, diagnostic companies, ...) before adopting the required or recommended use of such genomic biomarker in the label of a drug can be approved?

Conclusion

Thank you for this opportunity to comment on the draft guidance *ICH Topic E16: Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submission.* BIO has also provided specific comments on sections of the draft guidance in Appendix 1. In the left column of the table, we identify the paragraph in the draft guidance; the middle column contains BIO's comments and rationale to support our position; and the right column carries our suggested changes, where applicable (single strikeout for deleted text and underlined type for added text). We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Katie McCarthy
Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS ON TEXT

Location	Comment and Rationale	Proposed Change
Page 2 : INTRODUCTION, Objective, First Paragraph	Please explain why/whether "genomic" biomarkers (i.e., DNA, RNA) deserve special guidelines for a qualification submission, as compared to other biomarkers (e.g., proteomics-based markers), and whether other types of biomarkers will be addressed in future guidance.	
Page 2: INTRODUCTION, Background, First Sentence	The sentence describes the potential of biomarkers to facilitate safer and more effective medicines. In fact, however, biomarkers may facilitate the use of medicines; the medicine itself is unchanged.	We suggest the revised language, "The use of biomarkers in drug discovery, development and post-approval has the potential to facilitate ~~development of safer and more effective medicines~~ the safer and more effective use of medicines, to guide dose selection and to enhance the benefit-risk profile of approved medicines."
Page 2: INTRODUCTION, Scope of the Guideline	Will the guideline also apply to "derived" biomarkers, such as predictive algorithms (e.g., clustering method), that make use of (non-) qualified genomic and non-genomic biomarkers?	
Page4 : INTRODUCTION, General Principles, First and Fourth Paragraph.	Please explain whether "genomic" biomarkers (i.e., DNA, RNA) are different as compared to other biomarkers (e.g., proteomics-based makers), in a manner that requires special guidelines for a qualification submission.	
Page 4: INTRODUCTION, General Principles, First Paragraph.	**"**Reference should be made to the specific use of the genomic biomarker in drug development." Please broaden this statement to other application areas.	We suggest the revised language, "Reference should be made to the specific use of the genomic biomarker in drug discovery, development or post-approval or, where appropriate, in regulatory decision-making."

Location	Comment and Rationale	Proposed Change
Pages 5-6: STRUCTURE OF GENOMIC…, Context, examples (Non-Clinical Safety, Clinical Pharmacology/Drug Metabolism, Clinical Safety)	The inclusion and purpose of the three examples would be clarified if they were separated from the formal part of the document, for instance by putting them in a box.	
Page 7: STRUCTURE OF GENOMIC…, Methodology and Results, Bulleted List	Please clarify which of the bulleted items are required and which are optional.	We suggest the following language, "To achieve these objectives, this section ~~can~~ should..:" with the key sections listed, and then follow with "This section may also include..."
Page 7: STRUCTURE OF GENOMIC…, Section 3: Quality	As "drug quality and manufacturing data" are typically part of the NDA/MAA submission of a compound, one could refer to that document if applicable, and these data could be omitted from the biomarker qualification submission. This section might, however, be appropriate to describe available QC data on the "biomarker assay" characteristics.	We suggest applying this section to biomarker assay QC data. The quality standards that apply to the genomic biomarker assays should be described.
Page 8: STRUCTURE OF GENOMIC…, Nonclinical and Clinical Study Reports, First Paragraph.	It is unclear whether "full reports" of the whole (non-clinical / clinical) studies should be provided, or whether the requested "full study reports" should focus on the results of a main study that are related to and relevant for the qualification of a genomic biomarker. We recommend the latter. Please clarify.	
Page 8: STRUCTURE OF GENOMIC…, Nonclinical and Clinical Study Reports, First Paragraph.	We request that the guideline indicate that information on compliance with GLP or GCP may be included *if appropriate*. As it is now, it could be read to imply that studies should be in compliance with one or the other, which is not the case.	

Appendix 1

Location	Comment and Rationale	Proposed Change
Page 8: STRUCTURE OF GENOMIC…, Nonclinical and Clinical Study Reports, Fourth Paragraph.	Determining sample evaluability is critical to assessment of a biomarker. Therefore, the minimum criteria to ensure the quality of the specimen should be described. For example, if the proposed biomarker were a tumor DNA mutation, critical characteristics for sample evaluability may include specimen age, proportion of metabolically active cells that are tumor, DNA yield, etc.	We suggest the additional bullet, "Criteria for determining sample evaluability (e.g. age of specimen, DNA yield, etc.)".