May 20, 2014

Dear Sir/Madam:

Novartis appreciates the opportunity to comment on this important guidance document and believes labelling considerations for human prescription drug and biological products approved under the accelerated approval regulatory pathway are important for achieving effective communication of important product information. We submit the following comments for FDA’s consideration.

General Comments

Broaden The Use of Accelerated Approval Pathway

In September, 2012, the President’s Council of Advisors on Science and Technology (PCAST) issued the “Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation”.

It was highlighted that the pace of new therapeutic development has not kept up with the explosion in scientific knowledge. The number of novel drugs has remained constant for several decades, even as Research and Development budgets have substantially increased. Among possible solutions to facilitate innovation, PCAST encouraged FDA to more broadly use its current authorities.

“Expand the use in practice of FDA’s Existing Authorities for Accelerated Approval and for confirmatory evidence: The FDA should make full use of Accelerated Approval (AA) of all drugs meeting the statutory standard of addressing an unmet need for a serious or life-threatening disease, and demonstrating an impact on a clinical endpoint other than survival or irreversible morbidity, or on a surrogate endpoint, likely to predict clinical benefit. The FDA should also fully enforce its requirement for post approval confirmatory studies demonstrating that the drug indeed results in desired long term clinical benefit.”

FDASIA, Title IX, further encouraged FDA to more broadly use its AA authorities.

Novartis takes this opportunity to encourage FDA to work with stakeholders, including industry and patient groups to discuss, identify and prioritize which serious and life threatening conditions (outside of HIV and Oncology), as supported by the availability of potentially predictive surrogate endpoints or
intermediate clinical endpoints, would allow for AA of a novel therapy to bring promising treatments to patients sooner.

**Adaptive Licensing**

Over the past decade there has been ongoing debate about regulatory adaptive pathways for new medicinal products to come into the market sooner. The term provisional approval, progressive licensing, and staged approval have all been used at various times. Adaptive Licensing can be described as a prospectively planned, adaptive approach to bring drugs to market; starting from an authorized indication for a given drug and through iterative phases of evidence gathering and progressive licensing, further therapeutic uses of the drug can be approved for marketing over time. An adaptive pathway to marketing approval can maximize the positive impact of new drugs by balancing timely access for patients with the lengthy time needed to collect evidence to further characterize the drugs.

Novartis takes this opportunity to encourage FDA to formally consider a Adaptive Licensing pilot where stakeholders may convene with FDA to discuss programs for molecules that might benefit from such a staged development approach.

**Specific Comments**

Please find below our specific comments to this guidance.

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<tr>
<th>Line Number</th>
<th>Comment and Rationale</th>
<th>Proposed Action</th>
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<tr>
<td>137-140/145-147</td>
<td>For prescribers who are less familiar with regulatory pathways for expedited drug development, highlighting that the drug was approved via ‘accelerated approval’ without further context, may trigger confusion and uncertainty.</td>
<td>Novartis proposes that the Indications and Usage section include a statement that the product has satisfied the substantial evidence standard, or that the FDA considers the surrogate or early clinical endpoint(s) as reasonably likely to predict the specific clinical benefit.</td>
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<td>149-172</td>
<td>The guidance states “Although regulatory postmarketing study requirements typically are not included in labelling, a brief summary of the confirmatory study requirements can further emphasize the limitations of usefulness given the available data supporting the approval.” Novartis respectfully disagrees. It is important to keep the indication statement as clear and concise as possible. Including more specific information about data required from postmarketing studies and the data those studies</td>
<td>Novartis believes that a statement explaining Continued Approval for the indication may be subject to the requirements of confirmatory study (ies) is unnecessary. Please consider deleting all references to “continued approval”. Should FDA insists that some information explaining that continued approval is subject to verification and description of clinical benefit, Novartis believes a</td>
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might generate would not contribute to information pertaining to the appropriate patient population but instead could cloud the appropriate use information that is important for prescriber.

Prescribers would already be alerted to the fact that there are limitations to the usefulness of the product and that the clinical benefit is unknown from the other language proposed in the guidance (see lines 123-147 pertaining to Clinical Studies section). This would more likely be the information that would influence a healthcare provider’s decision to prescribe or not prescribe.

Furthermore, Clinical studies often change over time and could trigger an otherwise unnecessary revision to the full prescribing information for the product.

Conditions of continued approval as a part of a regulatory process do not belong in labelling.

general statement is more appropriate than a statement identifying specific clinical benefit objectives of confirmatory studies, e.g. “continued approval for this indication may be contingent upon verification and description of clinical benefit”

Most important, Novartis recommends that FDA take a consistent approach to the Accelerated Approved product labels.

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<td>192-194</td>
<td>Sponsor and FDA will usually collaborate on the design of the confirmatory studies such that that the study design, endpoints, etc. are agreed by FDA to decrease the chance of study failure to verify clinical/safety benefit.</td>
<td>Novartis encourages close collaboration between FDA and Sponsor on all post market required studies to confirm clinical benefit.</td>
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<td>209-215</td>
<td>If an accelerated approval indication is withdrawn, we agree that the indication, related dosage and administration and CLINICAL STUDIES section information should be removed from the respective section. If a statement is needed for the withdrawn indication, consistent language across all Accelerated Approved withdrawn indications from FDA would be helpful to the public.</td>
<td>Novartis recommends that any information pertaining to a withdrawn indication should also be removed from the CLINICAL STUDIES section. If emphasis regarding the withdrawn indication is necessary, the statement “Drug X is no longer indicated for [state indication]. Clinical studies did not confirm that Drug X is effective for the treatment of [condition/disease]” could be added to the indication statement. Additionally, Novartis believes</td>
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<td>219-228</td>
<td>The Adverse Reaction section should reflect those adverse events which occurred in the failed study should be listed in the label.</td>
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<td>Novartis agrees that only those adverse events from the failed study which are not already included in the label (from other studies) remain in the label.</td>
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<td>Most important, Novartis recommends that FDA take a consistent approach to the Accelerated Approved product labels.</td>
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Sincerely,

**Chin Koerner**

Chin Koerner  
Executive Director  
US Regulatory and Development Policy  
Drug Regulatory Affairs  
Novartis Pharmaceuticals Corporation