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Re: Request for Public Comments on Promoting U.S. EC Regulatory Compatibility[1]

On behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA) and the European Federation of Pharmaceutical Industries and Associations (EFPIA), we appreciate the opportunity to provide our collective comments on how greater regulatory compatibility could be achieved between the United States (U.S.) and the European Union (EU) for the biopharmaceutical sector. The innovative biopharmaceutical industry strongly supports efforts to address regulatory differences and duplicative requirements that can impede efficiency in global drug development, review and evaluation. Addressing these important issues can help to enhance efficiency of drug development, reduce redundant testing and optimize deployment of limited regulatory agency resources, and at the same time, lead to expedited patient access to new, innovative and life-saving medicines.

Consistent with the notices in the U.S. and the EU, we have limited these comments to specific regulatory compatibility proposals. It remains our strong position, however, that any negotiations between the U.S. and the EU to enhance the trade relationship between these regions should be comprehensive and ambitious, addressing not only regulatory compatibility initiatives, but also intellectual property protections, market access provisions, and customs, tariffs and public procurement measures. In addition to the enhanced partnership between the EU and the U.S., efforts should be made to ensure alignment in engagement with third parties. Currently both the EU and the U.S. have engagements with many countries around the world: such engagements can only be enhanced by developing a common understanding and (where relevant) a joint approach between the U.S. and the EU on key issues, to allow for high pharmaceutical policy standards and access to innovative medicines throughout the world.

[1] *See* Solicitation to EU and U.S. Stakeholders, *available at* http://trade.ec.europa.eu/doclib/docs/2012/september/tradoc_149893.pdf (last visited Oct. 31, 2012), and Request for Public Comments on Promoting U.S. EC Regulatory Compatibility, 77 Fed. Reg. 59702 (Sept. 28, 2012)

Further, as in prior free trade agreements negotiated by the EU and the U.S., our industry would strongly support the creation of a "Working Group on Biopharmaceuticals" to provide a venue for the Parties to discuss implementation issues, to ensure ongoing coordination and compatibility, and to provide a venue to address joint approaches to future compatibility topics.

Finally, the list of proposals below is not intended to be exhaustive, nor indicative of our expectations of a successful outcome of trade negotiations between the United States and Europe.[2] The list of proposals are separated into three sections: the first are those proposals that we believe could best be dealt with through a trade agreement; the second are areas that have been and will continue to be part of discussions and agreements carried out through the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH); and the third are those that also merit attention by the U.S. and the EU either in the context of a trade agreement or some other forum. The biopharmaceutical industry looks forward to further engaging with the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to explore these and any other regulatory compatibility proposals that respect the agencies' rights to ensure the public health, safety and welfare of the patients in their regions, while reducing both the regulators' and the industry's administrative burdens.

Regulatory Compatibility Proposals

As an initial matter, the biopharmaceutical industry would like to emphasize the significant partnership and coordination between the FDA and EMA, both bilaterally and internationally at the ICH. Most of the regulatory compatibility proposals identified below are founded on these existing efforts. The innovative biopharmaceutical industry believes that an enhanced EU-U.S. relationship could be a unique opportunity to seek even greater compatibility and to create streamlined processes and procedures between the EU and the U.S. To this end, our specific regulatory compatibility proposals are as follows:

I. Greater Coordination to Reduce Regulatory Burden for Sponsors and Agencies

A. Mutual Recognition of Inspection Findings

Background

The FDA and EMA have taken steps to coordinate inspections assessing compliance with Good Manufacturing Practices (GMP) and Good Clinical Practices (GCP). To date, efforts have included pilot programs and have focused on: (1) sharing of information on inspection planning, policy and outcomes; and (2) conduct of collaborative inspections. The agencies have a confidentiality agreement governing these and other exchanges. In addition, in December 2011, the FDA and EMA issued a strategy document indicating each agency's intent to defer or waive certain GMP inspections of establishments in the other's territory based on a number of factors. Further, both the U.S. and the European Commission are signatories to the Pharmaceutical Inspection Convention and participants (via the individual Member States) to the Pharmaceutical

[2] For example, there may be some instances where greater regulatory compatibility is neither feasible nor desirable, *e.g.*, in the area of orphan drug development.

Inspection Co-operation Scheme (jointly referred to as PIC/S), which provide together an active and constructive cooperation in the field of GMP. Despite this high level of cooperation, each agency currently does not routinely rely on the other's inspection findings. Moreover, until recently, the FDA was barred from sharing trade secret information related to an inspection with a foreign regulator.

Proposal

The EU and U.S. should mutually recognize each other's GMP and GCP inspections. This recognition could encompass inspections by European inspectors within the European Economic Area (EEA), FDA inspections of U.S. sites, and inspections that both European and U.S. inspectors conduct outside the U.S. and EEA. As part of these efforts, and in line with the EU's longstanding approach of conducting risk-based inspections, the regulatory authorities could work together to identify systematically high-risk sites and coordinate inspection schedules.

Legal Provisions or Policies Requiring Amendment

No amendments to EU law are necessary, though individual member states of the European Union may need to revise their laws to provide mutual recognition of FDA GMP and GCP inspections. The FDA now has express authority to implement this proposal for GMP inspections, and the agency likely has implicit authority to do so with respect to GCP inspections. The FDA will need to follow statutory procedures, however, and the parties likely will need to execute a new confidentiality agreement.

Specifically, the Food and Drug Administration Safety and Innovation Act (FDASIA), enacted July 2012, granted the FDA explicit authority to implement this initiative with respect to inspections of registered facilities (*i.e.*, facilities that manufacture, prepare, process, propagate, or compound drugs). FDASIA created new section 809 of the Federal Food, Drug, and Cosmetic Act (FDCA), which allows the FDA to enter into "arrangements and agreements" to recognize the foreign agency inspections of registered facilities and use them as evidence of compliance with GMP.

To utilize its authority under section 809, the FDA first must follow statutory procedures. The FDA first must determine that the foreign government is capable of conducting inspections that meet the applicable requirements of the FDCA, after performing appropriate reviews of the foreign agency's standards and systems. The parties will then need to enter into an "agreement or arrangement." Given that the EMA and FDA have already been collaborating extensively in this space, these procedural aspects likely can be discharged quickly.

In order to share "trade secret" information gleaned from inspections with European regulators, the FDA will need to take two steps under another new FDCA provision, section 708(c). The FDA would have to obtain a written agreement from the EU affirming: (1) the EU's authority to otherwise obtain this information; (2) its commitment to protect the information from disclosure, except in certain narrow circumstances; and (3) its commitment to use this information only for civil regulatory purposes. The Secretary of Health and Human Services also must certify that the

EU has the authority and demonstrated ability to protect the trade secret information, before sharing such information.[3]

B. Parallel Scientific Advice

Background

The FDA and EMA have established a program to provide parallel scientific advice. Under the current program a sponsor has no right to parallel scientific advice and may obtain it only in limited circumstances. More specifically:

- The scope of products covered by the program is limited (*e.g.*, products covered by a current "cluster" of interest between the FDA and EMA, products with significant clinical safety, animal toxicology, or unique manufacturing concerns).

- A sponsor may request parallel scientific advice, but must justify the request, and there is no guarantee that the EMA and FDA will grant it.

- After the parallel scientific advice meeting, each agency provides its own independent advice, according to its own standards and procedures.

Proposal

The EMA and FDA should amend the current policy document governing parallel scientific advice to: (1) expand its applicability to all medicines; and (2) grant sponsors the right to receive parallel scientific advice upon request.

Legal Provisions or Policies Requiring Amendment

EMA/FDA, *General Principles*, *EMEA-FDA Parallel Scientific Advice* (July 2009) (EMEA/24517/2009). The EMA and FDA should modify this policy document in three respects.

- Eliminate the statements, in the current policy preamble and current paragraphs 2 and 3, which limit the scope and number of parallel advice meetings. Substitute text stating that the parallel scientific advice procedure is available, upon request, to sponsors of all medicines.

- In current paragraphs 5 and 6, delete the requirement for sponsors to justify a request for parallel scientific advice and the statements that FDA and EMA may decline such a request. Substitute language providing that sponsors have a right to receive parallel scientific advice upon request.

- Revise current paragraphs 4 and 8 of the policy to provide for a procedure for reaching agreements on the development plan for a medicine.

[3] FDA will need to revise its current regulations, including 21 C.F.R. 20.89 (on sharing information with foreign government officials) to reflect the new FDASIA provisions.

C. Parallel Evaluation on Quality by Design (QbD) Applications

Background

The FDA and EMA are piloting an effort to conduct parallel assessment of "Quality by Design" (QbD) applications that is intended to allow for the parallel evaluation of relevant development and manufacturing quality components that are submitted to both agencies.

Proposal

If the current pilot program for the FDA and EMA to conduct parallel assessment of Quality by Design applications is successful, it should be formally adopted by the agencies.

Legal Provisions or Policies Requiring Amendment

A formal policy for the FDA and EMA to conduct parallel assessment of Quality by Design applications should be adopted.

II. Increase Collaboration under the Auspices of the ICH to Secure Greater Regulatory Compatibility

The FDA and EMA cooperate under the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) to achieve greater compatibility in the interpretation and application of technical requirements for product registration. This cooperation has been fruitful in bringing harmonized regulatory expectations forward and has helped reduce some levels of uncertainty associated with global pharmaceutical development. At the same time, efforts should be made to avoid future divergence in the regulation of medical products. The following topics describe areas where the EMA and FDA could further collaborate under ICH to avoid continued divergence and encourage greater regulatory compatibility.

A. Pediatric Medicines

Background

Although the EU and U.S. requirements for the conduct of pediatric studies for certain new drugs and biological products are similar, there are significant divergences in approach between the EMA and FDA. Different requirements imposed by the agencies with respect to the design of studies can lead to additional exposure of children to investigational products in clinical trials, while issues regarding timing of submissions and content of pediatric plans can lead to significant burdens on pharmaceutical companies and delays in the approval of medicines. More specifically:

- The scope of the paediatric investigation plan (PIP) in the EU and the pediatric plan in the U.S. are different. In particular, in the U.S., companies are required to generate pediatric data for the indications that the company intends to apply for with respect to the

adult population. The EMA, however, requires companies to generate data for the condition, rather than the specific indications within that condition, and so requires more studies to be conducted than is the case in the U.S. Further, the EMA requires studies in indications for which the applicant has no intent to seek a corresponding indication in adults, including in orphan indications.

- In addition, for the same pediatric indications the EMA and FDA may require different study designs or end-points, leading to duplication of studies and additional exposure of children to investigational products in clinical trials.

- The different timing for PIPs and Pediatric Plans in the EU and U.S., respectively, presents a challenge to the industry as the PIP, including specific pediatric clinical trials, as agreed to with EU regulators may not necessarily be accepted by the FDA Pediatric Review Committee. Due to different requirements in the regions, there is a risk of having to conduct separate trials in the U.S. and EU.

Proposal

The FDA and EMA should work together to achieve greater regulatory compatibility in the scope, content and timing of submission of PIPs and pediatric plans, so that companies are required to prepare only a single plan for submission in both territories. Agreement on the requirements of pediatric plans between EU and U.S. regulators could help drive greater research efficiencies and speed the completion of pediatric trials. Greater convergence of templates and requirements for the development of pediatric medicines should be encouraged. The use of a common planning milestone would greatly improve the industry's ability to conduct efficient clinical trials and result in speedier access to information derived from the trials. Companies should be given greater flexibility to decide when to submit PIPs/pediatric plans so that companies can submit the plans in both territories at the same stage of product development.

Legal Provisions or Policies Requiring Amendment

This proposal requires longer-term collaboration between the EMA and FDA within ICH to revise and develop policies for the content, review, and timing of submission for PIPs/pediatric plans.

B. Safety Reporting Requirements

Background

There are disparities between the EU and U.S. approaches to safety reporting requirements, including safety reports for drugs subject to an investigational new drug application (IND) in the U.S. In addition to existing disparities, many recent changes in pharmacovigilance practices are leading towards greater divergence. These changes include the safety reports for the IND in the U.S. and the Good Vigilance Practices in the EU. Some of the U.S. requirements at issue were added to the FDCA or regulations somewhat recently, and the FDA's approach to their implementation, is still evolving. Therefore, specific harmonization proposals would not be

appropriate at this time, but both agencies could benefit from further collaboration on these issues. Such collaboration could be advanced under the auspices of the ICH.

Proposal

The agencies should add a cluster on pharmacovigilance issues to their existing slate.[4] Although the EMA and FDA collaborate on some pharmacovigilance topics already, a cluster would help formalize this arrangement and expand its scope to include topics such as post-market testing and risk management requirements and format and deadlines for adverse event reporting.

Legal Provisions or Policies Requiring Amendment

The EMA and FDA could establish this cluster under existing law, with information exchange activities governed by existing confidentiality agreements. A more harmonized approach to safety reporting requirements, including those required for drugs subject to an IND, should be considered within ICH.

C. Duplicative Clinical Testing Requirements – Revision of ICH E5

Background

The FDA and EMA have adopted ICH E5, which describes considerations for accepting foreign clinical trial data to support approval of the tested medicine in the EU or U.S. In practice, the EMA and FDA may require unnecessarily burdensome bridging studies before a sponsor may gain approval of a medicine based on foreign studies of that medicine. The U.S. and EU should work together, under the auspices of ICH, to significantly reduce the requirements of these bridging studies.

Such an agreement between the EU and U.S. to eliminate requirements for local bridging studies would have further benefits in discussions with third countries, such as China, where these studies are a major source of delay in the introduction of new medicines.

Finally, multi-regional trials with an appropriate number of subjects in the EU and U.S. have the potential to reduce or eliminate the need for bridging studies, but existing guidance on multi-regional trials is not detailed.

Proposal

The EMA and FDA should work under the auspices of ICH to revise existing guidance, with the aim of significantly reducing requirements for local bridging studies.

The agencies also should collaborate to provide harmonized advice on design of multi-regional trials that could support approval in both regions. The agencies should consider providing this

[4] Clusters are topic areas of mutual interest for the two agencies, which they have identified as benefiting from the regular exchange of information and collaborative meetings.

advice in the form of a new ICH guidance or revisions to existing guidance on acceptability of foreign studies.

In addition, the agencies should grant applicant requests for joint advice meetings on design of multi-regional studies. These meetings could occur under the EMA/FDA parallel scientific advice policy, revised as described above.

Legal Provisions or Policies Requiring Amendment

Revise the following two existing guidelines' content on bridging studies: *ICH E5: Ethnic Factors in the Acceptability of Foreign Clinical Data* and *ICH E5 Questions and Answers.*

New ICH guidance on multi-regional trial design (or revise and expand above guidances' content on this topic).

The above-described revisions to EMA/FDA, *General Principles, EMEA-FDA Parallel Scientific Advice* (July 2009) (EMEA/24517/2009).

D. Benefit-Risk Assessment

Background

Both the EMA and FDA have efforts underway to develop methods and tools for a structured, systematic, and transparent approach to benefit-risk assessment in the drug review and approval process. Although these efforts have shown progress, this progress is occurring at different rates and in the absence of agreement on a common framework and methodology for benefit-risk assessment. Such divergence in approaches could significantly burden industry as regulatory requirements evolve.

Proposal

The EMA and FDA should develop a harmonized structural framework and methodology for benefit-risk assessment, while retaining authority to make different risk-benefit judgments under their individual approval schemes.

Legal Provisions or Policies Requiring Amendment

The agencies could begin this harmonization effort in connection with the FDA's execution of its five-year plan, under PDUFA V, to develop and implement a structured risk/benefit assessment. Pursuant to the PDUFA V performance goals, the FDA is due to publish a draft risk/benefit assessment plan in the first quarter of 2013 and implement it by the end of 2013. The FDA could seek EMA input on its initial plan, integrating feedback where appropriate, at this time.

As a longer-term plan, the agencies could collaborate within ICH to agree jointly on a procedural/policy document describing a harmonized structural framework for risk-benefit assessment.

E. Submissions Requiring Manufacturing Changes

Background

At a high level, the EMA and FDA have similar requirements for submissions about manufacturing changes. Both have broadly divided these changes into minor, moderate, and major variations and tailored requirements for submissions and preapproval by category, with the most significant changes requiring preapproval. The details of these schemes, however, are discordant. We believe there is merit in considering a more strategic approach to life-cycle management of Chemistry, Manufacturing and Controls (CMC). Specific consideration should be given to the need for a common approach to the format and content of post-approval change management protocols and harmonization of ICH guidelines of technical criteria to evaluate manufacturing changes.

Proposal

The agencies should work together to develop a harmonized approach to post-approval variation submissions for manufacturing changes, including with respect to: (1) the types of changes that should be considered minor, moderate, and major; (2) the type of submission that needs to be filed for each type of change and the time frame for that submission; (3) the ways (platform-) changes over different products can be bundled; and (4) situations when pre-approval is needed.

Legal Provisions or Policies Requiring Amendment

Depending on the changes proposed, the following legal provisions or policies might require amendment:

- U.S.: FDCA § 506A, 21 C.F.R. 314.70, 21 C.F.R. § 601.12, and related guidance documents.

- EU: Commission Regulation (EC) No 1234/2008, and *Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products* (2010/C 17/01).

III. Miscellaneous Proposals

A. Data Field Requirements for Clinical Trial Disclosure

Background

The U.S. and EU have similar policies for the reporting of clinical trial results in public databases, although the data fields are not identical. There are also differences between the U.S. and EU in terms of the clinical trial result data fields disclosed to the public.

Proposal

The EU and the U.S. should collaborate to establish a harmonized list of clinical trial result data fields, and agree on which of these data fields may be disclosed to the public.

Legal Provisions or Policies Requiring Amendment

The following policies or provisions would need to be amended:

- Commission Guideline — Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 (2012/C 302/03).

- Public Health Service Act § 402(j)(3) (with release of a proposed rule implementing this provision supposedly imminent).

Moreover, it is imperative that both the U.S. and the E.U. have uniform protection of confidential commercial information and trade secrets in their respective clinical trial disclosure programs. Such protections are necessary to maintain incentives to invest in innovative medical research and are consistent with 21 C.F.R. §§ 312.130; 312.45(c); 314.430; 601.51(c) and Article 39(3) of the World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights.

B. Collaborative Process for Developing Therapeutic Area Guidelines

Background

The FDA and EMA currently develop their own independent guidelines for the development of products in specific therapeutic areas. The different regulatory requirements can be burdensome for companies and lead to delays in getting new treatments to market.

Proposal

The FDA and EMA should establish a procedure for collaborative development of scientific and other regulatory guidelines for specific therapeutic areas.

Legal Provisions or Policies Requiring Amendment

The Agencies should adopt a new policy to describe a process for collaborative development of therapeutic area guidelines. Both the FDA's and the EMA's existing rules for the development of guidance permit consultation with interested parties and the guidelines would still be independently adopted by the agencies, so no legislative changes should be necessary.

C. Falsified Medicines – Product Verification

Background

The U.S. and EU are each working towards the creation of national/ regional coding systems for use through the entire medicines supply chain, from manufacturer to prescriber.

In the EU, Directive 2011/62/EU introduces obligatory "safety features" to allow, inter alia, verification of the authenticity of medicinal products for human use ("unique identifier"). The Directive places the European Commission under an obligation to adopt delegated acts setting out the details relating to the unique identifier. A concept paper has been published for public consultation with a view to preparing both the impact assessment and the delegated act.

Proposal

The EU and U.S. should work together to ensure national/ regional coding systems are based on common standards for the use of unique identifiers, developed using non-proprietary, harmonized international standards.

Legal Provisions or Policies Requiring Amendment

The EU and U.S. could collaborate under existing law to ensure systems are based on common standards for the coding systems of medicines. This system could then be implemented in the EU through delegated acts adopted by the European Commission pursuant to Directive 2011/62/EU. In the U.S., new legislation could be required to implement the system.