Public consultation on the future of EU-US trade and economic relations.

Proposals for the EU-US High Level Working Group (HLWG) for Jobs and Growth and the High Level Regulatory Cooperation Forum (HLRCF): October 2012

Introduction

This paper provides 4 **regulatory harmonization and standardization** proposals affecting the EU and US **pharmaceutical industries** for consideration by the EU-US HLWG for Jobs and Growth and by the HLRCF, viz., a Mutual Recognition Agreement, Regulatory Assessment of Changes, Harmonisation of Pharmacopoeia, and Good Manufacturing Practices (GMP) Certification.

I. A MUTUAL RECOGNITION AGREEMENT (finished drug products and active pharmaceutical ingredients (APIs))

In the late 1980s considerable exchange took place between the US FDA and the EU to establish a Mutual Recognition Agreement (MRA)[i] in the field of GMP Inspections for pharmaceutical products. This was in line with similar such initiatives in other industrial sectors and with other regions such as Australia, Canada and Israel. However, the US and EU were unable to successfully conclude such an agreement.

In 2007, under the auspices of the Transatlantic Economic Council (TEC), a Transatlantic Administrative Simplification Workshop was held. An outcome of this was an action plan devised to support collaboration between the US FDA, The European Medicines Agency and National Medicines Agencies of the EU Member States. An important component of this was a joint inspection programme piloted by the US FDA and The European Commission and EMA in 2009. This pilot was deemed such a success at the end of 2010 that a continuing FDA-EU cooperation was confirmed [ii] in January 2012. However, the joint inspection program is limited (to only a few sites), uses a duplication of resources, and does not meet the need of today's challenging regulatory environment.

It is paramount to have a mutual agreement between the US FDA and the EU as soon as possible, thus the need to restart discussions around an MRA in the context of the Regulatory Cooperation Component to the EU-US Economic Agreement given the extended and cooperative contacts that have been on-going for the last 20 years culminating in the Simplification Action Plan. The benefits to EU-US trade are as follows:

1. There would be an immediate savings in inspection resources to agencies on both sides of the Atlantic.
2. Given the continued growth and current high level of dependency in the supply of pharmaceuticals and active pharmaceutical ingredients from so-called third countries, EU and US Agencies would be able to refocus their inspection efforts to 3rd countries - where no mandatory inspection of API and final dosage form suppliers is currently in

place. This would be very much aligned with the objectives of the EU through its Falsified Medicines Directive and the US GDUFA (Generic Drug User Fee Act [iii]) initiative. It would also be supportive of the Medicrime Convention and works towards improving product quality; in the GDUFA negotiations, industry presented a strong case for mutual agreements and FDA committed to reviewing this request.

3. It would benefit the health of EU-US citizens. It would promote EU-US trade and lead to further harmonisation of GMP standards aligned with International Conference on Harmonisation (ICH) process.

It is recommended that discussions between the US FDA and the EMA should be commenced as soon as possible with a view to finalising an MRA for pharmaceutical products including APIs. The Transatlantic Simplification Action Plan can be used as a basis for commencing this dialogue.

II. REGULATORY ASSESSMENT of CHANGES

From the pharmaceutical regulatory perspective there is also a concern that a certain type of change in the manufacture or control of APIs is assessed differently in US versus EU. For instance, what one region would consider a major change could in the other region be an annual reportable change? A change that can be implemented and only *after* implementation be reported to the health authorities versus a change that needs to be reviewed and thoroughly assessed *prior* to formal notification from the health authorities that implementation of the change is allowed.

That difference in assessment costs time and money for global companies since for API manufacturers it is difficult to implement changes *per region*. The revision of the EU Directive (COMMISSION REGULATION (EC) No 1234/2008) was an attempt or first step, but definitely not the end.

It is recommended that the US FDA and EU work an agreement for annual reportable changes as a first step.

III. HARMONISATION OF PHARMACOPOEIA

Given the globalization of the pharmaceutical industry, it would be beneficial to also have a global standard for pharmacopoeia, starting with those for the EU (Ph Eur) and US (USP).In reality, the different requirements rarely show any differences in the quality of the raw materials or products, yet the cost to industry of unnecessary multiple testing is significant without any improvements in efficacy, quality or safety to benefit the patient.

Since the Ph Eur and USP each have to cope with a huge work programme, harmonized monographs or mutually recognized monographs elaborated by one party and acknowledged by the other would bring considerable relief to both the Ph Eur and the USP.

Whilst recognising that there has been some progress on harmonisation over the past 20+ years (e.g., via the Pharmacopoeial Discussion Group in the 90's and ICH Q4B in 2003), this has been a slow process and more effort is needed. An EU-US common standardization initiative could re-vitalise this activity, irrespective of the different regional status of the issuing bodies (the Ph Eur is

issued by the European Directorate for the Quality of Medicines (EDQM), a European authority, whereas the USP is a private organization).

IV. GOOD MANUFACTURING PRACTICES (GMP) CERTIFICATION

The EU has reformed the rules for importing into the EU APIs for medicinal products for human use. As of 1st January 2013, all imported APIs must have been manufactured in compliance with standards of GMP at least equivalent to the GMP standards of the EU. As of 1st July 2013, this compliance must be confirmed in writing by the competent authority of the exporting country and the certification accompany the API being imported. The European Commission has provided a template for the compliance letter that would communicate all of the required information. The EC has stated that the certification is independent of the existence of MRAs, and the only means of exception from the written certification will be for exportation from a country which, following its request, has been assessed and considered as having equivalent rules for GMP to those in the EU.

Both the EU and USFDA subscribe to the use of the standards of the International Conference on Harmonization (ICH) Q7 for the manufacture of APIs, and so equivalency of standards should not be an issue for US manufacturers of APIs that wish to export to EU countries. The US FDA has historically refused to issue GMP certifications to US manufacturing sites other than by issuance of a Certificate of Pharmaceutical Product; however, this certificate does not provide all of the information specified by the EC in its template.

It is recommended that discussions should commence as soon as possible between the US FDA and the EC with a view to determining a way forward so as to prevent the construction of a trade barrier to the exportation of APIs from the US to EU countries. Possible ways for resolution include application by the US for assessment of GMP equivalency, or acceptance by the EC of the current or a modified Certificate of Pharmaceutical Product as satisfying the need for written confirmation. Failure to resolve this issue will result in the reduction of trade between the EU and US, and the possible creation of drug shortages in the EU resulting from the unavailability of APIs manufactured in the US.

Footnotes:

[i] Mutual Recognition Agreements or MRAs allow trading countries to mutually recognise technical standards and/or quality systems, hence removing a technical barrier to trade. In order to enhance trade with its main partners the EU has been active in pursuing such MRAs with a number of them. MRAs cover a wide range of industrial sectors. Of primary interest to the pharmaceutical sectors are annexes to MRAs that deal specifically with Current Good Manufacturing Practices (cGMPs). CEFIC's APIC and EFCG have supported the establishment of MRAs for a number of years as they see these developments as being supportive of both the continued growth of the API sector in the EU and the expansion of trade. They also see MRAs playing a supportive role in the harmonisation of standards

across the globe and, therefore, would view MRAs as being complimentary to the International Conference on Harmonisation (ICH) process...

[ii] News Release "Joint FDA-EMA Inspection program to Launch in January 2012" and the document "Enhancing GMP inspection cooperation between the EMA and FDA"

[iii] For details please see

http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm
or
http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf

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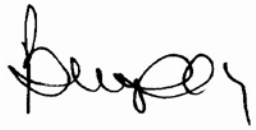

October 9, 2012

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