Technical paper for regulatory cooperation on generic medicines Proposal of the European Union

I. Introduction

The EU position paper on TTIP and pharmaceutical products[1] states that one of the areas were EU-US cooperation should be pursued is the further harmonisation of EU and US technical requirements for the authorisation of generics. The purpose of this paper is to explore some ideas to foster that objective.

Aside of innovative medicines, generic medicines are an important part in the therapeutic offer both in the US and the EU. In the EU, it is reported that more than 55% of all dispensed medicines are generics. Similarly, in the US, nearly 8 out of 10 prescriptions are filled for generic drugs. In both regions, generic products allow substantial savings for patients and contribute to the sustainability of healthcare systems.

The globalisation of the production of medicinal products results in the fact that generic products, similarly to innovative products, are increasingly subject to applications for authorisation in the EU and the US. This creates new opportunities for the protection of public health and calls for strengthening collaboration amongst regulatory authorities. The convergence of authorisation requirements for generic medicines that will be placed on the market in the EU and the US can notably bring substantial benefits in terms of improving patient access to medicines. Timely access to new generic medicines may be facilitated through strong synergies in the preparation and the submission of marketing authorisations. In addition, it offers opportunities to reduce the number of clinical trials and thereby the exposure of human subjects.

The following objectives are proposed as potential short-term objectives where substantial progress could be expected prior to the conclusion of the TTIP negotiations. The experience registered in the context of a reinforced EU-US collaboration on generics may pave the way to shape the regulatory cooperation in this area after the conclusion of the TTIP. Although the objectives hereunder are primarily identified as being beneficial for generic medicines, some of them are also relevant for market applications of all medicinal products. Similarly, the objective of achieving mutual recognition of Good Manufacturing Practice (GMP) inspections that has already been identified as a TTIP objective is beneficial for all medicinal products, including generic medicines.

[1] *http://trade.ec.europa.eu/doclib/docs/2014/may/tradoc_152471.pdf*

II. Proposed objectives

Objective 1. Working with other strategic partners on the development of international regulatory collaboration on generics

The International Generic Drug Pilot (IGDRP)[2] was launched in April 2012 in Washington by an international group of regulators and WHO. Given the success of the initial phase of the Pilot, members of the IGDRP have decided to deepen the exploratory phase through engaging in a Program that will end in December 2016[3]. As part of IGDRP activities, the EU with the regulatory agencies of Health Canada, Swissmedic, Taiwan FDA and Therapeutic Goods Administration of Australia, is involved in an information sharing pilot. The objectives of this pilot are to facilitate and to strengthen the scientific assessment of generic medicines through the exchange of information related to the assessment of applications submitted to the different jurisdictions. This information sharing is building on the mechanisms that are in place in the EU in the framework of the decentralised and the centralised procedures for the authorisation of medicinal products. IGDRP is also pursuing other projects aiming to facilitate the exchange of information for the scientific assessment of generic products notably through the development of converging requirements for the presentation of the Active Substance Master File (ASMF)/Drug Master File (DMF) or BCS (Biopharmaceutics Classification System) Biowaiver assessment reports and documentation.

The EU and the US should be fully engaged on these activities and seize the opportunities to increase regulatory collaboration for generic medicines and convergence of authorisation procedures. This collaboration would contribute to improve patient access to generic products meeting high standards of safety, efficacy and quality in the EU, in the US as well as in international partners.

Objective 2. Harmonisation of BCS (Biopharmaceutics Classification System)-based biowaivers

As described in the EMA guidance[4], the BCS-based biowaiver approach allows to reduce the number of *in vivo* bioequivalence studies by addressing, under certain conditions, the question of bioequivalence between specific test and reference products on the basis of satisfactory *in vitro* data. The approach may be used to establish bioequivalence in applications for generic medicinal products, extensions of innovator products, variations that require bioequivalence testing, and between early clinical trial products and to-be-marketed products.

The EU and US could work towards the harmonisation of their guidelines on BCS-based biowaivers. This work could be performed in the framework of the International Conference for Harmonisation of technical requirements for the registration of medicinal products (ICH).

[2] *http://www.who.int/medicines/publications/druginformation/DI_28-1_Regulatory-Harmonization.pdf*
[3] *http://www.igdrp.com/*
[4] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

Objective 3. Towards harmonisation of clinical data requirements for products subject to hybrid applications often referred to as "complex generics"

In the same way than biosimilars, "complex generics" require the performance of pre-clinical tests and clinical trials for their authorisation. Applications for this type of products are subject in the EU to Article 10.3 of Directive 2001/83 (« hybrid applications ») and in the US to "abbreviated applications". In line with the common EU-US approach on biosimilars, the EU and the US could consider whether it is appropriate to review their respective guidelines for hybrid/abbreviated applications. The objective would be to decrease the duplication of clinical trials and facilitate the global development of this type of products. In the case of the EU, this revision would allow an applicant to compare its product, in certain studies and under certain conditions, with a non-EU comparator that is authorised by a regulatory authority with scientific and regulatory standards similar to the EU (e.g. US). Further joint EU-US scientific work is needed to develop these guidelines that would specify the requirements that a product would have to meet to be acceptable as comparator (i.e. the requirements to be considered as representative) as well as the studies and the conditions under which the use of such comparator would be acceptable.