



PHARMACEUTICAL COMMITTEE
7 November 2019

Subject: Note to the Pharmaceutical Committee updating on the actions undertaken with regard to the quality of Active Pharmaceutical Ingredients (API)¹

Agenda item 7

One of the priorities identified by the Pharmaceutical Committee in its working programme is to enhance the security and oversight of the global manufacturing chain. The purpose of this note is to update the Pharmaceutical Committee on the actions undertaken in order to ensure the quality of API used for the manufacturing of medicinal products.

1. Background information

The availability of APIs of high quality for manufacturing of medicinal products for the EU market is a growing concern. The manufacturing issues, often related with the API quality, are one of the major reasons of shortages of medicinal products in the EU.

The Pharmaceutical legislation requires that the API used for manufacturing of medicinal products for the EU market comply with EU Good Manufacturing Practices. National competent authorities of the Member States supervise the compliance to good manufacturing practices by conducting risk-based inspections of the active substance manufacturers. In 2013, the 'Falsified Medicines Directive'² introduced two additional distinct control mechanisms for the import of active substances:

- An imported active substance shall be accompanied by a written confirmation issued by the competent authority of the third country of origin. The written confirmation must state that the active substance has been produced according to EU equivalent standards of GMP.

¹ This document has not been adopted by the European Commission and, therefore, it does not reflect an official position of the European Commission. It is only meant to be a tool for discussion and the views expressed therein do not necessarily reflect those of the Commission and its services.

² Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products; OJ L 174, 1.7.2011, p. 74–87

- Alternatively, third countries can opt to be listed as having a regulatory framework and the respective control and enforcement activities in place to ensure a level of protection of public health equivalent to that in the EU. The Commission is responsible for carrying out equivalence assessments before and after listing. Active substances from listed countries such as Australia, Brazil, Israel, Japan, the Republic of Korea, Switzerland and the United States of America can be imported without a written confirmation.

The majority of APIs used for manufacturing of medicinal products for the EU market come from India and China. Neither India nor China are listed. Compliance of the APIs coming from these countries with the EU GMP relies on the written confirmations issued by their competent authorities. The recent quality incidents involving the APIs sourced from China and India (cases of nitrosamine contamination of Valsartan and Ranitidine) raised questions on whether the system of written confirmations provide sufficient guarantees that imported APIs are manufactured in accordance with GMP rules. DG SANTE is taking several actions to remedy the identified shortcomings in the implementation and design of the system. Actions proposed focused on increasing the oversight on the GMP system of the third countries in question. This is meant to be achieved by promoting the cooperation, encouraging these third countries to align the regulatory framework with international EU standards and undergoing a fact-finding assessment of their GMP system. In the long run, this could eventually lead to the listing of these countries as equivalent.

2. Progress report on the actions undertaken

Short-term actions

- In order to **strengthen the verification by the EU national competent authorities of the written confirmation and their oversight**, DG SANTE proposed during the 95th meeting of the Good Manufacturing and Distribution Practices Inspectors Working Group (GMDP IWG) at EMA amendments of the Compilation of Community Procedures for inspection. The amendments aim at ensuring the proper verification by the authorities of the related obligations of manufacturer as well as address the issue of handling the situations when the written confirmation is issued for the sites that had been found non-complaint. The proposed amendments will be tabled for the GMDP IWG approval in mid-2020.
- In order to **promote listing and encourage non-listed countries to undergo an assessment of the regulatory and control system** DG SANTE raised the issue of cooperation with regard to APIs during the bilateral EU/China meeting in October 2019. It was agreed with the Chinese National Medical Products Administration (NMPA) to establish an EU/China working group on APIs. This working group would involve DG SANTE (B4 and F5), EMA, EDQM and some Member States (to be identified). A gap analysis is planned in order to identify similarities and differences between the Chinese and EU regulatory systems for APIs. This gap analysis would be used to identify the Chinese training needs on APIs matters. The programme foresees as well a fact-finding visit of EU experts to China , in order to assess the regulatory, control and enforcement system in place governing the implementation of GMP API standards. The European Commission has secured a budget for this purpose.

- As regards the proposed **relocation of the inspection resources from listed to non-listed countries**, metrics were requested by EMA from Member States on the number of inspections not conducted every year in the US thanks to the US-MRA. Once the metrics are available, DG SANTE would like to raise the question with GMDP IWG, Pharmaceutical Committee and HMA on possible relocation of saved inspection resources to API inspections in India and China.
- While the final **lesson learned in cases of unexpected nitrosamine impurities in APIs** are not available yet, the preliminary draft suggest the necessity to better ensure that marketing authorisation holders (MAHs) fulfil their legal responsibilities for the quality of their product. It is important to strengthen the overview by the MAH taking into account that some of APIs manufacturers concerned did not carry out an investigation of the root cause of the quality issue and did not understand the principles of the quality risk management. Another point of concern was that in some cases, the MAHs do not have access to enough information regarding the API manufacturing and control process where API is registered via active substance master file (ASMF) or certificate of suitability (CEP), as this information is considered as commercially confidential by API manufacturers. The lesson learned points also to the necessity **to increase the exchange of information on planned GMP inspections with international partners and support EU national competent authorities' participation in collaborative inspection programs of active substance manufacturers** such as the EDQM inspection programmes and the International API inspection programme. Once the lessons learned document is finalised (planned in 2Q2020), it would be necessary to analyse how it could be implemented, taking into account the Commission, EMA and Member States responsibilities.
- As regards the **strategic dialogue with US** on the strengthening of the monitoring of the quality of the APIs manufactured in third countries, the FDA was contacted on a project of a joint training plan for Indian and Chinese inspectors involved in the inspections of APIs manufacturing sites. Japan and WHO also expressed interest in being involved in the project. Information on inspectors trainings in China and India in the 3 years 2019-2020 were requested from EMA, FDA, Japan and WHO. The information received included only relevant events in 2019, so an update for 2020-2022 will be requested. EMA is organising collection of information on scheduled events for 2020-2022 and a further teleconference during 1Q2020.
- In addition to that, a working group has been established by EMA to analyse the practical modalities and conditions for **recognition of inspections conducted by US and Canada in third countries** (including of the API producing sites) in order to give full effect to the provisions of those Agreements. A possibility of reliance on the inspection findings by US and Canada would facilitate a better allocation of the Member States inspection resources. Therefore, the amendments of the other MRA agreements that does not provide for such a recognition could also be also considered. EMA Working group mandate is to propose the set of measures necessary to implement the relevant provisions of CETA and US MRA, including if necessary a proposed amendments to the Compilation of the Community Procedures.

Long-term actions:

- As regards the EU dependency on the API manufactured in China, DG SANTE initiated a dialogue with GROW **to explore the possibility of facilitating production of the API in Europe**. SANTE and GROW organised meetings in December 2019 with the representatives of the pharmaceutical value chain (API producers and representatives of pharmaceutical industry) to explore the current market situation and possibilities of alliance between API and finished medicinal products producers.
- The nitrosamine contamination crisis confirmed the importance of the **cooperation on the quality standards for medicines with the Council of Europe**. DG SANTE plans to continue to cooperate with EDQM for incidents or crisis situations.
- The financial support will be pursued in annual working plan for 2020 for the **HMA Joint Audit Program**, which allows the Member states an assessment of their audit system, including the assessment of the training needs of their inspectors.

The Pharmaceutical Committee is invited to **provide comments** on the actions presented. DG SANTE would also like to ask the Pharmaceutical Committee members **to volunteer to join the join the EU/China working group**.