Pharmaceutical Industries Ltd.

Date: November 24, 2015

To: European Commission
DG Health and Food Safety
Unit D6 "Medicinal products – Quality, Safety and Efficacy"

(by email to: SANTE-D6-DA-GMP-IMP@ec.europa.eu)

From: Teva Pharmaceutical Industries Ltd

Subject: DA on GMP for IMP – Public consultation on Commission Delegated Act on principles and guidelines on good manufacturing practice for investigational medicinal products and on inspection procedures, pursuant to the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014

Dear Madams, Dear Sirs,

See below Teva comments on the European Commission Delegated Act submitted for public consultation.

Teva Pharmaceutical Industries, duly represented by the private individual(s) indicated herein below, is a stakeholder company with affiliated companies incorporated and active in many Member States of the European Union ("EU"), manufacturing, marketing, distributing and selling Active Pharmaceutical Ingredients ("APIs") and/or Finished products.

Teva does not fall within the EU definition of a small or medium- sized enterprise.

Question 1a:
Would a requirement for a product specification file (a reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product) be useful to be introduced?

Response
Teva considers the Product Specification File (PSF) as a useful set of documents provided the information and terminology of documents in the PSF is aligned with the manufacturing information submitted as part of the Clinical Trial Application, and no submission of additional documents will be required. We recommend that only the relevant part of the PSF for the on-site activities will be required at the manufacturing site.

Question 2:
Different options exist for the retention period of batch documentation:
a) Retention for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used, whichever is the longer period.
b) Retention for at least 25 years after the end of the clinical trial in line with the retention period of the clinical trial master file.
Please indicate the preferred option with justification.

Response
Teva would prefer to align the retention period of batch records with the retention period of the clinical trial master file.

Question 3:
Would it be feasible to require that Certificates of Analysis should accompany each shipment of imported investigational medicinal products as a means to ensure that analytical control had been carried out in the third country? Please elaborate your answer to this question.

Response
Teva believes that there is no added value to require that Certificates of Analysis (CofAs) accompany each shipment. Each imported investigational medicinal product batch need to be certified by a EU QP and one of the routine controls as part of this certification process is a detailed review of the CofA for compliance with the information submitted in the Investigational Medicinal Product Dossier as part of the Clinical Trial Application.

Lines 184-188:
Sufficient samples of each batch of bulk formulated product and of key packaging components used for each finished investigational medicinal product batch shall be retained by the manufacturer for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer.

Comment to lines 184-188:
We do not understand 'whichever period is the longer' since a trial is either completed or discontinued. Please clarify.

Question 4a:
Should retention samples also be required to be retained by the manufacturer?

Response
Retention samples could be retained e.g. at the manufacturing site, the packaging site, the testing site, the European batch release, the Sponsor, or at the European Distribution Centre. The responsibility for storage of (reference and) retention samples should be specified in a technical agreement between sponsor and manufacturer. The quantity of retention samples for each batch should be specified in the 'order'. We do not see added value to also require retention sample storage at the manufacturer if stored at another location.

Question 4b:
If only reference samples are required, would a requirement for photos of the investigational medicinal product, the packaging and the labelling to supplement the reference sample be useful? Please justify.

Response
If only reference samples are required, and retention samples and reference samples are interchangeable, Teva does not see added value to require photos to supplement the reference sample. The option for photos could be useful e.g. in case a batch is labelled in multiple packaging runs for different countries, and reference samples can be retained from the batch for one country, while for all other secondary packaging operations photos can be retained.

Question 5a:
In how many clinical trials authorised under the Clinical Trials Directive 3 has Article 13(3)(c) of that Directive been used? Please provide figures both as actual number of trials and as a percentage of the trials authorised, if available.

Response
We do use medicinal products that do not have an MA in Europe in clinical trials. For our innovative drug development, we use about 5-15 % of IMP with no EU licence in our clinical trials.

Question 5b:
In how many clinical trials authorised under the Clinical Trials Directive, is the comparator product not authorised in an ICH country (EU, US, Japan, Canada and Switzerland)? Please provide figures both as actual number of trials and as a percentage of the trials authorised, if available.

Response
Up to now, we generally use comparator product authorized in ICH countries.

Lines 254-256
The manufacturer shall record and investigate any complaint concerning a defect and shall inform the competent authority of any defect and shall inform the competent authority of any defect that could result in a recall or abnormal restriction on supply.

Teva proposes to change as follows:
The manufacturer shall record and investigate any complaint concerning a defect and shall immediately inform the sponsor ~~competent authority~~ of any defect. The sponsor, and if relevant also the manufacturer, shall inform the competent authority of any defect that could result in a recall or abnormal restriction on supply.

Lines 263-265
Teva proposes to add:
Where required by the technical agreement between the sponsor and the manufacturer and the protocol of a clinical trial, the manufacturer shall implement a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall. The manufacturer shall ensure that the procedure discloses the identity of the blinded product only in so far as it is necessary.

Justification:
Generally, the sponsor provides the blinding information to the manufacturer and has all information for rapid unblinding at his disposal. Contact with all clinical sites are usually maintained by the Sponsor (Clincial Trial Monitors), and-/or by the Clinical Supplies Distribution centre, and not by the manufacturing site.

Lines 289-295
Member States shall carry out inspections of manufacturers located in third countries to ensure that investigational medicinal products imported into the Union are manufactured by applying quality standards at least equivalent to those laid down in Union law. The frequency of such inspections shall be based on an assessment of risk, but shall in any case take place if the Member States have grounds for suspecting that the quality standards are lower than those laid down in Union law.

Comment:
Teva has concerns that the requirement of third country inspections may seriously extent the assessment time of the CTA and therefore may have impact on the targeted completion timelines of the clinical development plan. We would appreciate confirmation that third country inspections will not lead to extention of the assessment period as specified in articles 6 and 7 of Regulation 536/2014.

Regulation 536/2014 Annex VI
By way of the delegated Act, Teva wishes to see amendment of Annex VI of Regulation 536/2014.

Pursuant to the legislation currently in force, it is not required to specify the expiry date on the primary label of the investigational medicinal product. The current wording of Annex VI to Regulation 536/2004 requires the expiry date on both the primary as well as the secondary label. Given that pursuant to Article 70 of Regulation 536/2014 Annex VI thereto may be amended in order to ensure subject safety and the reliability and robustness of data generated in a clinical trial or to take account of technical progress, we propose that such amendment should be made by way of the delegated Act.

Teva has serious concerns about the changed requirement for labelling which requires printing the expiry date on both the primary and secondary label.
The majority of the clinical supplies is packed in a tamper proof sealed secondary pack. Due to minimizing risks of external factors potentially impacting product quality (e.g. temperature excursions), transportation of clinical supplies is minimized. As a consequence, re-labelling for expiry date extension is preferably performed at the clinical investigation site.
Re-labeling of every individual blister, syringe, bottle etc is a much more complicated operation compared to re-labelling of the secondary pack only, and this will increase the risk for potential labeling errors. Additionally, re-labeling of the primary label to extend the expiry date will require opening of the secondary pack and breaking the tamper proof seal. Replacement of the secondary pack seems no option since an additional label should be affixed to the investigational medicinal product as per new GMP guidelines for IMPs, neither does a new tamper proof seal on top of the broken seal seem to be a suitable option for obvious reasons.

Teva strongly believes that specification of the expiry date **only** on the secondary packaging will prevent shortage of clinical supplies due to expiry date extension and will reduce the risk to jeopardize the continuity of supply to the trial subjects.

Pursuant to the legislation currently in force, companies are allowed to have the expiry date included in electronic systems, a system which has worked effectively to date. The current wording of Annex VI to Regulation 536/2004 no longer allows this. Given that pursuant to Article 70 of Regulation 536/2014 Annex VI thereto may be amended in order to ensure subject safety and the reliability and robustness of data generated in a clinical trial **or to take account of technical progress**, we would like to request to re-consider allowing justification of the absence of the expiry date on both the primary and secondary label, e.g. by a use of a centralised electronic randomisation system. We believe a validated electronic randomisation system ensures full traceability of each pack, enables identification of the product and trial, and will prevent use of expired packs. Additionally, use of an electronic reandomisation system will make any re-labelling operation for expiry date extention redundant and therefore decrease the risk to jeopardize the continuity of supply to the trial subjects.