PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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By registered mail & e-mail
(xavier.prats-monne@ec.europa.eu)

Mr
Xavier Prats Monné
Director General
Health and Food Security (DG SANTE)
European Commission
B-1049 Brussels
Belgium

Dear Mr Prats Monné,

Subject: Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products

We refer to your letter dated 5 April 2017 in reply to our previous correspondence in connection with the above. Your proposal for engagement with PIC/S on this initiative is appreciated as well as your intent to ensure the quality of ATMPs and the protection of patient safety.

As patient safety is at the core of this EU policy, we would then like to invite you to take into account the concerns related to patient safety already sent by the competent authorities of your Member States, which are also PIC/S Members. A number of these have so far not been taken into account. It would appear a number of concerns expressed during the two stakeholder consultations have also not been considered, including those expressed by SME and Academia as well as PIC/S' contribution of 12 November 2015.

In addition to these concerns, we enclose an Annex that details a non-exhaustive summary of critical outstanding points, which pose a risk to patient safety, as identified by a PIC/S ATMP ad-hoc drafting group. As you will note, it is obvious that the draft Guidelines are establishing lower standards and lack details, such as definitions.

Your proposal to explain and discuss the draft Guidelines with non-EU PIC/S Members is welcome. Several non-EU PIC/S Members have already volunteered to share their experience and are prepared to contribute. In this perspective, we would be grateful if you could indicate how to proceed, in particular as the harmonised consultation procedure with the EMA has not been followed. A reply to our proposal for a joint Working Group has not been received.

Clarification on the scope of the co-operation you propose would be welcome. It would also be appreciated if the latest version of the draft Guidelines could be shared as soon as possible to allow us at least to comment prior to publication. A discussion after the finalisation and publication of the Guidelines would have little purpose.

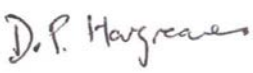
We have been informed that a meeting has been scheduled on 26 April 2017 to finalise these draft Guidelines. Such a timeline will not allow for patient safety concerns to be adequately addressed. For the sake of transparency of the legal process, we would like to invite you to clarify the timelines and adoption procedure.

We also remind you that the risk of de-harmonisation – should the Commission decide to go ahead with its stand-alone Guidelines of lower GMP standards for ATMPs – could lead to serious consequences to the current global regulatory framework. Please advise on your position on the resulting responsibilities and potential liabilities for these lower GMP standards. As you know, this is an important issue, and not only for PIC/S.

While awaiting further clarification on your message of co-operation and proposed next steps, and while hoping that such future co-operation will allow to protect patients and reduce discordances, PIC/S will remain on its previous position, which as you are aware is also supported by a large number of stakeholders.

We look forward to hearing from you and to the opportunities to further engage in the Guidelines. Please note that for the sake of transparency and the rights of patients, this letter will be published on the PIC/S website.

Yours sincerely,



Paul Hargreaves
PIC/S Chairman
United Kingdom / MHRA

Boon Meow Hoe
PIC/S Deputy Chairman
Singapore / HSA

Annex: enclosed

Non-exhaustive summary of critical points impacting patient safety:

- The blanket reduction of the processing environment for products manufactured in phase I studies is a significant concern. A de-facto reduction of the controls for early phase trials and not for later phases is counter-intuitive; phase I trials where production experience and sterility data are limited require the same strict control of the cleanroom environment. Considering that in many clinical trials the population is not going to be made of healthy volunteers but sick and potentially immune compromised patients, it would be even more risky to inject an ATMP that could have been contaminated during processing. The same approach that is proposed for phase 2 and phase 3 clinical trials should be applied.
- There are no specific provisions for labelling and blinding of ATIMP (as in Annex 13). This could put participating patients at risk as it will be uncertain how this will be done. In addition, future patients of the approved therapy could be also at risk as the ATMP might have been approved on the basis of a non robust set of data;
- Current wording fails to prevent the production of low quality ATMP products due to lack of clearly defined minimal requirements. Due to the wording, most of the requirements in the document can be interpreted as a recommendation only (…it is recommended…, ..if possible.., ... when necessary.., ..as far as possible.., .. it is encouraged..). In some sections, it even allows overruling legal requirements (e.g. pharmacopoeia requirements).
- There are risks of reduced patient access to ATMP products and that current treatments with ATMP products may no longer be possible. Some sections of the guide are formulated in a way that prevent the use of new technologies which are already used today and ensure higher quality of ATMP products. These sections may also stop further development of some ATMP due to the fact that the new document requires specific issues (e.g. regarding seed lot and cell banks) that are not current state of art.
- The document is written in a way that it is rather a guidance document. It is not written in a way that it is suitable to represent a technical standard to be complied with. Some aspects are rather marketing authorization issues and should not be included in a GMP guide.
- There are risks to patients who may receive contaminated products due to a lack of stringent contamination control measures, lack of appropriate requirements to assure aseptic production and lack of appropriate cleaning process requirements.
- There are risks of transmission of infections due to insufficient requirements to control starting materials used for the production of ATMP.
- There are risks for patients to receive treatment with low quality ATMP products or non-conforming ATMP due to inappropriate use of quality risk management by overruling minimal GMP and quality requirements. The document fails to appropriately integrate internationally agreed QRM concepts and other new concepts to be used for the production of ATMP.
- There are risks for clinical trial subjects to receive insufficiently controlled investigational ATMP products as in the draft document, as the document fails to clearly define minimal requirements for ATIMP production.
- There are risks for patients to receive low quality products due to inappropriate organization of quality systems at ATMP manufacturer. Requirements and responsibilities for key personnel is insufficient to ensure high competence and well-organized quality systems.

- There are risks for patients to receive non-conforming products due to insufficient material management requirements.
- There are risks for patients to get treatment with ATMP products that have not been sufficiently validated. Process validation requirements are not state of the art and do not ensure sufficiently validated production processes.
- There are risks for patients to get treatment with non-conforming products as requirements for product release process are lacking.
- There are risks for patients due to insufficient control of outsourced activities.
- There are risks for patients due to inappropriate reconstitution before use. The guideline tries to address this issue. In general, reference should be made to the marketing authorization where suitability of reconstitution needs to be demonstrated and should be included in the use instructions. This problem cannot be solved in a GMP guidance document.
- There are risks for patients to be treated with products while quality information is available that should lead to recalls. Requirements for complaint handling, quality investigation, CAPA, recalls etc. are insufficient.
- There are risks for patients to be treated with non-conforming products due to a lack of sufficient control on automated systems used for the production of ATMP.