**Targeted stakeholder consultation on the draft Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products**

## Response from the National Pharmacy Clinical Trials Advisory Group (NPCTAG)

The NPCTAG ensures that there is appropriate expertise within the NHS to provide oversight and management of pharmacy aspects of Clinical trials. The expertise base of the NPCTAG comes from a combination of pharmaceutical, regulatory/QA backgrounds as well as operational clinical trials pharmacy staff and includes representation from a variety of NHS manufacturing and reconstituting sites including sites experienced with trials involving ATMPS. As such, the group is well placed to comment and advise in relation to GMP for ATMPs.

**The NPCTAG is not supportive of the draft guidelines on GMP for ATMPs.** The group considers that the document proposes a diluted form of GMP which will unnecessarily pose additional risk to patients and practitioners whilst failing to advance the speed of approval of novel ATMPs.

As this draft guidance document is written it is unclear where it is planned to sit within current EU legislation covering GMP production of medicines. The inclusion of some but not all aspects of GMP currently described within EudraLex volume 4 suggests that it is to be viewed as a standalone document; in which case it fails to provide sufficient depth and detail, and thus creates more uncertainty rather than providing clarity and simplicity. In general the ATMP WP recommends that it should to refer to existing GMP standards within EudraLex volume 4 and give advice (via an additional annex potentially) on the application of a risk based approach to the manufacture of ATMPs where a flexible approach is required. It is disappointing that there is no reference to the existing quality risk management approach based approach described in ICH Q9 and Chapter 1 of Eudralex volume 4.

The NPCTAG believes that ATMPs are high risk medicines manufactured for high risk patients and, as such, they warrant the highest standard of GMP throughout the lifecycle of the product.

Rationale for our assessment that ATMPs are high risk includes the following points;

* they are sterile products susceptible to contamination in that they often have a protracted incubation period and are growing in nutrient rich media
* manufacture often involves open systems
* differentiation may occur during manufacture compared to their source cell type.
* they are products that are rarely suitable for terminal sterilisation
* they are given to susceptible patients often using novel administration techniques,
* due to their mode of action they are retained and may proliferate in the patient

Pre-clinically these products are often innovated by academic researchers whose focus is not routinely on patient safety. The transfer to a GMP environment is therefore critical to ensure the potential benefits of these products are safely translated into medicine presentations with a quality assured specification. A dilution in the GMP standards required could lead to patient harm which will inevitably delay progress in the field and stifle the progress with these innovative products.

ATMPs are emerging as a global industry. The draft document gives no information with regard to the degree of harmonisation to existing international standards (e.g. PIC(S)) which is a point of serious concern since ATMP development is truly international and medicines are often in trials in multiple jurisdictions. It is essential that ATMPs and advanced therapy investigational medicinal products (ATIMPs) made within the EU are considered fit for import into countries outside of the EU; particularly as these medicines approach commercialisation. As this draft guidance stands it will not be recognised by third countries.

A similar concern exists around the processing of tissue and cell products which are not classed as ATMPs. Currently the EU tissue and cells directive relates directly to annex 2 of EU GMP which then references the standards for annex 1. The adoption of this draft guidance would create a double standard with the healthcare setting with the processing of lower risk non substantially manipulated cells and tissues being regulated to a higher standard than ATMP medicines. This is not logical and should be avoided.

A further risk of these guidelines is a perceived reduction in quality of ATIMPs, and, either a subsequent increased risk of failure to develop to the standard required for a marketing authorisation, or (eventually) a reduction in the rigour applied to obtain a marketing authorisation for this group of high risk medicines which would be detrimental to both patient safety and potentially could erode the public confidence in the regulation applied to medicines generally. This is a real problem and is demonstrated by the difficulties being faced by commercial drug developers trying to move from early phase academic trials in the US to late stage commercial trials and marketing authorisation. The lack of rigour in cGMP manufacture in academic sites in the US has led to significant gaps in process development so promising results in academic phase II trials have delayed transition to phase III and registration because the whole manufacturing process has to be re-engineered to meet a standard fit for a licensed product. This delay in product development can kill a promising medicine because the field moves so fast that the phase III trial can’t even enrol patients since the next generation of the product is already available for early phase trials and these are seen by academic clinicians with the appropriate patients as more exciting and have a greater chance of high impact publication. The NPCTAG’s recommendation is to ensure that the expectation is that products comply with EU GMP (EUDRALEX volume 4) expectations throughout the product lifecycle from validation through phases I, II and III clinical trials and ease the pathway to marketing whilst ensuring patient safety via optimal product quality. It is particularly disappointing that the validation requirements of annex 15 have been largely ignored in this draft.

We recognise that there is a new Clinical Trials Regulation being introduced into Europe, and that this new regulation allows for some flexibility in relation to phase 1 studies. ATMPs used as IMPs should not be considered exceptional and should fall in line with the new clinical trials regulation. It may be useful for the GMP guidance to give an indication/examples of the required release specifications for ATIMPs during their development i.e. minimum specification requirements for Phases I, II and III. This would then overtly encourage developers to begin to define potency and impurity assays etc. at an earlier stage.

We recognise that due to the nature of the products there is inevitably variability in the starting materials, however we feel that it is vital that this must not be added to during the manufacturing process as this will prevent the gaining of a full knowledge of the inherent variability in the finished product. As a simple illustration – if an incubator is not mapped to demonstrate even temperature control then a variation in product assay results may be inappropriately attributed to a starting material where it is in fact caused by inconsistent processing temperature – something which is easily rectifiable and produces a better quality product.

In summary, the NPCTAG cannot support the publication of a stand-alone GMP guidance for ATMPs. Members of the group are experienced in working to EU GMP and using risk based approach to make justified adaptation only where necessary, and fully complying wherever possible recognising that this is in the best interests of product quality and therefore patient safety. As a standalone document there are huge gaps in areas of basic GMP for example room classification explanation, aspects of quality control and validation.

It is our hope that the need for this document will be re-evaluated and the impact of its introduction will be assessed within the wider global market for ATMPs and the wider EU in terms of other tissue and cell products. Whilst clarification of the risk based approach for the GMP of ATMPs is valuable, this draft guideline fails to provide clarity and risks undermining existing harmonised legislation.

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