

## Guidance on “non routine”

### Introduction

1. The scope of the hospital exemption is:

“any advanced therapy medicinal product, as defined in Regulation (EC) NO 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.”

(See Article 28 of Regulation EC 1394/ 2007 –this is the new Article 3.7 of Directive 2001/83/EC.)

2. The issue has been raised as to what constitutes “non routine” preparation of ATMPs. The MHRA takes the view that it is not feasible to provide a simple numerical formula that would delineate the boundary between routine and non routine production. However, the Agency considers that it is possible to give some pointers and these are set out below. The MHRA will monitor the use of the exemption and may amend or extend the guidance in the light of experience.

### What constitutes non routine preparation of a product?

3. There are two main areas for consideration in determining whether preparation of a product by an operator is routine/non routine:
  - Whether it is the same product under consideration
  - The scale and frequency of the preparation of the specific product.

#### *The product under consideration*

4. The MHRA will take the following approach:
  - Where a number of different products are under consideration the question of whether preparation is non routine should be considered separately in relation to each product prepared by that operator. So, the fact that an operator was preparing product X with an increasing frequency would be an important consideration in determining whether product X was being prepared routinely, but it would have no bearing on the issue of whether that operator’s other product, Y, was prepared routinely
  - Where a new product results from modifications to an earlier product, consideration of whether the new product is produced

routinely will be based on consideration of the pattern of production of that new product (and not that of the old product)

5. In determining what constitutes the same product the MHRA will take into consideration the nature of the advanced therapy medicinal product in question. These considerations will include, but are not limited to, the product's mode of action and its intended use (indication, mode of administration, presentation i.e. liquid, powder, pre-filled syringe etc), as well as the manufacturing processes used to generate the final product, and any product intermediates or product specific starting materials i.e. genetically modified retrovirus used to transduce patient specific stem cells, that are required. The Agency would not, for example, accept an argument that depended on the premise that all autologous (i.e. derived from the patient, and therefore patient specific) ATMPs were by definition different products, where their intended use, manufacturing processes and final product presentation are the same.

#### *Scale and frequency of production*

6. Repetition of preparation of the same product by an operator gives rise to the possibility that production of that product should be regarded as routine. In determining whether preparation is non routine the MHRA will take the following approach:
  - the Agency will take into account the overall numbers of the particular product prepared by the operator, the regularity/frequency of production, and the time period over which the preparation of that product has become established
  - The Agency's initial thinking, which may be modified in the light of experience, is that in a scenario where the scale/frequency of manufacture of a particular product starts off as very small/low, but the manufacturing rate progressively increases over a period of time, it should typically be possible to determine within a period of one to three years where the scale and frequency of production means that preparation has become routine
  - However, where preparation remains on a very small scale and spasmodic, eg with some months elapsing between each preparation, it is possible that a significantly longer period would need to elapse before preparation could be reasonably regarded as routine
  - By contrast, if large scale production were launched, preparation could be regarded as routine very rapidly – and well within one year.

#### The wider context

7. It will also be necessary to bear in mind that the applicability of the hospital exemption does not depend only on issues relating to the pattern and scale of the numbers. The other stipulations of the exemption are equally important and it is entirely possible that one or more of these conditions could serve to rule out a product from coming within the exemption before the point at which production of a product was regarded as routine.

#### Dialogue with MHRA

8. MHRA wishes to see a situation in which as far as possible operators are aware in advance that preparation of a specific product is likely to be regarded as routine. Accordingly:
  - Operators preparing products which they believe may come within the hospital exemption are encouraged to seek advice at an early stage from the Agency **[give contact details]**
  - Where an operator holds a manufacturer's licence permitting manufacture of ATMPs under the hospital exemption they will be asked to make an annual return on this activity, as part of the return used to determine the Agency's risk based inspection programme. This information will be used where appropriate as a basis for dialogue with operators and to inform MHRA decisions on the issue of non routine.
9. This guidance should not be taken as a complete or definitive statement of the law, which may only be given by the Courts. It is not intended as a substitute for legal or other professional advice. The responsibility remains with the operator to ensure they are clear on the regulatory position of products which are, or may be, ATMPs and to seek the necessary advice.