UK Comments on Revision to Part IV of Annex 1 to Directive 2001/83/EC

Definition

1. The term 'nucleic acid sequence' could lead to ambiguity, as it could be interpreted that any medicinal product containing a nucleic acid sequence, the effect of which is to regulate, repair or replace a targeted genetic sequence would be defined as a gene therapy medicinal products (GTMPs). In this case live viral vaccines may also fall within the definition, as viruses contain nucleic acid sequences, and these sequences frequently down regulate cellular gene expression to enable immune evasion and/or up regulate cellular genes involved in DNA replication, to enable their own replication. The UK would therefore propose the definition is modified to avoid such a mis-interpretation. The UK does not consider that vaccines against infectious agents (whether the vaccine is given prophylactically or therapeutically) should be considered to be GTMPs.

   The UK strongly endorses the terminology that the nucleic acid sequence is used with a view to 'regulating, repairing or replacing' a sequence, as the technology is advancing to a stage where in-vivo gene repair or replacement may become an eventuality. However, this terminology does not allow for the addition of a 'nucleic acid sequence'. As the definition currently stands the first GTMP to apply for a MA will fall outside of the definition of a GTMP as this product introduced a therapeutic gene to the cell. The mode of action of this sequence did not involve regulating, repairing or replacing a target sequence within the cell. The UK would consider this type of product as a GTMP and would therefore suggest the definition is modified to include them.

2. The inclusion of '*ex-vivo'* use within the definition is not considered to be relevant. For an ex-vivo therapeutic approach, for example where a viral vector is used to transduce cells in-vitro, and the genetically modified cells are re-administered to the patient, it would be the genetically modified cells that are considered to be the final (medicinal) product. The viral vector in this case would be considered to be a starting material. The revised section 2.3.5 of annex 1 also defines the vector as a starting material as such the definition would appear to be inconsistent with the technical requirements for GTMPs.

   If a viral vector received a market authorisation for *ex-vivo* use, regulatory control over the genetically modified cells would be lost. This may have quality (e.g. contamination, cross-contamination, mix up), efficacy (e.g. from poorly controlled manufacture) and

safety implications as the vectors used most frequently in this way are derived from integrating viruses, and the transduction rate i.e. the number of viral genome copies per cell, may correlate with severe adverse events such as insertional mutagenesis. The transduction process should therefore be licensed and well controlled.

The UK does not agree that viral vectors used in an 'ex-vivo' therapeutic approach should be considered to be starting materials. The UK would consider the vector itself to be a component of the medicinal product, as such the statement in annex I confirming that vectors used in this way should be manufactured in accordance with GMP is fully endorsed, however we would suggest that it is also made clear that the manufacture should be carried out by an authorised manufacturer named on the marketing authorisation.

It is considered that the ex-vivo transduction processes are likely to be carried out at the sites of treatment i.e. hospitals, and it would be difficult for the MA holder to be held responsible for these activities. However, in order to ensure the quality of the transduced cells, these ex-vivo processes should be carried out under GMP control, which will require the hospital or other clinical facility to hold an appropriate manufacturing authorisation.

Given these difficulties the UK would suggest that the marketing authorisation procedure for 'ex-vivo' therapeutic approaches should be considered more carefully, and may require a dual licensing procedure for both the vector and the genetically modified cells.

4. Gene deletion using viral vectors is currently under investigation. This may eventually become a reality, in which case inclusion of gene deletion within the definition should be considered.

Proposed modification of the definition:

Gene Therapy Medicinal Product means a medicinal product:

- that contains or consists of a recombinant nucleic acid sequence, which is used with a view to regulate, repair, replace or delete a targeted genetic sequence and/or to add a therapeutic or diagnostic sequence to a cell; and
- whose therapeutic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.
- prophylactic or therapeutic vaccines against infectious diseases are excluded.

Justification for the changes proposed

a. Introduction of 'recombinant'

Defining the nucleic acid as 'recombinant' should alleviate most of the ambiguity of 'nucleic acid sequences' as described in point 1 above. Live vaccines would not fall within the definition as their genomes are not usually genetically modified.

b. Introduction of 'deletion'

Refer to point 4 above.

c. Introduction of 'to add a therapeutic or diagnostic sequence to a cell'

As described in point 2 above, GTMPs are frequently used to add 'new' sequences to a cell. For example: gene directed pro-drug therapies, where a gene (usually an enzymatic sequence) is introduced into a cell, the protein product from which acts on an innocuous pro-drug resulting in a cytotoxic compound which ultimately kills the cell. Such products are under study for cancer therapy, and are considered to be GTMPs. Adding the proposed sentence to the definition would incorporate these products into the definition.

d. addition of 'prophylactic or therapeutic vaccines against infectious diseases are excluded'.

As described in point 1, the inclusion of prophylactic or therapeutic vaccines against infectious diseases as GTMP is not endorsed by the UK. Viral vaccines containing a genetic sequence which encodes an antigenic protein from, for example, TB are currently under investigation. If there is not a specific exclusion of prophylactic or therapeutic vaccines against infectious diseases, this type of vaccine would fall within the definition of a GTMP.