ATMPs & EU GMP Update

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Outline

- ATMPs – What they are?
- Why are we looking at this subject?
- The Licensing position of ATMPs and use of PRIME
- ATMPs and GMP Inspections
- The usual GMP regulatory process in EU and that for ATMPs
- Position of IWP, NCA and PIC/S in relation to EC GMP proposals
- Other important considerations e.g. Brexit
- Summary of important points

ATMPs – What they are

Advanced **T**herapy **M**edicinal **P**roducts are medicinal product which are either:

- a gene therapy medicinal product.
- a somatic cell therapy medicinal product.
- a tissue engineered product.

Definition given in Directive 2001/83/EC as amended by the ATMP Regulation 1394/2007 (this includes combination ATMPs).

ATMPs in the EU must have a marketing authorisation and are regulated through the centralised authorisation procedure.

The decision on whether a product is an ATMP can be complex – UK has a flow chart approach & EMA's web site refers to summary reports

Background

Why are we looking at this subject?

- Patient need
- ATMP development
- Regulatory expertise

ATMPs and EU Licensing

EMA ran a workshop in May 2016 aimed to foster ATMP development and enable expanded patient access by exploring solutions to various identified challenges

Fourteen proposals were put forward for consideration by the EU and NCAs to optimize the current regulatory framework e.g.

- GLP for ATMPs
- Focus on risk to benefit assessment
- Risk Based approach to dossier preparation
- Procedural Guidelines on MAA evaluation
- Increased awareness of regulatory process for Investors
- Increase awareness of support for early development

PRIME

- ATMPs are now one of the most common types of product in the European Medicines Agency's PRIME (**pri**ority **me**dicines) scheme
- This scheme is designed to make cutting edge medicines available to patients as early as possible
- There is an electronic application form, specific data requirements (re unmet patient need), guaranteed response time from regulator
- EMA provides early and enhanced support to optimize development, plus rapporteur from CHMP or CAT to provide continuous support & build knowledge prior to MAH application
- There is the potential for fee waiver for scientific advice & and the aim of the scheme is that patient need is met more quickly

ATMPs and the EU GMP Regulatory Process

The usual EU GMP regulatory process

- Issue raised and problem statement generated
- Expertise from MS brought to bear on a problem statement
- If problem concerns a number of MS then agreement reached at EMA and changes introduced across the EU via EC

The ATMP GMP process

- No problem statement as such
- EC generated document

ATMPs and the EU GMP Guide

At the moment - One Guide with three Parts

- Part 1 & Part 2 with Annexes enforceable
- Part 3 with advisory/reference documents

Changes – potentially more than one Guide in the future

- In Sept '15 EC launched two consultation documents (effectively the legal framework was changed to allow the issue of two additional GMP guidelines)
- The consultation was centered around withdrawal of Annex 13 from the current guide and re issue as a separate GMP guideline on IMPs
- Similarly a second consultation was launched for ATIMPs/ATMPs guidelines (with an impact on Annex 2 of the guide)

GMP for IMPs

- **Annex 13** to be replaced by **EC GMP Guidelines for IMPs**
- This is in line with the new Clinical Trials regulations (No 536/2014).
- Annex 13 will be removed and replaced with commission guidelines on GMP for IMPs. Directive 2003/94 will be replaced with a new Directive for marketed products
- Above to be limited to the responsibilities of manufacturers. Responsibilities of sponsors and associated sponsor- manufacturer interaction will be covered by a separate guideline to be published in Eudralex Volume 10
- The EC aim is for the new documents to be published in Q3 2017

ATMPs and EMA IWP

- Pointed out difficulties with **stand alone GMP ATMP document**
- I understand that they wrote a letter to EC expressing their concerns – this letter is not in the public domain (cf PIC/S)
- Discussed these at a meeting with EC in March 2017
- Above meeting resulted in a second (this time) all day meeting with EC in April 2017 to fully explain their concerns
- EC going ahead with adaptive procedure and intend to publish a stand alone GMP Guide in 2017

ATMPs and NCAs

The EC have issued two consultation documents

- Nov 2015
- June 2016

- The second took into account concerns from MS
- Surprisingly neither documents indicates that the new ATMPs for GMP would be stand alone documents
- It is also a bit disappointing that concerns from MS are not highlighted / made public in summaries

ATMPs and PIC/S

PIC/S has also expressed their concern at the EC proposed stand-alone ATMP GMP Guidelines

- They have repeatedly attempted to draw attention to the potential detrimental impact of this initiative – letters written to EC in:
  - November 2015
  - October 2016
  - February 2017
- These letters are open and in the public domain

ATMPs and PIC/S (2017)

The EC initiative will lead to a revision of EU GMP Guide Annex 2 (Biological Products), will also result in the PIC/S GMP Guide and the EU GMP Guide no longer being equivalent.

- This will lead to an internationally non harmonised approach to the implementation of GMP for ATMP and. lower GMP standards for ATMPs
- PIC/S has repeatedly tried to engage with the EC to point out risks to public health and in terms of non harmonisation of international GMP requirements
- Put forward a proposal to form a joint working party with the EMA Inspectors Working Group in order to produce an internationally harmonised, fully integrated GMP Guidance for ATMP, which would serve to both fulfil the European Union's objectives and the PIC/S harmonisation needs.
- The Commission has ignored all requests for co-operation All PIC/S can do is draw the Commission's attention to its responsibilities. A new letter to this effect has been addressed to the Director General for Health and Food Security of the EC, published on the PIC/S website for reasons of transparency.
- it is hoped that the Commission will reconsider its draft guidelines, prior to publishing them, and that the drafting process will be restarted in order to ensure a more inclusive and international approach

Extracted from PICs Press Release following the Geneva meeting Feb 2017

PIC/S Proposals

- That the EC reconsider their proposals on the basis that they lower the basis of GMP for ATMPs and hence put patients at risk
- An international harmonised approach to GMP for ATMPs is proposed
- This to be achieved by means of a joint working party with EMAs IWP
- Working party to produce a harmonised approach which will meet EU objectives and that of PIC/S
- This fully integrated harmonised approach will be safer for patients than the current EC proposals

ATMPs and Brexit considerations

- All Union (EEA) primary and secondary law ceases to apply to the UK from 30 March 2019, At that time the UK will become a 'third country'. For centrally authorised medicinal products the marketing authorisation holder will need to:
- transfer its marketing authorisation to a holder established in the EEA
- specify an authorised importer established in the EEA and submit the corresponding variation
- change the location of its current UK based site of batch control to a location established in the EEA and submit the corresponding variation
- transfer its current UK based site of batch release to a location established in the EEA and submit the corresponding variation
- This is in addition to sorting out the location of the QP and location of SMF for PV

Extracted from the EMA Q & As related to UK withdrawal from EU within the framework of the centralised procedure – see web site updates

- http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/general/general_content_001707.jsp&mid=WC0b01ac0580a809a7

Conclusions

- The Licensing situation for ATMPs is progressing
- In contrast the GMP process for ATMPs in the EU remains confused
- Situation is complex – it looks like a stand alone document for GMP will be produced which EU inspectors will be required to implement and this could raises a number of issues
- Academics strive to produce products that meet patient need but at the moment there is only a relatively small number of products on the market
- It is difficult to see how the lack of a harmonized GMP approach will benefit the patient and/or remove delays in ATMP MAH approval
- Other issues e.g. Brexit and the cost of such products to National Health Authorities simply add to the complexity of the situation

Glossary

- ATMPs – Advanced Therapy Medicinal Products
- IMPs – Investigative Medicinal Products
- CAT – Committee for Advanced Therapy
- CHMP – Committee for Human Medicinal Products
- IWP – EMA Inspectors Working Party
- EU – European Union
- EEA – European Economic Area
- NCA – National Competent Authority
- EMA - European Medicines Agency
- SMF – System Master File
- PV – Pharmacovigilance
- MS – Member State

Useful links

ATMP Definition

http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf

EMA Meeting on ATMPs & PRIME

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/02/WC500220952.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2016/03/WC500202670.pdf

Commission Consultation

http://ec.europa.eu/health/sites/health/files/files/advtherapies/2016_06_pc/2016_06_draft_guideline.pdf

http://ec.europa.eu/health//sites/health/files/files/advtherapies/2015_pc/publ_cons_doc_2015.pdf

Commission Meeting

https://ec.europa.eu/health/documents/pharmaceutical-committee/human-meeting_en

PIC/S Letter & Press Release

PS_L_11_2017_Letter_to_EC_concerning_GMP_ATMP.pdf

https://www.picscheme.org/useruploads/files/press_release_geneva_2015.pdff

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Thank you for your time.

Questions?

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