

Out of Specification Advanced Therapy Medicinal Products - Guidance for Healthcare Organisations

**Pan UK Pharmacy
Working Group
for ATMPs**

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Introduction

Advanced Therapy Medicinal Products (ATMPs) are an innovative group of medicines providing life-changing alternative treatments for patients. They comprise of somatic cellular therapies, tissue-engineered products and gene therapies. Whilst some in-vivo gene therapies are not cell or tissue derived, many ATMPs do use tissues or cells as starting materials. Some of these cell/tissue based products are autologous (the starting material comes from the patient for whom the medicine is intended), others are allogeneic (the starting material is obtained from a donor).

As is the case for all medicines, the product release specification is pre-agreed with appropriate medicines' regulatory authorities for both marketed products (EMA) and for IMPs (MHRA), and is agreed with the prescribing clinician in the case of unlicensed medicines.

Due to the unique nature of these cell/tissue-based medicines, however, there are occasions (often but not always due to inherent biological variation of starting materials) when the manufactured medicines are not in full compliance with their release specification. It is recognised that due to the specialised nature of the medicines and depending on the nature and degree of non-compliance it may be that the administration of an out-of-specification (OOS) ATMP remains in the best interest of the patient and that administration is the correct course of action.

Administration of out-of-specification (OOS) ATMPs, however, poses challenges to the NHS. The aim of the Pan UK Pharmacy Working Group for ATMPs in producing this document is to clarify the regulatory perspective regarding OOS ATMPs, and to provide guidance to NHS organisations which are provider sites for ATMPs, about governance in the event of an OOS ATMP being supplied for one of their patients. Additionally the document will discuss the need to ensure that the reimbursement pathway is clear in this circumstance. This guidance, where applicable, should be read in conjunction with the relevant NICE / Scottish Medicines Consortium guidance and NHS contract terms for specific ATMPs which set out the commissioning and reimbursement arrangements for regulated products.

Regulatory Position

Manufacture of all medicinal products occurs in accordance with Good Manufacturing Practice (GMP) as laid down in 2003/94/EC. The ATMP Regulation EC 1394/2007 directs that manufacture must be performed in line with GMP. In November 2017 the European Commission issued standalone Guidelines on Good Manufacturing Practice specific to ATMPs ([Part IV Eudralex Volume 4](#)) which detailed the circumstances in which use of OOS ATMPs is deemed acceptable from a regulatory and legal perspective:

“Exceptionally, the administration of the cells/tissues that are contained in a cell/tissue based ATMP that is out of specification may be necessary for the patient. Where the administration of the product is necessary to avoid an immediate significant hazard to the patient and taking into account the alternative options for the patient and the consequences of not receiving the cells/tissues contained in the product, the supply of the product to the treating physician is justified.”

It further goes on to state:

“When the request of the treating physician is received, the manufacturer should provide the treating physician with its evaluation of the risks and notify the physician that the out of specification product is being supplied to the physician at his/her request. The confirmation of the treating physician to accept the product should be recorded by the manufacturer.”

Cell / Tissue based ATMPs holding Marketing Authorisations (licensed products)

GMP for ATMPs was reinforced and interpreted for ATMPs holding marketing authorisations in April 2019 by the issue of [EMA Questions and Answers on the use of OOS batches of authorised cell/tissue based ATMPs](#). This document clarifies the responsibilities of the manufacturer and the marketing authorisation holder and, whilst it is clear that these products are not certified by a QP (which is required for marketed products released in compliance with their licence (MA)), the MA holder cannot waive all responsibility for their use. Indeed a concept of QP verification is introduced which, although not specifically defined, expects the QP to verify that the product has been manufactured in compliance with GMP and to provide details of the results achieved against the expected specification for the MA.

As such, the administration of an OOS licenced ATMP is **considered to be exceptional use of a medicine** which is not in compliance with its marketing authorisation. Whilst the guidance referenced above indicated the requirements for manufacturers and MA holders, it should be noted that with respect to healthcare organisations it refers specifically to the treating physician only. Cell / tissue-based ATMPs which are autologous in nature or have a very short shelf life, are permitted to be used on a “do and tell” basis. This means that prospective regulatory approval is not required. The manufacturer can present the treating physician with a written risk evaluation and allow them to make an informed request for the OOS product if, after consideration of the risks, they consider it is in the patient’s best interest to receive it. This minimum regulatory process for OOS ATMP is shown in figure 1.

It should, however, also be noted that the typical wording on the informed request transfers liability to the administering organisation via the treating physician. In practice hospitals will have governance mechanisms in place for medicines management. These will need to be amended to ensure that treating physicians are aware of the local governance procedures required in the event of being made aware of, and wishing to request the use of an OOS licensed ATMP. **The minimum hospital process recommended to be followed in the event of an OOS licensed ATMP being considered for use by a physician is shown in Figure 2**

The manufacturer/importer/ MA holder must inform the regulator within 48 hours of the supply. In the UK the local regulatory contact is via the MHRA Defective Medicines Reporting Centre.

Figure 1 Minimum Regulatory Requirement in the Event of an OOS Licensed ATMP

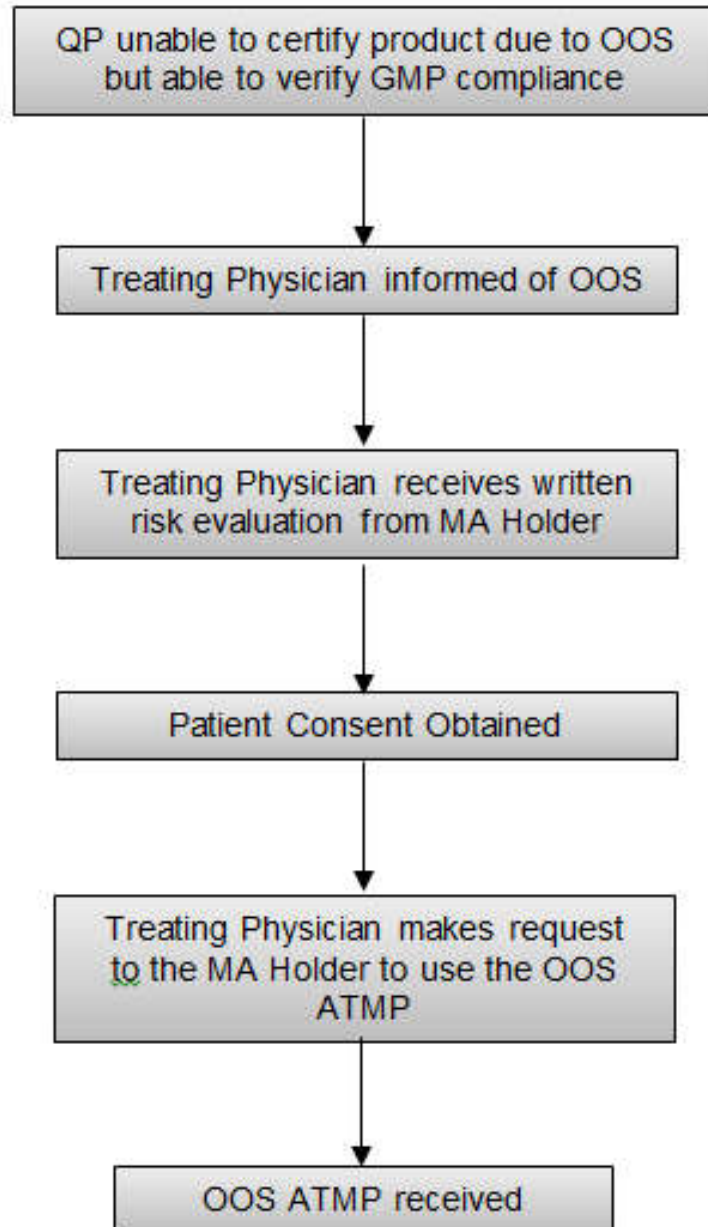
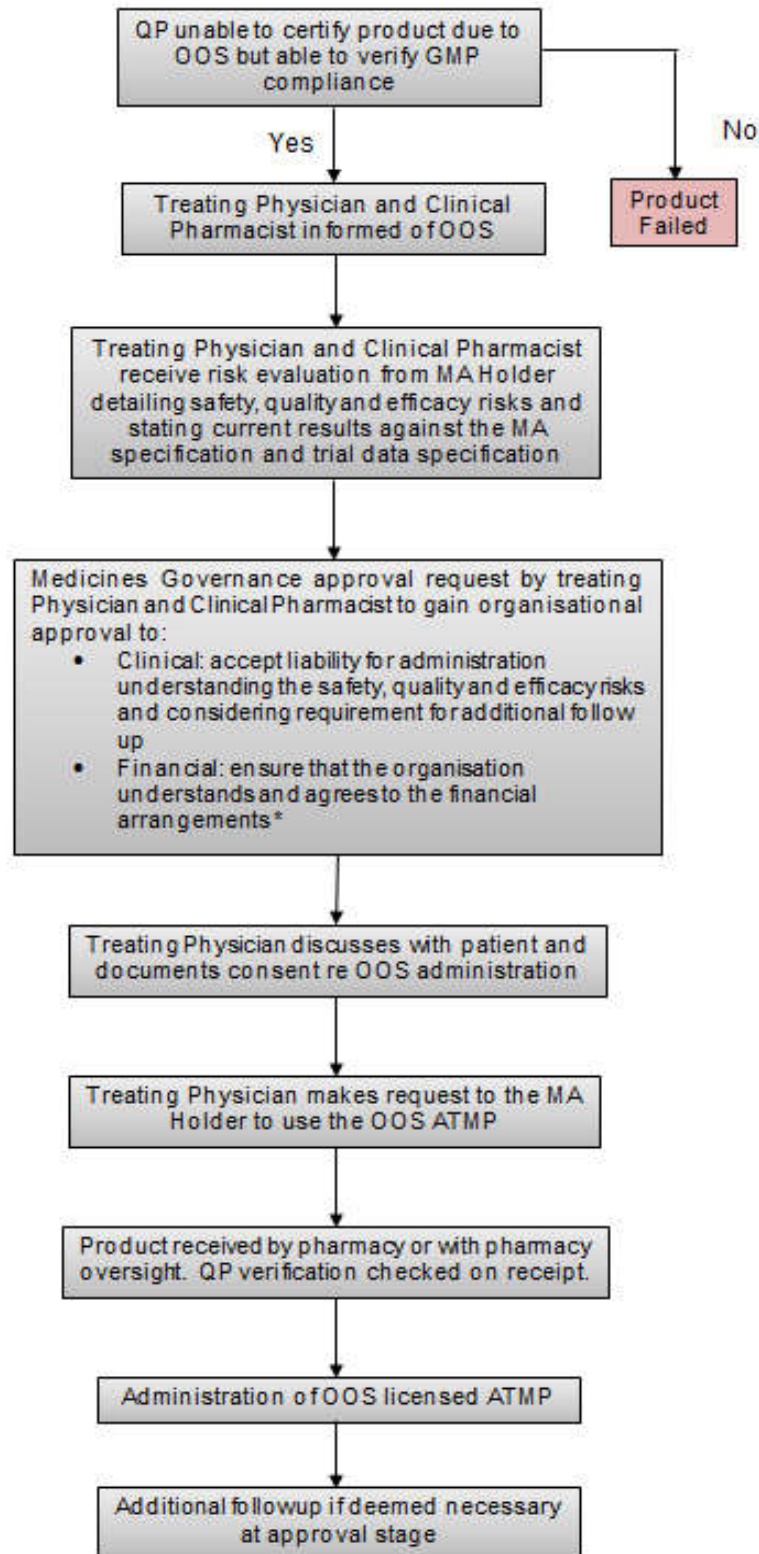


Figure 2 Recommended Minimum Hospital Process in the Event of an OOS Licensed ATMP being considered for use by a treating physician



* see Financial and Commissioning Considerations (page 10)

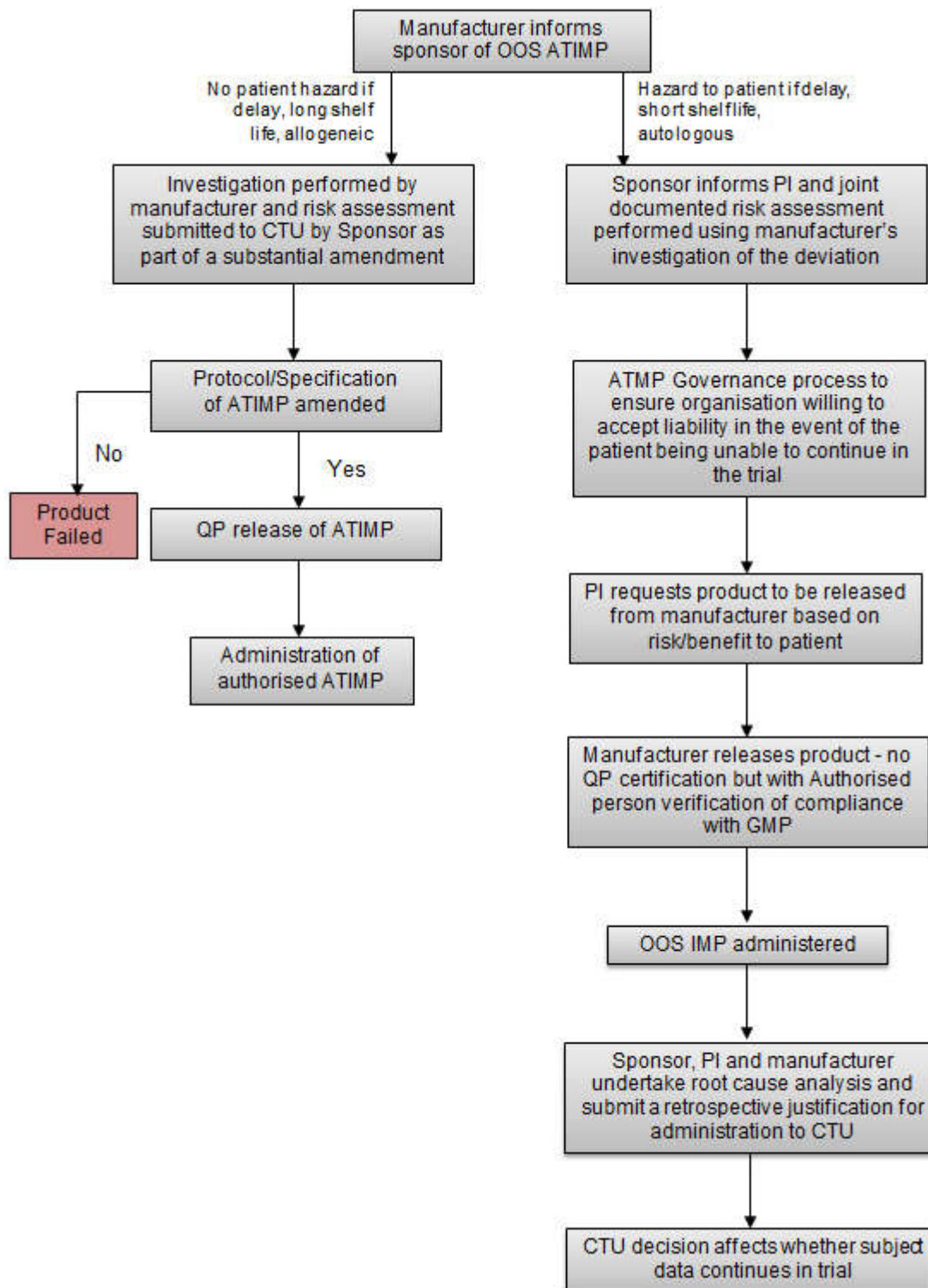
Investigational Medicinal Products

From a regulatory perspective, similar principles to those for marketed medicines apply to the administration of OOS Advanced Therapy Investigational Medicinal Products (ATIMP). However, in the context of a clinical trial the integrity of the data generated needs to be taken into consideration and the impact of administering the OOS ATIMP on the trial as a whole needs to be taken into account. If time permits (e.g. patient is stable, cryopreserved product etc.), then the sponsor should apply to the MHRA Clinical Trials Unit for a “substantial amendment” to the trial protocol and investigational medicinal product dossier (IMPD), informing the regulator about the OOS and providing a justification for both varying the specification and for continued use of the product. In this way the subject’s data will remain suitable for inclusion in the trial.

Where time does not permit (e.g. patient is unstable, autologous and very short shelf life ATIMP etc.) then an OOS ATIMP may be administered if it is considered to be in the patient’s best interest and the sponsor and Principal Investigator, after liaison with the manufacturing site and QP, are agreed. Every effort should be made to discuss this with the MHRA Clinical Trials Unit prior to administration of an OOS ATIMP in this circumstance. There may however be an impact on the trial data in this circumstance. A root cause analysis investigation report of the reasons for the OOS should be submitted retrospectively by the sponsor to the MHRA Clinical Trial Unit as a substantial amendment to provide a justification and request ongoing inclusion of the subject in the trial which should not be assumed. Where inclusion in the trial is not permitted by the regulator, liability will transfer for use of this OOS medicine to the healthcare organisation. It is therefore recommended that use of an OOS ATIMP is approved via a local governance mechanism prior to administration in case of this eventuality.

The recommended healthcare organisation process in the event of an OOS ATIMP is shown in figure 3.

Figure 3 Recommended Hospital Process in the Event of an OOS ATIMP



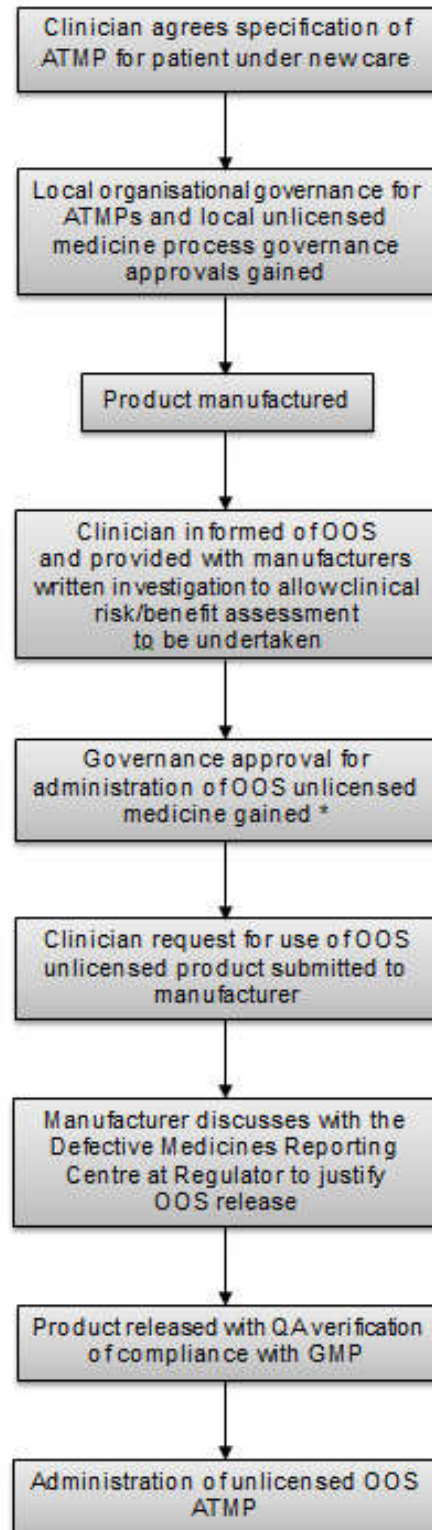
Unlicensed ATMPs

In the case where in advance of manufacture a clinician has identified that a patient under his or her care has a special clinical need which cannot be met by a licensed ATMP, it may be that the manufacture of an unlicensed ATMP has been requested.

In the case where the ATMP manufactured as a Special does not meet its pre-agreed release specification, a local organisational governance step is required. This step should ensure that local governance committee has approved the use of the OOS unlicensed ATMP and clarified, consulting relevant commissioning policies where applicable, that any reimbursement will apply to the OOS unlicensed ATMP.

Where local governance approval is given to administer the OOS unlicensed ATMP, the MHRA's Defective Medicine Reporting Centre should be informed by the manufacturer and an appropriate course of action agreed. **The recommended process for OOS unlicensed ATMPs is shown in Figure 4.**

Figure 4 Recommended Hospital Process in the Event of an OOS Unlicensed ATMP



*see Financial and Commissioning Considerations (page 10)

Financial and Commissioning Considerations

It is recommended that organisations are careful to understand the reimbursement pathway, including commissioning where applicable, when approving the use of an OOS ATMP.

Issues include:

OOS licensed ATMP – some managed access agreements require administration of an MA product and therefore product reimbursement and funding/tariff arrangements should be confirmed as part of the local governance/medicines management process. Only under exceptional circumstances would the NHS expect to pay for an OOS licensed product i.e. any product that sits outside the agreed specification cited in the marketing authorisation. In addition, healthcare organisations will need to confirm whether activity costs will be reimbursed by the responsible commissioner. The NHSE default is that it is unlikely that such costs will be reimbursed.

OOS licensed ATIMP – in the event of administration occurring prior to regulatory approval of the subject's continuation in the trial, confirmation of sponsor's intention to fund the product and any other costs associated with administration of the OOS ATIMP should be gained.

OOS unlicensed ATMP – the governance approval process should consider whether there is any financial impact by the administration of the OOS unlicensed ATMP. Only under exceptional circumstances would the NHS expect to pay for an OOS unlicensed product. In addition, healthcare organisations will need to confirm whether activity costs will be reimbursed by the responsible commissioner. The NHSE default is that it is unlikely that such costs will be reimbursed.

Conclusion

Although the use of OOS ATMPs is permitted from a regulatory perspective, it is recommended that healthcare organisations wishing to administer an OOS ATMP should ensure that their governance process allows for this eventuality. The safety, efficacy and financial risks should be fully understood. It is, therefore, recommended that any such administration should formally be approved from a local organisational perspective.

The Pan UK Pharmacy Working Group would like to thank MHRA and NHSE colleagues for their review of this document.

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