Product Design Considerations for optimising ATMP Implementation in the NHS

Pan UK Pharmacy Working Group for ATMPs

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August 2021
Version 1

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Foreword

The Pan UK Pharmacy Working Group (PWG) for Advanced Therapy Medicinal Products (ATMPs) acts as an expert body to support the activities of UK Pharmacies to facilitate ATMP usage. The group consists of pharmacists from across the UK that specialise in the governance, prescribing, administration and monitoring of ATMPs. The aims of the group are to promote good practice, identify and resolve pharmacy issues to maximise the effectiveness and development of services for hospitals to administer advanced therapies. The Pan UK PWG for ATMPs has a regulatory and governance subgroup, which identified a need for learning about optimal product design to be fed back to industry and ATMP developers.

For further information about the advice or about the Pan UK Pharmacy Working Group for ATMPs, please contact anne.black7@nhs.net.

Guidance to Support the Development of ATMPs

Recommendations for Successful Product Delivery

Scope

This guidance provides practical advice for the development of Advanced Therapy Medicinal Products (ATMPs) to ensure their suitability for NHS implementation. This document is aimed at industry and researchers in the ATMP field and encourages developers to reverse engineer to deliver products that can be successfully integrated within the hospital ecosystem. Implementation challenges faced by the NHS and experience with ATMPs in clinical trials, as well as licenced and unlicensed ATMPs, are highlighted with the aim of encouraging developers to take them into consideration throughout the product development lifecycle. The NHS commissioning pathway is not in the scope of this document.

Background

The number of cell and gene therapy clinical trials in the UK continues to increase year on year. Many products fall at the first hurdle of clinical trial implementation due to some challenges and barriers, which could be overcome or eliminated entirely if considered early during product development. Others prove exceptionally difficult to implement after commercialisation. Delays caused prevent timely benefit to patients as well as incurring significant avoidable costs to the manufacturers, marketing authorisation holders, sponsors and to the NHS.

For the purpose of this document, an “undeliverable product” is a product, which cannot easily be fitted into current NHS treatment pathway due to multiple challenges, including logistical, shelf life, storage, and administration issues.

There are many aspects to consider in the development of ATMPs, not just for early phase clinical trials, but also for later stages of development and wider implementation after marketing. Many ATMPs are on accelerated pathways and therefore the opportunity to develop the product between early-stage clinical trials and pivotal trials is limited. This guidance discusses factors that NHS centres with experience of ATMP administration have highlighted to date as barriers to wider implementation of these novel treatments and adoption as NHS business-as-usual.

Useful Considerations Prior to Implementation

During lead up to regulatory approval and NHS commissioning of a new ATMP, it is advised that companies also engage with delivery centres to facilitate timely implementation and set up in clinical settings. Discussion with the Pan UK Pharmacy Working Group for ATMPs is recommended who may be able to advise on practical challenges. For example, the contracting process can be the cause of a delay after centres have been commissioned. Early engagement can allow a collaborative approach to identify common hurdles, which can minimise later delays and duplication of work.

Pharmaceutical requirements for ATMPs

The following is a list of pharmaceutical requirements/issues for consideration when developing ATMPs. This list is non-exhaustive and includes core requirements. Other requirements may be applicable depending on the type of ATMP, treatment indication and stage of development:

- Shipping and Receipt: Handling risks to product or operators must be understood.
- There should be a clear chain of custody upon receipt in pharmacy and release for administration.
- Storage conditions should be overt.
- Reconstitution/preparation instructions should be provided; how is the product prepared for administration?
- Stability of product should be maximised: is the shelf life long enough to minimise risk of product wastage.
- In-Use Stability i.e Shelf life after reconstitution: is the shelf life after any reconstitution / preparation activity long enough to allow safe preparation and delivery to the patient?
- Batch-to-batch consistency of drug product (especially autologous therapies).
- Labelling of products on primary/secondary containers: is it comprehensive, clear, unambiguous and readily understood?
- Visibility of pack contents: can the ATMP itself be visually inspected and its integrity be assessed when in the primary and secondary containers (including over-bags and storage cassettes).
- A clear communications plan is needed for raising quality issues and ensuring prompt responses from the manufacturer.
- Key logistic issues identified with realistic timelines e.g. import

Clear pharmacy instructions are required, e.g. Pharmacy Manual for a clinical trial or summary of product characteristics (SmPC) for marketed product, which include all of the above.

NHS Implementation Challenges

The table below summarises some of the key challenges and obstacles from current NHS experience:

Category	Issue/Challenge
Procurement *(Harvesting of patient starting material)*	Complex harvest procedure and/or short time for delivery to processing facility
	Procurement procedure inconsistent with existing processes increases disruption.
	Governance – HTA export licence and/or third-party agreement may be required https://www.sps.nhs.uk/wp-content/uploads/2019/09/Regulatory-Requirements-for-Export-of-ATMPs-starting-materials-FINAL.pdf
Processing *(of starting material)*	Bespoke processing procedure required (e.g. freezing profile, cryopreservation protocol and profile). Systems inconsistent with existing NHS processes increase the likelihood of error
Packaging/ Labelling	Validation of additional packaging to allow hospital storage if applicable (e.g. double wrapping of cryopreserved cellular products requiring storage in vapour phase nitrogen)
	Poorly considered (e.g. open systems) or characterised primary containers
	Secondary container that obscures product in the primary container
	Autologous products require additional labelling for safety reasons. The lack of standardisation for these additional labelling requirements leads to potential difficulties across clinical sites.
Product related	Ideally formulate in ready-to-use (requiring thaw or withdraw only) or ready-to-administer presentation
	Minimise use of undesirable excipients in drug substance or in final drug product (e.g. antibiotics)
Storage	Ensure compatibility with routinely used clinical consumables/disposables
	Poorly defined storage requirements gene therapy products
	Containment requirements for Genetically Modified Organism containing products Class 1 is always preferable.
	Maximise the available shelf life for both product and post thaw/preparation
	Consider healthcare practice and avoid requirements set in marketing authorisations that contradict widely available facilities and recommended practice(e.g. double bagging of cryopreserved products, or non-standard temperature requirements)
	Consider physical space for shipping containers and storage of equipment (e.g. thawing equipment)

Shipping/ Transport	**Clear delivery / addressing for logistics companies, especially in multi-hospital trusts**
Infrastructure Assumptions	Imported products with limited shelf life are a challenge to book surgery times and have staff available 'at the door' to be ready to receive and take straight for administration
	Where short shelf life is unavoidable, map out shipping plan and procedures in case of deviation
	Lack of definition of storage temperature standardisation can lead to challenges in implementation (e.g. lower deep freeze temperatures prevent the use of mechanical freezers and mandate vapour phase liquid nitrogen).
	Computer access for scanning of documents or transfer of electronic data upon receipt or destruction may be an infrastructure challenge. Sites must be allowed time to prepare
	Poor Wi-Fi or mobile phone signal coverage in parts of many hospital buildings to allow tracking of shipping containers and monitoring temperatures after delivery to site. Sites need time to plan mitigation
Reconstitution/ Preparation	Complex reconstitution procedure prior to administration should be minimised
	Consistent thawing protocols for frozen products is desirable
	Ensuring availability of competent staff to undertake reconstitution activities (where not done by pharmacy staff, it can be performed under pharmacy oversight, for further details see Pharmacy Oversight and Supervision Requirements for Preparation of Licensed ATMPs). Sites need time to plan.
	Maximise in-use shelf-life post reconstitution or thawing to facilitate optimal location for preparation (optimal location for preparation is not in the clinical area)
Administration	Minimise requirement for dose calculation (i.e. avoid inconsistent concentration, volume or potency)
	Avoid complex administration procedures, particularly where short-shelf life is unavoidable

Case Studies

These are anonymised real-world examples for each product type that have created a barrier to patient treatment and hindered adoption. These issues are not exclusive to the product type under which they are stated.

Product Type	General Issues	Resolution
In-vivo GTMP	Requirements to use a specified clean air device for preparation but hospital pharmacies do not routinely use such devices. Class II Biological Safety Cabinets specified, however pharmacies use negative pressure isolators.	In-vivo gene therapy recommended to be prepared in pharmacy where negative pressure isolators are available routinely. Better to specify Grade A preparation environment only, not specify a particular device requirement.
Ex-vivo GTMP	Freezing profile for apheresis material was too specific and required a change from business as usual practice for clinical sites. Product presentation was not cryopreserved.	No resolution possible after marketing. Early consideration of local practice and procedures is vital to reduce the requirement of disruptive and high-risk implementation at clinical sites. Patients could only be treated by travelling internationally to location of manufacture for local delivery. This was not patient focussed.
sCTMP	Post-thaw process step required manufacturing expertise and MHRA Licence. Short expiry date when delivered from one country in Europe.	Administration and delivery must consider requirements of the clinical sites. Product design should ensure that only activities regulated as preparation/ reconstitution step only are required on site. Any product with a shelf life that can be measured in hours requires multidisciplinary team co-ordination, including that of the courier service. This level of co-ordination within the hospital is always very challenging to achieve and only likely to be acceptable for highly efficacious/curative products. It is likely the healthcare team will have to receive the product directly 'at the door' and complete appropriate checks in a short time frame to ensure it is for the right patient.
TEP	Impractical commercialisation. Short post-release/in-use shelf-life requiring unrealistic assurance of availability of NHS theatres. Additionally, initial contract placed all financial risks on the clinical sites and deviation was considered unacceptable.	Centralised renegotiation of the contract to redistribute and reflect an acceptable risk for all parties.

Autologous ATMPs	Release specification may not be achievable. Process for out-of-specification (OOS) risk assessment not pre-agreed or in the contract for all parties.	Pre-agree OOS risk assessment process determined in centralised contract negotiations.

References

(ATMPs)-The Role of Pharmacy in the Successful Delivery of Advanced Therapy Medicinal Products Information for Chief Pharmacists

Ex-Vivo (cell based) Gene Therapy Medicinal Products – Pharmacy Institutional Readiness Guidance

In-Vivo (virus based) Gene Therapy Medicinal Products – Pharmacy Institutional Readiness Guidance

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

Pharmacy Institutional Readiness for Marketed CAR-T Therapy: Guidance for Chief Pharmacists V4 (updated January 2020)

Pharmacy Oversight and Supervision Requirements for Preparation of Licensed ATMPs

Somatic Cell Therapy Medicinal Products – Pharmacy Institutional Readiness Guidance

Tissue Engineered Products – Pharmacy Institutional Readiness Guidance

Acknowledgement

The Pan UK Pharmacy Working Group would like to thank Louise Ellis, Regulatory Affairs Manager, Cell and Gene Therapy Catapult and Tim Root, Assistant Head of SPS, for their support in the production and review of this document.

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