Health by Advanced Therapies

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Strategy paper on GMP-conform cell sorting approaches
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Table of contents

1. Deliverable's description

For clinical cell manufacturing, there are several solutions commercially available. Approved cell products like Kymriah, Yescarta or Strimvelis still use conventional manufacturing strategies that rely on multi-step manufacturing in open systems involving several separate devices. Those concepts require considerable manual handling and consequently are expensive and error-prone. Also, the protocols and technologies are difficult to transfer to other manufacturing sites and hence spreadability of ATMP manufacturing is highly limited. (Bak et al., 2019: Iyer et al., 2018).

Advanced manufacturing solutions that were developed recently enable a higher grade of automation within GMP compliant closed systems. Those concepts may serve to overcome many technological and regulatory obstacles that presently restrict broad translation of ATMPs into clinical routine. Hence, in the following we will focus on future directions for clinical implementation of ATMP manufacturing.

2. State of the art

"ATMPs as "living drugs" are different from conventional drugs in their requirements for implementation into clinical routine. This lies in the complexity of the manufacturing, logistics and supply chain processes with multiple steps and high technical demands. In addition, treatment of the patients is extremely complex and requires an experienced multidisciplinary team (clinicians and nurses, geneticists, biologists, regulators, quality experts, pharmacists, etc) that is able to handle the specific requirements of cellular therapies as well as their possible complications (e.g. cytokine release syndrome or neurotoxicity in case of CAR T therapies).

Consequently, this strategy paper would like to examine the 3 broad stages involved in the routine adoption of these products; the manufacture, supply and clinical adoption. These are each influenced by the phase of development (clinical trial vs licensed supply), the indication and the patient group. In this workgroup we also want to tackle some issues which are particularly prevalent for ATMP's such as short-shelf-life products, ultrarare orphan products and single centre treatment. Recently, these products have made big advances in development with more products making it through to licensure. With these advances come challenges for the manufacturers, supply chain and the clinical sites delivering these therapies. Within this roadmap we seek to highlight these challenges and propose to examine the feasibility and effectiveness associated with centralised and distributed models of manufacturing for cell therapy ATMPs.

Currently two general routes for large-scale delivery of ATMPs to patients exist: centralized and decentralized manufacturing.

Centralized manufacturing is illustrated in Fig. 1A: A single facility carries out production and serves to supply ATMPs to a large geographic region. For personalized treatment, this may occur

in a discreet region or may require transportation of patient cells across long distances. In contrast, **decentralized manufacturing** (Fig. 1B) is dependent on regional centres ("hubs") that are close to the treatment centres and deliver products to their immediate surrounding. Both manufacturing models have benefits, disadvantages and challenges which are summarized below in Table 1.

Figure 1: Centralised and decentralised manufacture strategies. A) Centralised - Main characteristics: Single facility: cells in -> product out; delivery validated suppliers; controlled process: reduced product variation; higher dependency on integrated supply chain. B) Decentralised - Main characteristics: regional hubs; close to point-of-care; technology transfer of process and analytics; controlled consumables supply chain.

	Centralized Model	Decentralized Model
Manufacturing	Single facility carries out production	Multiple regional hubs close to treatment centres & deliver to immediate area
Logistics demand	High due to shipment of product over large geographical regions	High – complex supply chain (donation sites, multiple points of manufacture and distribution)
Process control	High	Lower - multiple production sites add complexity to process control to ensure a standardized output of cellular products.
Quality control	High	Complex (as above)
Risk to product variation	Lower due to single site manufacture, intrinsic variability of starting material/process	Higher (as above) – multiple sites and operators add to intrinsic variability
Tech transfer requirements	Low	High – with respect to manufacture and analytics across all sites
Overheads	Lower (due to single site) but require larger space	High – replication of equipment at multiple sites
Geographical distribution range	Supplies to a large region	Small (dependent on hub size)
Specialist resource requirements	Lower	High – production in multiple hubs requires the duplication of specialist resource across all sites
Suitable for product types	Autologous and allogeneic cell products that are not sensitive to cryopreservation and/or transportation	Autologous and allogeneic cell products with limited stability and/or maximum efficacy requirements

Table 1. Centralized and decentralized models for ATMP manufacture and clinical adoption (Haddock et al., 2017; Harrison et al., 2018; Iyer et al, 2018; Rutherford et al, 2017).

To date, whilst decentralised manufacturing has been widely discussed, it has not been systematically evaluated for feasibility, practicality and cost in the context of a busy healthcare environment in comparison with centralised manufacturing models.

As is evident from Table 1., the nature and complexity of cell therapy production means there is a trade-off between the **costs of manufacture** and the **costs of the supply chain**. Hence, a centralised manufacturing strategy (up-scaling) is best suited to high complexity and costly manufacturing, especially where the supply chain costs are low (Rutherford et al, 2017). However, the greater the complexity of the incoming and outgoing supply chain processes (e.g. for labile/short-shelf life product), the more distributed the physical supply chain could be, assuming the manufacture of the product can be relatively easily standardised and out scale (simple e.g. automated manufacture process). Hence, such products should benefit from a distributed decentralized manufacturing model (Fig.2B) (Rutherford et al, 2017).

In practice, **centralized manufacturing** has already been implemented by pharmaceutical companies for a number of the licensed ATMPs such as Strimvelis (Orchard), Zalmoxis (Molmed), Holoclar (Chiesi), Kymriah (Novartis) or Yescarta (Gilead). This model is in keeping with routine pharmaceutics and as such is tried and tested, however for ATMPs there are some points of criticism associated with this model, such as the high costs that are claimed by the suppliers and the dependency on a single supplier. For the medical centres, there is a lack of transparency with respect to details of the cell processing by the manufacturer. Currently, this strategy is the model of choice for autologous products and it might be the option of choice for **off-the-shelf (allogeneic) cell products** when many doses with long shelf-lives can be produced for a large number of patients (Harrison et al., 2018). In this case the cost/benefit ratio will be advantageous in comparison to decentralized manufacturing of off-the-shelf ATMPs (Harrison et al., 2019).

Decentralized manufacturing has not been established in practice so far as clinical application of cellular therapies is still in its infancy and most clinical trials are still in their early stages. Despite the challenges with batch reproducibility there is considerable interest in this model which might be best suited for **autologous cell products** and applicable to pharmaceutical approaches as well as smaller biotech companies and importantly, to specialized hospitals that are producing ATMPs at POC. However, in order to avoid product variations each hub must be able to deliver equivalent ATMPs regardless of location or operators. This may be best ensured by use of integrated management and automated systems (Harrison et al., 2018; Kaiser et al., 2016).

3. Challenges and Limitations

Regardless of manufacture model the following **challenges** need to be addressed to facilitate broad clinical implementation of ATMPs:

a) Specialist facilities and knowledge at clinical sites – from initial treatment decisions, apheresis (where required), pharmacy, treatment, follow-up, JACIE accreditation, etc.
b) Seamless and robust supply chains and logistics covering starting materials, consumables, products and samples
c) Complexity of treatment procedures and requirement for long term follow-up – patient and physician engagement
d) Market approval
e) Complex administrative and financial processes linked to treatment of ATMPs, novel reimbursement models will require payers to adopt new processes
f) Additional requirements for ultra-rare diseases where small numbers of patients may have to be relocated to specialist centres for extended periods of time.

4. Putative solutions

A central goal of RESTORE is to enable the spread of advanced therapies (respectively ATMPs) for a range of broad applications. By achieving this, RESTORE would be serving the needs of thousands of patients, **democratizing ATMP manufacture**, smoothing clinical adoption and enabling broad access to these highly promising treatments. To ensure this vision becomes a reality, commercially viable infrastructures and manufacturing models must be established that facilitate advanced therapies (including local hospitals e.g. in rural areas that do not possess specialized GMP facilities). We will also need to develop and implement a training system that will ensure the expertise required to manufacture, deliver and administer these innovative treatments which are now available. In the following, some of the putative solutions are outlined.

Centres of excellence (Hubs)

Clinical centres of excellence "hubs" should provide both strong research and translational capabilities and include both point of care and manufacturing capabilities. Overall, a requirements standard should be set for all these clinical facilities, e.g. like JACIE standards (Joint Accreditation Committee ISCT-Europe & EBMT) establishing the minimum criteria that the clinical centres must fulfil. Establishing a network of Hubs, with individual specialisms, but alignment on standards around procurement, processing, delivery of products, training, efficient long term follow up and streamlined patient access would be the most efficient use of resources and enable the widest range of therapeutic options to be made available.

The clinical centres will address research and routine delivery requirements for advanced therapies including procurement and processing of starting materials and products, pharmacy, cell labs, clinical infrastructure and service design in a collaboration between healthcare organisations, ATMP developers, service industry partners and academia. They will play a key

role in developing therapy and manufacturing guidelines, developing and implementing training across the supply chain, standardisation of processes and procedures as well as overall service design, delivery and integration into the wider eco-system. Training at all levels and steps along the process will be key to the success of broader implementation of ATMPs.

The manufacturing facility will provide ATMPs with consistent, proven quality for internal use and for external, local hospitals (Fig. 2). This will require standardized technology transfer including logistics, supply chains, quality management systems, staff training, patient counselling, advice on reimbursement matters etc. – not only within the centre-of-excellence but also involving the local hospitals. Moreover, the centre of excellence will need strong research capabilities to use the expertise from established Advanced Therapies for further improvement and for extension to other new indications.

Figure 2: Centre of Excellence. For internal use, the "hubs" will serve for procurement of the biological material, ATMP manufacturing and patient treatment. Moreover, they will transfer ATMPs, technology, know-how and standards to local hospitals that by themselves don't provide manufacturing infrastructures.

In summary, one of the challenges for RESTORE for broad clinical implementation of Advanced Therapies will be to elaborate a concept with general specifications and requirements for European Infrastructure of centres of excellence. In a second step, the specific therapeutic conditions to handle different disease entities will have to be integrated (e.g. regenerative medicine will have other requirements than immunotherapeutic therapies).

Seamless supply chain and logistics

Provision of seamless supply chains and corresponding logistics that apply to both centralised and decentralised manufacturing is crucial. Requirements are outlined in Figure 3. The concept only gives an outline of the complexity involved in supply and logistics. In real life, the requirements are even more challenging and require significant changes to current strategies and infrastructure. Hence, for implementation into clinical routine standardized processes have to be developed to help manufacturers to solve these issues. The requirement for specialised handling of the products at POC cannot be overlooked, this can be improved by the use of controlled equipment and thorough training and support of staff.

One solution to serve this need could be provision of blueprints e.g. for infrastructure, reagents, devices, QC, monitoring etc. Also, the whole administrative path within the hospital from the order for the ATMP drug placement has to be integrated and mapped to secure full ATMP cost reimbursement after patient treatment. Additionally, specialized handling of ATMPs in hospitals is often required (for instance, cell thawing, resuspension, etc.) and failure to provide appropriate instruction, train and support properly the staff has resulted in large variability in ATMP performance between centers participating in clinical trials. This is a significant issue that has made some products/companies go bust.

Figure 3: Seamless supply chains and logistics. Main characteristics: Trace and trace, supply logistics, remote monitoring and streamlined IPC/QC across sites.

Complexity of treatment procedures

It is not only the complexity of manufacturing but also structural issues and the complexity of treatment protocols (including control of possible side-effects) that are limiting roll-out of ATMPs from early experimental stages to clinical routine. Patient treatment may be extremely complex for cell- or tissue-based medicinal products. All hospital actors (clinicians, pharmacists, cell therapy staff, administratives) have to be familiar with the different treatment guidelines and also with management of the possible complications associated to the specific disease and with the ATMP administration (e.g. cytokine release syndrome or neurotoxicity in CAR T therapies). Guidelines for training similar to the one applied for stem cells transplants should be delivered. The definition of the amount of training and the resources for testing the quality of the learning should be defined.

For many of these ATMPs tested in clinical trials, including the ones that are potentially curative, there still only exist limited long-term safety and efficacy data. Thus, it is essential to continue the follow-up in the long term and to provide conditions that favour patient compliance for collecting these data. Also, the concept of “ATMP-treated patients registries” has to be taken into consideration.

Administration of these therapies requires engaging both, the patient and the referring physician, and to educate them on this new treatment perspective. Even though it might be transformative and curative, emotional difficulties should not be overlooked.

5. Summary

An overarching solution to face the challenges outlined above, will be setting up systems within the EU that will allow manufacture, distribution and administration of ATMP's across a wide range of therapeutic areas. This will involve:

a) Establishing a **European Network for implementation of ATMPs into clinical routine** involving already existing networks, projects, initiatives: Identification of most important stakeholders e.g. research, clinics, potential manufacturing hubs, industry, patients (national and European patient associations), health care providers, regulatory authorities (for drug and for cell-based procedures), payers, regional and national health technology assessment (HTA) bodies …

b) Developing a concept for a **European infrastructure / ecosystem of centres of excellence:**
   - Assessment of requirements for ATMP manufacturers, researchers and clinicians for late phase clinical trials and entry into market
   - Definition of format of potential hubs (will vary e.g. according to indication, country-specific requirements, cell product type (e.g. personalized vs. off-the-shelf), market …)
   - Definition at EU level of the minimum set of criteria - by product type - that the collection and administration centres must fulfil to qualify according to the applicable laws

c) Provision of blueprints and guidance to facilitate **approval and market access** of ATMPs for:
   - Regulatory issues
   - Inclusion into therapy guidelines, earlier lines of defence …
   - marketing authorization support, conditional MA, hospital exemptions …
   - seamless supply chains
   - reimbursement models

d) building-up an **European infrastructure of ATMP hubs** involving:
   - Identification/appointment of potential clinical centres of excellence
   - implementation of selected cellular therapy trials within centres of excellence network

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