Advanced Therapy Medicinal Products and the Changing Role of Academia

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Abstract
Academic institutions coin the ATMP landscape but do not possess an industry-like capacity to vigorously pursue the full developmental pathway to marketing authorization. At the same time, industry has fostered clinical trials with ATMPs, brought the first products to marketing authorization, and defined novel modes of interaction with academia. A regulatory niche for local manufacturing of ATMPs within an academic institution had been foreseen in Regulation (EU) 1394/2007 under the term “Hospital Exemption” but remained ill-defined. Manufacture in close proximity to the patient is difficult to accomplish, as “point of care” systems for the manufacture of ATMPs have encountered regulatory challenges hovering between process and product. The efforts and costs for the development of ATMPs continue to be dramatically underestimated, and few academic centers were persistent enough to invest in the GMP infrastructure needed and to recruit personnel trained in ATMP development. As a consequence, the contribution by hospitals to ATMP development has shifted from the finished ATMP toward the procurement of starting materials, selected manufacturing steps, storage of the product, clinical application, and participation in clinical trials. As the development and use of cell-based therapies and ATMPs continue to attract and challenge clinicians and scientists, this review aims to discuss logistical, financial, and regulatory issues that might contribute to the changing role of Academia in ATMP development, with an outlook into possible developments in the future and proposals for ways to reshape the academic environment under the auspices of what might truly have been meant by the hospital exemption clause.

Introduction
Advanced therapy medicinal products (ATMPs) are medicinal products for human use, based on gene therapy, somatic cell therapy, or tissue engineering. Representing one of the most rapidly growing areas in translational research, they have reached front stage as the “next generation” of complex medicines for complex diseases. Regulation (EC) No 1394/2007 defined ATMPs and was designed to ensure their free movement within the European Union (EU), to facilitate their access to the EU market, and to foster the competitiveness of European pharmaceutical companies while guaranteeing the highest level of health protection for patients [1]. As ATMPs are regulated as medicinal products, Regulation (EC) No 1394/2007 led to the amendment of the EU Medicinal Products Directive 2001/83/EC with Directive 2009/120/EC. For cellular starting materials, EU Directives 2004/23/EC, 2006/17/EC, and 2007/83/EC apply. The manufacture of ATMPs requires compliance with the standards of Good Manufacturing Practice (GMP), dealt with in a distinct part of the EU GMP Guideline [2] that continues to be challenged for a plethora of reasons [3, 4].

Academic institutions are major contributors to the development of ATMPs [5]. They respond to clinical
needs and provide medicinal products in an environment which, albeit compliant with generic standards originally devised for and subsequently informed by industry, is by definition not industrial. They find themselves in a challenging position between various, sometimes conflicting, interests in the transition of ATMPs from bench to bedside. European investigator-initiated multicenter trials on ATMPs critically depend on academic GMP facilities [6, 7].

**CAR-T Cells: A Turning Point for Academia**

A “breakthrough therapy of the century” [8], chimeric antigen receptor (CAR)-transduced cells represent a quantum leap in the ATMP arena, giving a boost to clinical attention, public demand, and technical exploitation [9, 10]. While five CAR-T-cell products have already been authorized for the USA and the EU market, there are more than 40 other CAR-T-cell products currently under clinical development [11] and more than 500 trials employing CAR-T cells are currently recruiting [12].

The development of CAR-T-based therapy has become an example of how ATMP concepts have reached beyond academia and how they were brought to marketing authorization by major pharmaceutical companies. Of course, this has had major implications on existing resources and on the position of academia in the ATMP landscape. CAR-T-cell manufacture and distribution now reside to a large part with the pharmaceutical industry. At the same time, the procurement of starting material, i.e., apheresis products, and the application remain at the point of care, at least as long as off-the-shelf allogeneic products derived from healthy donors will not replace autologous cells. The clinical infrastructure needed for CAR-T-cell therapy in late-phase clinical trials and for authorized products is complex, mandating a structured, interdisciplinary approach as described [13]. The major burden of high-risk investment and costs involved in the provision of this infrastructure has remained with academic institutions and public funding.

The position of academia as described previously [6] has changed substantially, being now at the front and at the end of the trajectory of clinical development. When some centers focused initially on the establishment of a manufacturing platform for the early stages of ATMP development and initial clinical trials, many more centers are now reaching up to the challenge of providing the environment needed for (a) procurement of starting materials, (b) patient recruitment, (c) a GMP environment for storage, final stage preparation for application of products tested in late-phase, industry-sponsored trials and for authorized products. Standards for a structured CAR-T-cell environment have been developed in detail by professional societies [14, 15]. At the same time, individual certifications by the companies themselves mandate repetitive certification procedures, distinct and company-specific storage places, individualized quality assurance, company-specific electronic documentation platforms, and distribution logistics. The race for the use of CAR-T cells asks for a price in terms of logistics, infrastructure, personnel, regulatory expectations and costs that few centers are able to pay.

**Regional ATMP Competence Centers**

European research institutions have begun to network available GMP facilities at an EU level to promote academic-led “first-in-man” gene therapy trials by linking the available expertise, GMP production facilities, and human skills, with the aim of providing a proof of efficacy for a range of technologies. At this point, the technology could be transferred to the private sector, which would then undertake further development while building on academic knowledge and know-how [16]. Robust and promising network structures have been initiated more recently on a national level (DARE-NL [17]). However, the extent of such efforts is underestimated and the capacities within academia to handle this work are limited.

It has been proposed that regional ATMP competence centers could manufacture and provide for ATMPs locally, in a highly skilled environment and in the structural and regulatory framework needed, as an alternative to centralized manufacturing with a global rollout [18, 19]. The lessons learned with ATMPs that have been brought to marketing authorization by industry have impacted the academic position in ATMP manufacture substantially. However, the perception still prevails that regional centers, with their collected experience in cell therapy, early-phase clinical trials, and serious and rare diseases, could provide an ATMP platform with the required GMP and GCP environment for the manufacture of ATMPs on site in regulatory compliance:

- As confirmed in several surveys [6, 7], an existing infrastructure for cell processing, immunoselection and cryopreservation forms a structural, regulatory, and logistical basis for further development into ATMP manufacturing hubs, including the budget needed to run the place. A coverage of costs by routine processes is essential to allow for an expansion towards development and implementation of new processes and products.
- Also, manufacturing devices and technology platforms have become available for “point of care” use that pose similar challenges to all users but could be implemented in a similar fashion in various ATMP...
competence centers, leading up to a decentralized manufacturing concept that would allow for redundancy and mutual assistance. Key issues to be addressed here include the definition of standards to qualify these centers as ATMP competence centers and challenges relating to clinical trials as recently discussed [9].

- Based upon a (hitherto undefined) certification or qualification, such ATMP competence centers could become recipients of funding by sponsors and health care insurers where the costs related to ATMPs such as CAR-T cells have to be tackled by public health care systems and by society.

Hospital Exemption

Article 5 of the EU Directive 2001/83/EC has been adapted to include an exemption from central authorization for ATMPs which are “prepared on a non-routine basis and used within the same member state in a hospital in accordance with a medical prescription for an individual patient.” Member states have been requested to lay down rules for authorizing these products by the national competent authority while at the same time ensuring that relevant community rules related to quality and safety are not undermined. It was initially hoped that the “exemption was included in the regulation in recognition of the small scale and developmental nature of activity carried out in some hospitals, which argued for a degree of flexibility over the nature of regulatory requirements” [20]. However, it has not been defined how this relates to “development” as part of clinical trials. The usefulness of the hospital exemption clause has found limitations not only in the extent to which the member states have recognized and interpreted the provision but also in the fact that the hospital exemption clause is outside the arena of Advanced Therapy Investigational Medicinal Products (ATIMPs) raising the question of how parallel systems can be merged when no regulatory overlap seems possible.

Quality Assurance in ATMPs: Structure, Process, and Product

The implementation of Part IV to the EU GMP Guideline [2] has brought substantial flexibility to many facets of manufacture, including qualification of materials, clean room environment, and release. Pursuing this concept of process-inherent flexibility further, ATMP competence centers might benefit from a structure- and process-driven approach, offering:

- a qualified environment and personnel for ATMPs,
- the existence of a GMP certificate and a manufacturing license in the field of cell therapies,
- a certain process, technology, or production line in a generic fashion,
- a quality assurance system that would include standards for the delivery, storage, and issuance of an AT(I)MP as well as standards for the implementation of a new process,
- a qualified person for ATMPs who:
  - similar to a study pharmacist, would supervise the delivery, storage and issuance of the investigational medicinal product,
  - would also be responsible for the release of products manufactured or finalized for application on site.

Apart from the storage, supervision, and distribution of an investigational or authorized cell-based medicinal product, the manufacture of an ATMP on site based on the existing infrastructure and an existing manufacturing technology could then allow a standardized and validated process to be used in a modular fashion, with single components such as a new CAR-T target defining the transition from an existing process into a new product. Taking CAR-T cells as an example, a generic technology that has been implemented on site could be used with a new batch of a previously qualified and used vector structure, now coding for a CAR with another specificity.

Such a streamlining would ease the access to “standard technologies” and products derived thereof. However, complex and new products would require the full inventory of GMP development, at their disadvantage in terms of finding an opportunity of being developed at all. This, in turn, is a scenario familiar to most academic GMP centers: with standard products for patient care in the background, such as autologous hematopoietic progenitor cells, some advanced therapy medicinal products may find a harbor for early clinical trials on site, as the environment needed would be available already. The same may be the case for ATMP development once certain ATMPs are handled on a routine basis. It is the step toward this next level that will demand an investment on site to be ready for the future of cell therapy.

ATMP competence centers could, from a quality risk perspective, also help to dissolve the often dichotomous and controversial approach of classifying the results of procedures using devices either as advanced therapy medicinal products or as similarly advanced clinical interventions. The use of such devices for the processing of tissue and extraction of cells, or for clinical interventions like extracorporeal photopheresis, would be jeopardized by a classification as an ATMP where others may find it difficult to see a product. In these cases, the term: “hospital exemption” could be helpful: A “release” of such a procedure by a qualified person, and its proper documentation in a registry could be envisaged to pave the way to regula-
tory compliance. Similarly, interventions based on products that have previously been applied following an individual prescription by a physician but, from the perspective of a product, would be classified as an ATMP could, in the hands of an ATMP competence center, achieve authorization as foreseen in the German Drug Act [21]. In any case, this channeling approach appears suitable to counteract the plethora of cell-based products and interventions of a quality questionable by design or claim [22].

**Conclusions**

Academic medical centers have an inherent focus on complex and orphan indications and are expected by the public to provide an environment where specialized clinicians and scientists integrate best patient care with pathophysiological, fundamental research, and clinical development. Scientific curiosity and the confrontation with rare and life-threatening diseases are driving forces behind ATMP development that academia and industry share. A successful collaboration between academia and industry will need to integrate the academic and hospital roots of the product into their value creation. Furthermore, the gain of clinical evidence, patients in hope for therapeutic benefit, cohorts of potential study participants and access to clinical samples provide an inspiring and creative environment for the design of innovative cell therapies and a value that deserves an appreciation which is constantly underestimated, also and especially in academia.

Driven by promising preclinical data, a large number of academic institutions have constructed cell therapy manufacturing facilities that are compliant with GMP guidelines over the past 15 years. Recent estimates suggest there are approximately 50 GMP cell therapy facilities in academic institutes in both the USA and Europe, providing wide geographic coverage [7]. The difficulties faced by these institutions are enormous, in terms of costs, timelines needed for drug development, and scarcity of qualified personnel. This, however, is not unique to academia. The fact that licensed GMP manufacturing capabilities and capacity are available in academia could drive strategies and innovative business models. The recognition by competent authorities will depend on a precise definition and distinction of academia and industry, as conflicts of interest may not interfere with the responsibilities in manufacture, quality control and release.

A modular approach to the manufacture as pointed out could be accompanied by a modular approach to the regulatory frame. Especially in the ATMP arena, the manufacture of an intermediate product, an active pharmaceutical ingredient or a drug substance could be manufactured in Academia and handed over via a certificate of compliance signed by the respective qualified person. This product could be moved forward for different purposes in different pathways (and at different points in time): (a) as an investigational medicinal product for clinical use within a trial; (b) as a product to be used under the hospital exemption clause; (c) to a partner institution (or an industry partner) for further processing; and (d) for the release by the partner institution (or industry partner). In summary, the collaboration with industry could follow a Y-shaped developmental pathway:

- a joint collaborative effort to yield a validated technology,
- a licensed manufacture of an intermediate product or drug substance in academia,
- separate licenses for the release of the product, with
  - the academic institution being granted the right to release the product for clinical use within their institution or in clinical
  - the industry partner acting as an independent entrepreneur or sponsor who has contracted the academic institution for the manufacture, under license for the release of the product.

A precise delineation of responsibilities in development, validation, and manufacturing, together with a Y-shaped approach to distinct release scenarios would also pave the way to accommodate and to solve issues related to intellectual property, for instance by a nonexclusive license granted to the academic institution as part of an ongoing collaboration with an industry partner. The use of existing codes such as ISBT128 would be most helpful, as products could be unambiguously labelled for their intended use, i.e., for further processing or for administration.

Academic GMP manufacture is not exempt from drug regulation. Albeit misleading, the term “hospital exemption clause” represents an attempt to better define the role of academia in ATMP development and provision. In addition, instances exist where an “exemption” truly awaits definition, i.e., in the transition between therapeutic intervention and product.

A focus on the availability of GMP infrastructure in close proximity to the patient, with “generic” processes in place, including storage, logistics, and distribution, could help shape the position of academia and to better define the different but interdependent roles of academia and industry in ATMP development. Also, unproven therapies based on tissues and cells could be channeled toward regulatory compliance once authorizations are handed to licensed facilities in ATMP competence centers that would manufacture under the auspices of Section 4b of the German medicinal products act. As long as academic institutions and hospitals manage to hold on to their...
identity as representatives of a public stakeholder community, collaboration with industry will continue to present an opportunity for more involvement, transparency, partnership in clinical development and therapeutic advance.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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