Life Science
Insights Centre

Life Science Insights Centre: ATMP

A fact-finding mission

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Content

Executive Summary

Background

The purpose of this work is to identify the framework for introduction of advanced therapy medicinal products, ATMPs, in Denmark and compare it to the situation in a selection of other countries within the EU/EEA, Sweden, Norway and England.

Scope

The review focuses on the business framework for ATMPs in Denmark and surveys the possible levers and bottlenecks for commercial introduction of ATMPs.

To illuminate the perspectives, the conditions for business given by the political and administrative terms in comparable countries (Sweden, Norway and England) are listed.

We will address the situation from three domains:

- Political and administrative
- Healthcare structure
- Market access

Methodology

Data collection

The basis for this analysis is the experiences from companies which are either in the process of preparing for launch of ATMPs in Denmark or have recently (since 2019) applied for recommendation for use in a HTA process in the Danish Medicines Council.

The project team has selected seven pharmaceutical pharma affiliates in Denmark and invited them for a one-hour interview session each. Five out of these companies accepted the invitation:

- Pfizer
- Novartis
- BMS
- Janssen
- Bluebird Bio

Similarly, the project team invited stakeholders from the public health system in Denmark and up interviewing: Danish experts have been consulted to retrieve their immediate perception of the market access situation for new ATMPs offered to Danish patients

- The Danish Health Authority
- The Danish Society of Hematology Society
- The Danish Cancer Society, Kræftens Bekæmpelse

Definition

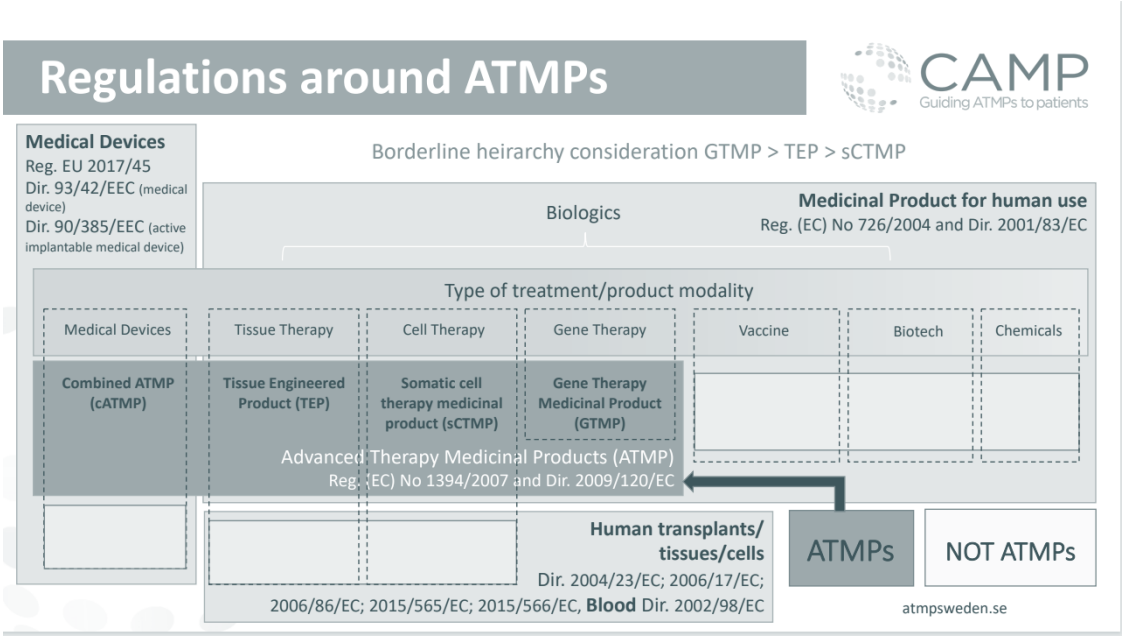
"Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells. They offer groundbreaking new opportunities for the treatment of disease and injury."[1]

ATMPs offer opportunities for disease-modifying and potentially curative treatment of diseases and conditions where traditional pharmacological intervention has shown limitations, for example within cancer, serious chronic diseases, such as Parkinson's disease, rare diseases and tissue regeneration after injury[1-4].

Within the EU, ATMP is the classification that guides the legal and regulatory framework for product development and marketing authorisation. All advanced therapy medicines are authorized centrally via the European Medicines Agency (EMA). ATMPs include three main classes, namely gene therapy medicines, somatic-cell therapy medicines and tissue-engineered medicines.

- Gene therapy medicines contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body.
- Somatic-cell therapy medicines contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body.
- Tissue-engineered medicines contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue.

In addition, some ATMPs may contain one or more medical devices as an integral part of the medicine, which are referred to as combined ATMPs. An example of this is cells embedded in a biodegradable matrix or scaffold[5].



ATMP - What are ATMPs? (atmpsweden.se)ATMP - What are ATMPs? (atmpsweden.se)

[1] Advanced therapy medicinal products: Overview | European Medicines Agency (europa.eu)

In gene therapy medicines, the recombinant gene can compensate for an abnormal gene or allow the cell to produce increased amounts of a beneficial protein.

The recombinant gene is delivered into cells by a gene carrier (vector). Depending on the vector, the recombinant gene may either be integrated into the human chromosome or delivered to the nucleus of the cell without integration[6].

If the new gene is integrated into the human chromosome, it will be passed along to daughter cells during cell division, and hence the effect of one or a few doses of the gene therapy medicine may be permanent. In the absence of chromosomal integration, the new gene will be diluted during cell division. In this case, the duration of effect of each dose will depend on cell proliferation rates, and regular dosing may be needed[7].

Somatic-cell therapy and tissue engineered medicines are based on the patient's own (autologous) cells or cells from a donor (allogeneic cells). Once administered into the body, the new cells replace unhealthy cells or damaged tissue and act to normalize cellular or tissue function. Cell therapy may be disease modifying and potentially curative[4].

For both gene- and cell-based ATMPs, research, development, production, supply chain and implementation in the healthcare system differ significantly from medicines based on chemical entities or of biological/biotechnological origin. Likewise, these aspects differ significantly between the different subclasses of ATMPs and indeed between products within the same subclass.

The purpose of the present project has solely been to survey the possible levers and bottlenecks for commercial introduction of ATMPs.

For reference, we have selected some features of potential interest:

Feature	Compared to traditional pharmacological intervention
Clinical values	Potentially curative
Administration	1 dose per patient
Indication	Rare diseases – but potentially broader
Mode of action	Engage immune system or the genome
Regulatory, EMA approval	Typical fast track approval based on single arm clinical studies
Batch-size	1

Quality of evidence	Based on small populations, therefore often sparse evidence. Long term safety uncertain.
Clinical implementation	Certification of highly specialized personnel and dedicated facilities. Approval of environmental and work safety

Introduction: (Market) situation and pipeline

We have observed a noticeable progress in development of ATMPs over the past years, leading to new and potential curative treatments with ATMPs for diseases that in general are considered un-treatable with conventional treatment. Mostly, the focus so far has been on rare and small diseases[2i]. As table 1 shows, 10 out of 12 ATMPs are orphan medicines for different rare diseases.

Table 1 provides an overview of ATMPs with EMA market access approval, May 2021:

ATMP	Gene therapy	Cell therapy	Tissue-engineered medicines	Indication, therapeutic area	Active substance	Orphan	Company
Alofisel		x		Rectal fistula	Darvadstrocel	x	Takeda
Holoclar			x	Corneal diseases	Cornea epithelial cells	x	Chiesi
Imlygic	x			Melanoma	Talimogene laherparepvec		Amgen
Kymriah	x			Tisagenlecleucel	x	Orchard Therapeutics	
Libmeldy	x			Treat children with metachromatic leukodystrophy (MLD)	Atidarsagene autotemcel	x	Orchard Therapeutics
Luxturna	x			Leber Congenital Amaurosis Retinitis Pigmentosa	Voretigene neparvovec	x	Novartis
Spherox	x		x	Repair defects to the cartilage in the knee in adults	Spheroids of human autologous matrix-associated chondrocytes		CO.DON AG
Strimvelis	x			Severe Combined Immunodeficiency	Autologous CD34+ enriched cell fraction	x	Orchard Therapeutics
Tecartus	x			Treat adults with mantle cell lymphoma (a cancer of B-cells, a type of white blood cell)		x	
Yescarta	x			Lymphoma, Follicular, Lymphoma, large B-cell, diffuse	Axicabtagene ciloleucel	x	Gilead

Zolgensma	x			Muscular Atrophy, Spinal	Onasemnogene abeparvovec		Novartis
Zynteglo	x			Beta-thalassemia	Betibeglogenautotemcel	x	Bluebird Bio

EMA has approved 12 ATMPs as of May 2021, five more ATMPs are pending approval at this time. Nine ATMPs for ten indications are currently on, or on the way to the market in Denmark. Table 2 shows an overview of the availability of the ATMPs across the Nordic countries and the UK.

Table 2 provides an overview of the access to the ATMPs in the countries included:

	Denmark	Norway	Sweden	The UK
Alofisel	No	No	No	No
Holoclar	Yes, with restrictions.	*	*	Yes, with restrictions.
Imlycic	Not assessed*	No	Yes	Yes, with restrictions.
Kymriah (Pediatric ALL)	Yes, with restrictions.	Yes, with restrictions.	Yes	Yes, with restrictions.
Kymriah (DLBCL)	No	No	No**	Yes, with restrictions.
Luxturna	Yes	No	No**	Yes
Yescarta	No	No	Yes, with restrictions.	Yes, with restrictions.
Zolgensma***	Yes	In progress, decision expected this autumn.	In progress Status with the HTA bodies: TLV has carried out an economic evaluation. The NT council has not yet made a decision on recommendation.	Yes (draft guidance – final recommendation 7 July 2021).
Zynteglo***	In progress	In progress	No	No

* No official assessment available/not launched. ** Regulatory approved, but negative recommendation from the NT council

*** Status 27 May 2021

One observation would be that two separate schools of conclusions emerge: Denmark and Norway versus the UK and Sweden (very limited data material).

Table 2 is a comparison of evaluations in Denmark, Norway and the United Kingdom for different ATMPs

ATMP	Denmark	Norway	The United Kingdom
	Status	Status	Status
Kymriah (DLBCL)	Not recommended	Not recommended Too high ICER New assessment based on updated data (ongoing)	Recom-mended with restrictions. Uncertainty to clinical data. Patient access through the "Cancer Drugs Fund" conditional on more data being collected from real world (MEA)
Luxturna	Recommen-ded (RPE65-nethindedys-trophia) Assessed as important clinical added value. Included in performance governed MEA*	Not recommended Too high ICER	Recom-mended. Flat discount agreement
Yescarta	Not recommended	Not recommended Too high ICER New assessment based on updated data (ongoing)	Recom-mended with restrictions. Patients should have tried at least two other treatments and be eligible for MEA arrangement. New evaluation in 2022

[*] MEA: Market Entry Agreement (Specially designed procurement structure to divide risk among supplier and public payor.

As of 11 March 2021, an additional five ATMP classified products were under assessment for marketing authorisation by EMA.

In addition, around 40 industry-funded interventional trials of gene and cell (incl. CAR-T) therapies are active in phase 3. Another 200+ industry-funded phase 2 trials are active (Fig. 1), and it is expected that ATMP classified products will constitute a continuously increasing proportion of new medicines within the coming years.

EMA has identified ATMPs as an area where pharmacology is developing, and consequently this area is in focus.

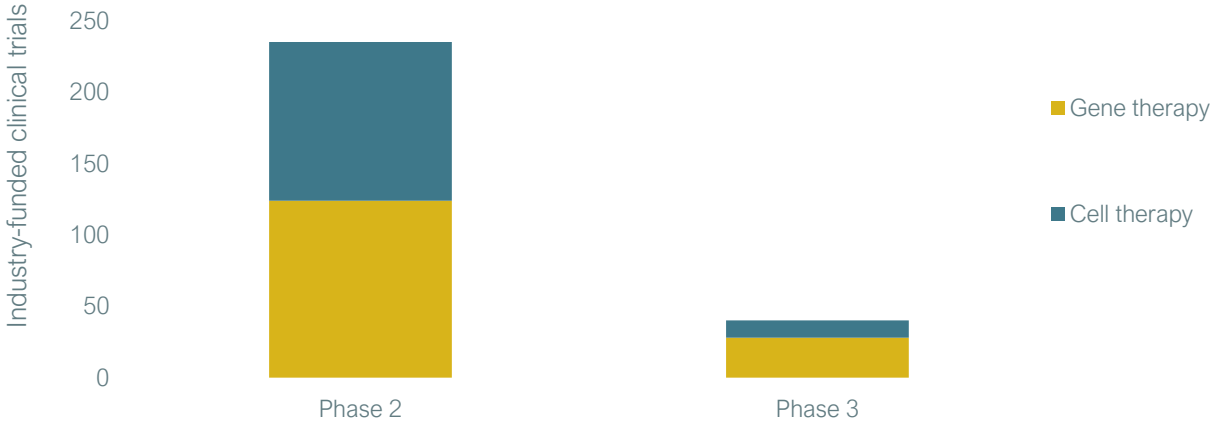


Figure 1. Industry-funded trials in gene and cell therapy. Source: clinicaltrials.gov accessed 15 April 2021. Trials listed as active, not recruiting, recruiting and not yet recruiting were included. CAR-T trials are included in cell therapy. Studies investigating autologous induced and/or expanded immune cell treatment or gene-based vaccines for prevention of infection were excluded.

International benchmarks

Within the Nordic countries, Denmark holds the least number of innovative companies pushing ATMP development but has a very high rate of research initiatives[ii].

In Denmark and in the three bench countries, market authorisation follows an EMA process after which the new product candidates undergo a country specific HTA assessment.

The United Kingdom:

ATMPs are handled under the AAC (Accelerated Access Collaborative) - Act. The AAC brings together industry, government, regulators, patients and the NHS to bring down barriers and accelerate the introduction of groundbreaking new treatments and diagnostics which can transform

care[iii]. The AAC Board agreed to prioritise advanced therapy medicinal products (ATMPs) for early-stage support[iv].

Activities in the ATMP field are further supported by the government-funded national initiative "The Cell and Gene Therapy Catapult (CGT Catapult)" which is established as an independent centre of excellence to advance the growth of the UK cell and gene therapy industry to bridge the gap between scientific research and full-scale commercialisation. The centre of excellence offers consulting and advice to academia and companies in areas as clinical trials, process development, manufacturing, regulatory affairs, health economics and market access.

Likewise, the CGP catapult supports a variety of network initiatives and projects to drive innovation across the advanced therapies field most notably:

- ATTC (Advanced Therapy Treatment Centre network programme). Clinical adoption. Aims to develop robust systems for the routine delivery of ATMPs as a standard of care throughout the NHS in the United Kingdom.
- ATSTN (Advanced Therapies Skills Training Network). Skills development. Physical and digital network of centres offering access to ATMP training facilities.
- ATAC (Advanced Therapies Apprenticeship Community). Skills development. Establishing apprenticeship programmes focusing on the development, manufacturing and delivery of advanced therapies.

Sweden:

Activities are gathered under 'ATMP Sweden', which is a government-supported national network of Sweden's activities within medicines based on genes, cells or tissue engineering, classified as Advanced Therapy Medicinal Products (ATMPs) in Europe. The goal is to promote the collaboration and communication needed for accelerated, effective ATMP-based patient solutions.[v]

In the period 2018 – 2023, the Swedish government has granted a total budget of SEK 320m to push for development of ATMP-medicines. A significant part of this is allocated for projects within a framework of public-private partnerships (PPP) bringing together universities, pharmaceutical industry, biotech, hospitals, hospital pharmacies, public regions, administration and trade organisations.

PPP-projects are organised in three programmes and managed by the Swedish centre for innovation, Vionna:

- ATMP innovation milieu
- Swelife-ATMP
- CAMP

The three programmes host a number of PPP-projects serving the entire pharmaceutical industry value chain. The strategic aim is to create a better framework for development of Swedish-based ATMP-medicines. As such, the programmes do not intend to serve as platforms for implementation of ATMP-medicines, however, in effect spillovers occur.

Some projects support preparations for and knowledge on the prerequisites for the Swedish healthcare system making ATMP-medicines available in clinical practice.

The European Commission:

The EU's regulation of advanced therapies is designed to ensure the free movement of advanced therapy products within Europe, to facilitate access to the EU market, and to foster the competitiveness of European companies in the field, while guaranteeing the highest level of health protection for patients.

The regulation focuses on the elements:

- A centralised marketing authorisation procedure.
- A multidisciplinary expert committee (Committee for Advanced Therapies), within the European Medicines Agency (EMA), to assess advanced therapy products.
- Technical requirements adapted to the particular characteristics of these products.
- Special incentives for small and medium-sized enterprises.

The regulation recognises that some advanced therapy products combine biological materials, such as tissues or cells, with chemical elements such as metal implants or polymer scaffolds. These combination products require adapted regulatory requirements. [vi]

Besides being the host for the clinical and research environments, the initiatives held by the UK, Sweden and the European Commission tend to support promotion of trade and the common life science agenda in general.

Interviews

Industry:

Below please find the summaries of pharma affiliate interviews, grouped by the headings the interviewees have pointed to as central:

General level of public knowledge on ATMP:

All interviewees point to lack of understanding and knowledge among administrative and political decision-makers of the special implications of ATMPs. Further to these, interviewees note that the public environment has difficulties distinguishing between personal medicine and ATMP. In addition, several pharma affiliates mention, the bare notion of ATMP-medicines makes more confusion simply because the terminology covers treatment with a wide range of direct implications to the health system.

Public-private partnership (PPP) concerning development and implementation of ATMP-medicines:

Companies point to a lack of a formal structure for handling PPP on ATMP-medicines in Denmark: Comparing to other countries, respondents find it difficult to be included in relevant central discussion on development of the environment. The interviewees mention the need for a facilitator or initiatives that could carry the torch for development regarding public-private projects for ATMP.

Attracting clinical research:

Interviewees are of the opinion that it has been difficult to attract ATMP-related clinical research. They debate that either projections for a small volume consumption of the ATMP-medicines or very limited size of population plays a role. Interviewees are suggesting a broader geographic approach (e.g. Nordic).

Complex operating procedures for initiating use:

ATMP-medicines require a considerable amount of knowledge to be transferred to the treating clinical unit before patient can have access to the treatments: The clinicians must operate under special precautions and new procedures must be established and effectively implemented. Interviewees find this work resource demanding without no explicit structure for renumerating the delivered services. Further among different technologies and hospitals, interviewees have observed important differences for which no structure offers a mending method.

The Danish Medicines Council (DMC), procurement models and availability of data:

The 1-year budget models engaged by the Danish Hospital Administration represent a concern and a special challenge for implementation of ATMP-medicines: The treatments are associated with very high upfront investments which unaltered challenge the local hospital budgets. The economic effect (return on investment) is most often realised at a later stage and in other parts of the taxpaid welfare system.

Every interviewed pharma-affiliate points to the difficulties in developing a satisfactory application on ATMP-medicines for DMC. They point to a major discrepancy between DMC's methodological requirements developed for "classical medicine" and the real world of ATMP-medicines as we have discussed in this paper. The DMC assessment should reflect costs and uncertainties related to drug handling and clinical requirements. Respondents believe that a methodological adjustment is required (e.g. innovative procurement structures) enabling DMC to consider the long term clinical and economic implications of ATMP-medicine usage.

Interviewees acknowledge that such procurement structures require access for all stakeholders to relevant data.

Strategic anchoring in the Danish healthcare system:

All interviewees mention the lack of a responsible authority for efficiently managing patient access to ATMP-medicines. They are afraid this will lead to a sub-optimised usage of these new innovations.

The National Board of Health operates with ATMP as it would do with any other new treatment modality and handle these technologies according to "Specialeplan, 1999".

Public stakeholders:

The project team invited a broad group for interviews but realized that knowledge and understanding of ATMP-medicines among public payors, health administrators and health politicians are limited.

Patient Organization (Kræftens Bekæmpelse (KB)):

KB has no official standpoint to ATMP-medicines; hence the interview reflects the personal experience from the interviewee:

By ATMP-medicines, KB clearly restricts this to concern gene and cell therapies.

The interviewee is skeptical towards this group of medicines. The new technologies do not appear to have delivered on the promised potential and visions. This is seen in the perspective of a lack of balance between cost-related to the treatment with ATMP-medicines and the effect as documented in the dossiers. In addition, KB finds the treatment related risk profile significant.

"We went from thinking: "wow! this is really something" to "viewing this as difficult".

KB considers ATMP-medicines as valid alternatives for treatment areas where no alternatives exist in reality, (e.g. Holoclar and Luxturna in ophthalmology). In oncology, other alternatives under development have proven more promising and the value of ATMP is regarded as less important. However, KB has an ongoing dialogue with the clinicians to secure those potential benefits, should they appear, are brought to the patients.

KB regards ATMPs costly, complicated, time-consuming and associated with a high resource burden before hospitals can commence standard usage of ATMP-medicines. Some of these obstructions, e.g. public manufacturing of ATMP-medicines in the hospitals, might reduce the market entry barriers.

Danish Health Authority (DHA) (Sundhedsstyrelsen, Enhed for Specialeplanlægning):

The interviewee underscores that DHA does not regard ATMP-medicines as one collected group of treatments: The agency will manage each separate medicine as a separate new treatment modality.

As of now, ATMP-medicines are not high on the agenda, it is, however, expected to change during the years to come. To the extent ATMP-medicines have been discussed so far, it has been CAR-T treatments, and to that extent, DHA has been involved in national planning of treatment services ("Specialeplanlægning").

DHA underscores that as far as they are concerned, the only relevant issues are the clinical relevance, any discussion of the costs of treatment is deferred to the hospital owners, Danske Regioner.

The point of reference is the guide for specialeplanlægning, 1999. With concern to the rapid development of technologies. The interviewees explicitly point to a potential need for an update caused by the technological development.

Danish Society for Hematological, Medical Society, hematology

The interview related to CAR-T treatment.

The experience with drugs in this class has been very good, and any side effects have been manageable. However, price is mentioned as an issue – regardless the total business case is promising – if it leads to a curative treatment. The societal benefits compared to treatment alternatives, including savings, the respondent expects to be considerable for patients who require life-long caretaking.

"If we acknowledge CAR-T treatment of patients to result in recovery, then it is a treatment that really makes a difference! In such scenario: We can avoid tying people up to the clinics for the remaining of their lives, and it might very well be that QALY turns out very favorable. In return patients gain improved quality of life and survival for many years. If so, yes treat as such seems costly, but it is a good investment. The current alternatives present an opportunity, but the life-extension for those are on average only half a year."

The interviewee describes allocation of hospital budget "challenging and difficult", however, manageable.

"We are used to finding budgets for new innovations within our existing budgets. We might often be able to bring down production costs by gradually minimizing the patient's hospital in-days. Historically we have proven that we can use our beds better and move patients to ambulatories:"

When it comes to CAR-T, the on-boarding process prior to implementation is cumbersome and would be more efficient should it be possible to generically extrapolate from one medicine to another. The respondent recommends considering the necessity of each and every step.

"As it is, we have an individual set-up for each of four separate pharmaceutical providers. Each method has its own merits. It is very resource consuming to initiate a new ATMP-medicine and, at the same time, comply to regulation just to document that we can handle our job. Each company has its own way, different software and different procedures – it is unbearable!

We have a need to have the cell-therapy on a common platform, let's get international standards and guidelines, and make the providers follow those.

For ATMPs – the resource consumption when it comes to clinical staff is tremendous and is more or less "potty training" on methodology for the same treatment, cell-therapy. I'm convinced that the suppliers know of this, but they have been forced to invent wheel individually. It cannot proceed, imagine we get 50 new ATMP-medicines form 50 individual manufacturers, such a scenario demands a common platform."

The respondent points out that CAR-T clinical development is restricted by volume of patients, and would like to see a broader international collaboration:

"Inevitably, Denmark is a small country, it is a valid discussion to ask why we should do everything ourselves. I would suggest that we share responsibility across the Nordics. Then one treatment could be in Copenhagen, one in Stockholm and so on. One could argue that 1-2 patients per national center is neither efficient nor living up to our thoughts on bringing quality to treatment."

Last, the interview stresses the importance of a stronger national coordination of treatment, and the interviewee is not at all satisfied with having ATMPs handled as the National Board of Health desire (Specialeplan): The objection is that such way of assigning responsibilities results in diluting critical competences. Rather, the interviewee suggests, the treatments should be centered at one national spot to secure optimal efficiency.

Research efforts to establish regional CAR-T manufacturing is not a regional- but a national task. On the other hand, all highly specialized treatments need not be centralized in one center, we can easily transfer patients to any regional center. I fail to see DHA taking lead on this.

Conclusions: Industry challenges

ATMPs will be a future part of the armamentarium of pharmacological interventions, in fact, already they have arrived in the hands of Danish clinicians.

We, however, predict a cautious and almost reluctant absorption:

These new innovations face the facts that they are neither commonly known to attract the necessary political attention, to fit the administrative infrastructure in the healthcare system and can nor be easily handled by the health technology assessment board (DMC).

From our understanding, the stakeholders from both sides agree that this could be mended as some sort of public-private partnership projects. To get this started, this investigation suggests that champions from industry as well as public administration are needed.

The specifics of the ATMPs are found as with other pharmacological agents for small and rare diseases and are so far isolated to operation of the hospital sector.

Attachments

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