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Current (non-scientific) challenges

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REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

(Text with EEA relevance)

Article 29

Transitional period

1. Advanced therapy medicinal products, other than tissue engineered products, which were legally on the Community market in accordance with national or Community legislation on 30 December 2008, shall comply with this Regulation no later than 30 December 2011.

2. Tissue engineered products which were legally on the Community market in accordance with national or Community legislation on 30 December 2008 shall comply with this Regulation no later than 30 December 2012.

3. By way of derogation from Article 3(1) of Regulation (EC) No 297/95, no fee shall be payable to the Agency in respect of applications submitted for the authorisation of the advanced therapy medicinal products mentioned in paragraphs 1 and 2 of this Article.

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„In God we trust, the rest bring data!"

W. Edwards Deming

Pioneer in Quality Philosophy, W. Edwards Deming is widely held to have been one of the leaders who helped create the **Total Quality Movement**. Deming's 14 points and his book "Out of the Crisis" are key documents in the development of Quality Systems for Business management. Dr. Deming is best known for his revolution in the quality and economic productions in Japan where from 1950 onward he taught top management and engineers, methods for management of quality. These teachings dramatically altered the economy of Japan. In recognition of his contributions the Union of Japanese Science and Engineering (JUSE) instituted the annual Deming prizes for achievement in quality and dependability of product.
http://www.resourcesystemsconsulting.com/blog/reference/glossary

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Efficacy data
(Marketing ≠ Efficacy!)
(„Experience“ ≠ Proof of efficacy!)

Which data can be used?

How to deal with claims like
„No reports on serious adverse events so far, so a very well tolerated and safe product“?

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Art. 28: the so-called "hospital exemption"

- Additional exclusion under very specific conditions e.g.:
  - Non-routine basis of production [what is this?]
  - Specific quality standards
  - Used in same MS in hospital (manufacturing authorized by Comp. Authority of MS)
  - Custom-made product for individual patient
  - Under the exclusive professional responsibility of a practitioner
  - National rules on the use of cells on ethical grounds
- An alternative Marketing Authorisation procedure?
- Creation of a second market?

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Art. 28: the so-called "hospital exemption"

HUMAN GENE THERAPY 23:7–12 (January 2012)

DOI: 10.1089/hum.2011.2529

The European Hospital Exemption Clause—New Option for Gene Therapy?

Christian J. Buchholz, Ralf Sanzenbacher, and Silke Schüle

Abstract

Gene-therapy medicinal products are currently applied to patients enrolled in authorized clinical trials to demonstrate safety and efficacy. Given a positive outcome, marketing authorization can subsequently be achieved via the centralized procedure coordinated by the European Medicines Agency. With Regulation (EC) No. 1394/2007 in force, advanced therapy medicinal products, including gene- and cell-therapy products, can be excepted from the obligation of obtaining a marketing authorization via the centralized procedure under specific conditions (so-called "hospital exemption"). This hospital exemption allows the application of gene-therapy medicinal products prepared on a non-routine basis for an individual patient and used under the exclusive professional responsibility of a medical practitioner. Here, we explain the requirements to be fulfilled in order to fall under this exemption, the implementation of this regulation into the German national legislation, and its impact on gene-therapy product development in the future.

Introduction

After a period of drawbacks questioning safety and efficacy, gene therapy is currently gaining renewed excitement as considerable clinical benefit has been reported for a number of severely debilitating genetic diseases (Sheridan, 2011). Basically, two different therapeutic strategies can be distinguished. In one setting, the vector that carries a functional allele of the gene mutated in patients suffering from disease is the ready-to-use and off-the-shelf produced gene-therapy product. This is, for example, the case when adeno-associated virus (AAV) vectors are injected intraocularly for the treatment of Leber's congenital amaurosis, an inherited form of blindness (Bainbridge *et al.*, 2008; Simonelli *et al.*, 2010). In another setting, the patient's cells or tissue are genetically modified *ex vivo* with a functional copy of the defective gene delivered by an integrating vector. For *ex vivo* gene therapy, hematopoietic stem cells are widely used. The modified cells are retransplanted into the patient's bone marrow, where they multiply and differentiate to reconstitute the patient's hematopoietic system (Naldini, 2011). Here, the genetically modified autologous patient's cells must be regarded as the gene-therapy medicinal product (GTMP). Clinical benefit by this *ex vivo* cell-based approach has been described for severe immunodeficiencies such as X-linked severe combined immunodeficiency (Thrasher *et al.*, 2006; Gaspar *et al.*, 2010) or adenosine deaminase-deficient severe combined immunodeficiency (Gaspar *et al.*, 2006, 2011), β-thalassemia (Cavazzana-Calvo *et al.*, 2010), Wiskott-Aldrich syndrome (Boztug *et al.*, 2010), and adrenoleukodystrophy (Cartier *et al.*, 2009, 2010).

Despite this progress, GTMPs have so far only reached the Asian market, where three different products are commercially available (Guo and Xin, 2006). In neither Europe nor the United States has any GTMP obtained marketing authorization so far. Reasons for this limited success of GTMPs are plentiful. Some are listed here: (i) The manufacturing process is often complex and costly. Especially, the transition from laboratory scale to a standardized and highly controlled industrial production process can be particularly challenging, *e.g.*, for products containing autologous cells, which can show an intrinsically broad batch-to-batch variability. (ii) The demonstration of clinical efficacy can often be hampered by too few eligible patients, especially for rare inherited diseases. (iii) To date, GTMPs are developed mainly by science-driven small- and medium-sized enterprises (SMEs) or university hospitals, both lacking sufficient personnel and financial resources in order to comply with state-of-the-art pharmaceutical standards. Their limited experience in regulatory processes turned out to be an additional burden when the European Commission decided to regulate GTMPs under the centralized European pharmaceutical legislation.

Here we illustrate the recent revision of the European GTMP regulation, especially focusing on the so-called hospital exemption clause, which was introduced by the Regulation (EC) No. 1394/2007 for advanced therapy medicinal

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frontiers in PHARMACOLOGY

PERSPECTIVE ARTICLE
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Advanced therapy medicinal products and exemptions to the Regulation 1394/2007: how confident can we be? An exploratory analysis

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The market authorization procedure for medicinal products for human use is relying on their demonstrated efficacy, safety, and pharmaceutical quality. This applies to all medicinal products whether of chemical or biological origin. Since October 2009, the first advanced therapy medicinal product (ATMP) has been authorized through the centralized procedure. ATMPs are gene therapy medicinal products, somatic cell therapy medicinal products or tissue-engineered products. An appropriate ATMP – Regulation is dealing with ATMP requirements. Two exemptions are foreseen to the ATMP Regulation: (a) Products, which were legally on the Community market when the Regulation became applicable, should comply to the Regulation by December 30, 2012. (b) The hospital exemption rule for non-routine products for an individual patient. In this work we explored whether the actual application of the Regulation on ATMPs is in line with the aim of the Regulation in terms of guaranteeing the highest level of health protection for patients. Based on the analysis of the relative efficacy of the only EC authorized ATMP and its exempted alternatives, there is evidence against this Regulation 1394/2007 assumption.

Keywords: advanced therapy, Regulation 1394/2007, exemption, patient outcome

INTRODUCTION

The market authorization (MA) procedure for medicinal products for human use is relying on their demonstrated efficacy, safety, and pharmaceutical quality (The European Parliament and the Council of the European Union, 2001). This applies to all medicinal products whether of chemical (e.g., blood pressure lowering diuretic) or biological (e.g., anti-inflammatory monoclonal antibody) origin. Modern biotechnology medicinal products obtain market approval through the centralized procedure as detailed in the EC Regulation 726/2004 (The European Parliament and the Council of the European Union, 2004).

Since 2008, a "lex specialis" – Regulation (EC) No 1394/2007 (The European Parliament and the Council of the European Union, 2007) – applies to advanced therapy medicinal products (ATMPs); these ATMPs are pharmaceuticals with high complexity (The Committee for Advanced Therapies (CAT) and the CAT Scientific Secretariat, 2010) linked to their development, manufacturing, or administration process.

The Regulation highlights the following:

- It provides an explicit ATMP definition: ATMPs are gene therapy, somatic cell therapy, or tissue-engineered medicinal products.
- An ATMP must comply with the existing MA requirements (quality, safety, and efficacy) and the post-marketing pharmacovigilance rules. For MA, the centralized procedure is mandatory: it aims to pool Community expertise and ensure a high level of scientific evaluation and facilitate access to market.
- Because of the complexity of ATMPs, a new Committee for Advanced Therapies (CAT) has been installed. The CAT's main responsibilities are:
  - The mandatory evaluation of MA applications by providing opinions to the Committee for Medicinal Products for Human Use (CHMP); the CHMP may adopt or refuse the CAT opinion.
  - The optional scientific certification (art. 18) of quality and non-clinical data of a proposed ATMP-compound in development.
  - The optional scientific recommendation on ATMP-classification (art. 17), prior to their clinical development.

The CAT (The Committee for Advanced Therapies (CAT) and the CAT Scientific Secretariat, 2010) is a multidisciplinary scientific expert committee: it also focuses on the scientific developments in the field. There is no doubt about the huge scientific, regulatory, and ethical challenges triggered by these complex products and a specific expert committee for ATMPs is necessary to deal with these challenges (similar to the creation of the Committee on Orphan Medicinal Products for drugs used in rare diseases) and beneficial to all relevant public and private stakeholders.

- The Tissues and Cells Directive (2004/23/EC) applies to donation, procurement and testing of human tissues and cells.
- The Regulation defines the pre- and post-authorization requirements: GMP and GCP standards, product follow-up on efficacy and safety, risk management plan, and traceability.

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Art. 28: the so-called "hospital exemption"

"Accordingly, there are many reasons why going for a hospital exemption may be a good choice for certain types of GTMPs. Advantages are already evident, e.g., the option to treat patients who then benefit from receiving otherwise unavailable treatments within an authorized setting, but under adapted requirements and a less cost-intensive application procedure."
(Buchholz et al)

"Obviously differences in development track will yield differences in the necessary R&D resources, which may result in substantial product price differences: this is a hurdle for the applicant submitting a centrally authorized ATMP when lower priced exempted alternatives are on the market."
(van Wilder)

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ATMPs are special:

Consequence:

Development and MA procedure may be difficult

Do we have to adapt our thinking to the products, not the products to our thinking?

Probably both: We have to adapt to the specificities of the products, but the developers will also have to adapt to the pharma framework.

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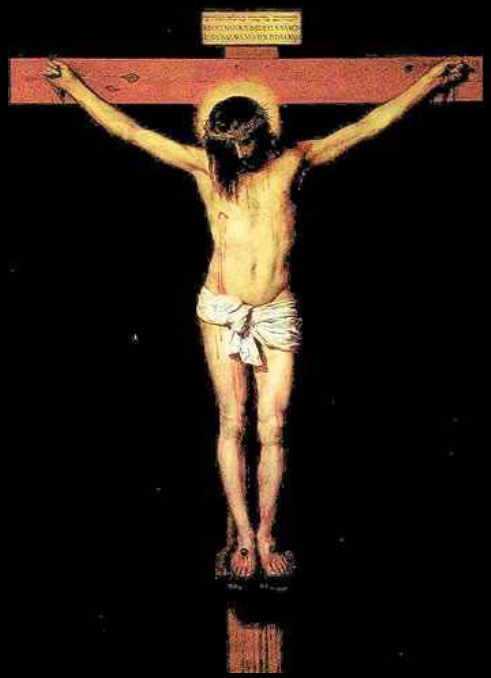
We need sense of proportion / visual judgement for regulating advanced therapiesin a balanced way.

www.stern.de

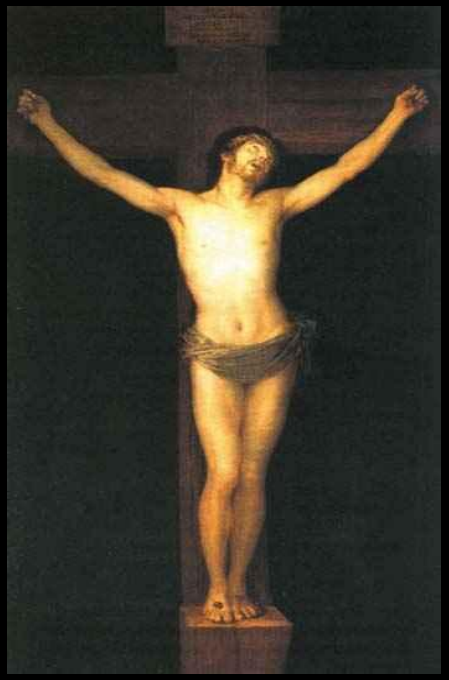
What is „the“ standard?



Velázquez

El Greco

Murillo



Goya

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How to regulate stem cells

Annex I to Directive 2001/83/EC: How to handle minimally manipulated ATMPs?
(e.g., bone marrow in non-homologous use)

- ”Starting materials”
- ”Validation”
- ”Identity”
- ”Purity”
- ”Potency”
- ”Mechanism of Action”

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It makes sense to ask questions…

The Pharmacogenomics Journal (2004) 4, 193–207

www.nature.com/tpj

ORIGINAL ARTICLE

Comparison of different isolation techniques prior gene expression profiling of blood derived cells: impact on physiological responses, on overall expression and the role of different cell types

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ABSTRACT
Owing to its clinical accessibility, peripheral blood is probably the best source for the assessment of differences or changes in gene expression associated with disease or drug response and therapy. Gene expression patterns in peripheral blood cells greatly depend on temporal and interindividual variations. However, technical aspects of blood sampling, isolation of cellular components, RNA isolation techniques and clinical aspects such as time to analysis and temperature during processing have been suggested to affect gene expression patterns. We therefore assessed gene expression patterns in peripheral blood from 29 healthy individuals by using Affymetrix microarrays. When RNA isolation was delayed for 20–24 h—a typical situation in clinical studies—gene signatures related to hypoxia were observed, and down-regulation of genes associated with metabolism, cell cycle or apoptosis became dominant preventing the assessment of gene signatures of interindividual variation. Similarly, gene expression patterns were strongly dependent on choice of cell and RNA isolation and preparation techniques. We conclude that for large clinical studies, it is crucial to reduce maximally the time to RNA isolation. Furthermore, prior to study initiation, the cell type of interest should already be defined. Our data therefore will help to optimize clinical studies applying gene expression analysis of peripheral blood to exploit drug responses and to better understand changes associated with disease.
The Pharmacogenomics Journal (2004) 4, 193–207. doi:10.1038/sj.tpj.6500240
Published online 23 March 2004

Keywords: peripheral blood; peripheral blood mononuclear cells; gene expression profiling; transcriptom

INTRODUCTION
Gene expression profiling has been applied to many aspects of human biology including stress responses of human cells,[1–3] identification of signaling cascades,[4–7] or regulated expression of cell cycle-associated genes. [8,9] For clinical investigation and medicine, gene expression signatures are used to better define biological processes that might be associated with disease, therapy or severe

Basic Res Cardiol (2011) 106:645–655
DOI 10.1007/s00395-011-0173-0

ORIGINAL CONTRIBUTION

Intravenous and intramyocardial injection of apoptotic white blood cell suspensions prevents ventricular remodelling by increasing elastin expression in cardiac scar tissue after myocardial infarction

Michael Lichtenauer · Michael Mildner · Andrea Baumgartner · Matthias Hasun · Gregor Werba · Lucian Beer · Patrick Altmann · Georg Roth · Mariann Gyöngyösi · Bruno Karl Podesser · Hendrik Jan Ankersmit

Received: 29 December 2010 / Revised: 17 February 2011 / Accepted: 9 March 2011 / Published online: 17 March 2011

Abstract Congestive heart failure developing after acute myocardial infarction (AMI) is a major cause of morbidity and mortality. Clinical trials of cell-based therapy after AMI evidenced only a moderate benefit. We could show previously that suspensions of apoptotic peripheral blood mononuclear cells (PBMC) are able to reduce myocardial damage in a rat model of AMI. Here we experimentally examined the biochemical mechanisms involved in preventing ventricular remodelling and preserving cardiac function after AMI. Cell suspensions of apoptotic cells were injected intravenously or intramyocardially after experimental AMI induced by coronary artery ligation in rats. Administration of cell culture medium or viable PBMC served as controls. Immunohistological analysis was performed to analyse the cellular infiltrate in the ischaemic myocardium. Cardiac function was quantified by echocardiography. Planimetry of the infarcted hearts showed a significant reduction of infarction size and an improvement of post AMI remodelling in rats treated with suspensions of apoptotic PBMC (injected either intravenously or intramyocardially). Moreover, these hearts evidenced enhanced homing of macrophages and cells staining positive for c-kit, FLK-1, IGF-I and FGF-2 as compared to controls. A major finding in this study further was that the ratio of elastic and collagenous fibres within the scar tissue was altered in a favourable fashion in rats injected with apoptotic cells. Intravenous or intramyocardial injection of apoptotic cell suspensions results in attenuation of myocardial remodelling after experimental AMI, preserves left ventricular function, increases homing of regenerative cells and alters the composition of cardiac scar tissue. The higher expression of elastic fibres provides passive energy to the cardiac scar tissue and results in prevention of ventricular remodelling.

Keywords Myocardial infarction · Apoptosis · Cytokines · Cell therapy · Elastin · Collagen

Electronic supplementary material The online version of this article (doi:10.1007/s00395-011-0173-0) contains supplementary material, which is available to authorized users.

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Introduction

Within the last decades early reperfusion therapy significantly reduced mortality following acute myocardial infarction (AMI) and also improved survival and prognosis of patients. However, the development of chronic

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…but how much can we ask for?

nature biotechnology

SIRPA is a specific cell-surface mark
cardiomyocytes derived from human pl

Nicole C Dubois[1], April M Craft[1], Parveen Sharma[2], David A Elliott[3], Edou
Anthony Gramolini[2] & Gordon Keller[1]

**To identify cell-surface markers specific to human cardiomyocytes, we screened cardio
human embryonic stem cells (hESCs) against a panel of 370 known CD antibodies. Th
protein alpha (SIRPA) as a marker expressed specifically on cardiomyocytes derived fr
stem cells (hiPSCs), and PECAM, THY1, PDGFRB and ITGA1 as markers of the nonm
antibody against SIRPA allowed for the enrichment of cardiac precursors and cardiom
cultures, yielding populations of up to 98% cardiac troponin T-positive cells. When pla
were contracting and could be maintained over extended periods of time. These findin
populations of cardiomyocytes from human pluripotent stem cell cultures, and thereby
for generating large numbers of enriched cardiomyocytes for therapeutic applications.**

Generation of cardiovascular cells from human pluripotent stem cells (hPSCs) in culture could provide a powerful model system for investigating cellular interactions and molecular regulators that govern the specification, commitment and maturation of these lineages, as well as a unique and unlimited source of human cardiomyocytes for drug testing and regenerative medicine strategies[1–4]. Translating this potential into practice, however, will depend on the development of technologies that enable the reproducible generation of highly enriched populations of cardiomyocytes, as contaminating cell types could affect drug responses and other functional properties *in vitro* and increase the risk of abnormal growth and teratoma formation following transplantation *in vivo*[5]. When induced under optimal cardiac conditions, hPSCs efficiently differentiate to generate mixed cardiovascular populations, including cardiomyocytes, smooth muscle cells, fibroblasts and endothelial cells[5]. Although cardiomyocytes can represent up to 70% of the population for any given hPSC line, the efficiency of generating this lineage varies considerably between different stem cell lines. Manipulation of induction conditions has not yet yielded strategies for the generation of pure populations of cardiomyocytes from a broad range of hPSC lines.

To enrich for cardiomyocytes from differentiation cultures, previous studies have introduced cardiomyocyte-specific fluorescent reporters or drug selectable elements into hPSCs[6–8], allowing enrichment by fluorescence-activated cell sorting (FACS) or the addition of appropriate selection drugs. However, these strategies suffer from a major drawback as the introduction of a reporter vector into an hPSC line results in genetically modified cardiomyocytes, reducing their utility for clinical applications. Recently, cardiomyocytes were isolated by FACS based on their high mitochondrial content[9]. This approach

appears useful for is
fewer mitochondria,
may be more difficul

To overcome these
egies for the enrichm
high-throughput flow
ers specific for huma
surface receptor SIRP
as well as on human
antibody against SIR
populations consistir
ferentiation cultures.

RESULTS

Surface of markers

When induced with
BMP4 (**Fig. 1a**), the
differentiates to gene
ses of the differentia
tal progression from
T (BRACHYURY) e
mesoderm (*MESP1*; c
ISLET1 (also known
Contracting cardiom
12 of differentiation
(also known as *αM*
(also known as *MLC2*
sion (**Fig. 1b**). The e
genes in the hESC-de

[1]McEwen Centre for Regenerative Medicine, Ontario Cancer Institute, University Health Network, Toronto, Onta
of Toronto, Toronto, Ontario, Canada. [2]Monash Immunology and Stem Cell Laboratories, Monash University, Cl
addressed to G.K. (gkeller@uhnresearch.ca).

Received 12 May; accepted 19 September; published online 23 October 2011; doi:10.1038/nbt.2005

Cell PRESS

**…w-Derived Cell Therapy Stimulates
…s Cardiomyocyte Progenitors
…tes Cardiac Repair**

… Matthew L. Steinhauser,[1,2] Joseph Gannon,[1] and Richard T. Lee[1,*]
…and the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital,
…mbridge, MA 02139, USA
…qually to this work
…ners.org
…002

…ove cardiac function in animals
…jury, but the mechanism is
…d cell therapy experiments in
…d mice that permanently ex-
…nt protein (GFP) only in cardio-
…e of 4-OH-tamoxifen. Myocar-
…the GFP⁺ cardiomyocyte pool,
…nt by non-GFP⁺ progenitors.
…e marrow-derived c-kit⁺ cells,
… stem cells, further diluted the
…nt with c-kit⁺ cell-mediated
…iomyocyte progenitor activity.
…be explained by transdifferen-
…ytes by exogenously delivered
…usion. Therapy with c-kit⁺ cells
…l stem cells improved cardiac
…ngs suggest that stimulation
…ogenic progenitor activity is a
… cardiac cell therapy.

…myocytes retain some capacity for
…2003; Bergmann et al., 2009; Hsieh
…onse is inadequate for prevention of
…njury (Lopez et al., 2006). Demonstra-
…sdifferentiation by a variety of progen-
…rationale for cell-therapy experiments
…umans with heart failure (Segers and
…e trials have shown improvements in
…ular therapies, the therapeutic effect
…studies, and the mechanism of action
…idated (Abdel-Latif et al., 2007).
…thanistic explanations for functional
…diac cell therapy have been proposed.
…tion into cardiomyocytes by exoge-
…e most obvious explanation for cell
…ements in cardiac function, yet the
…ferentiation by exogenously delivered

cells remains unclear (Balsam et al., 2004; Murry et al., 2004; Orlic et al., 2001). Additional proposed mechanisms of cell therapy include inflammatory modulation, transdifferentiation into endothelial or smooth muscle cells, or paracrine stimulation of angiogenesis or endogenous cardiomyocyte progenitors. Defining the contributions of these mechanisms represents a fundamental prerequisite to the future optimization of cardiac regenerative therapies.

Genetically engineered mice enable lineage mapping experiments to determine the role of progenitors in regenerative processes. We previously described a double-transgenic *MerCreMer-ZEG* mouse for genetic lineage mapping; the cardiomyocytes of *MerCreMer-ZEG* mice irreversibly express GFP upon treatment with 4-OH-tamoxifen, allowing for "pulse" labeling of existing cardiomyocytes (Hsieh et al., 2007). This lineage-mapping approach has demonstrated that myocardial infarction or pressure overload results in precursor-dependent replenishment of the cardiomyocyte pool. Here we used genetic fate mapping to determine the effect of exogenously delivered progenitor cells on endogenous cardiomyocyte refreshment.

RESULTS

Bone Marrow-Derived c-kit⁺ Cell Therapy Stimulates Endogenous Cardiac Progenitors after Myocardial Infarction

We generated an in-bred transgenic colony of *MerCreMer-ZEG* mice over a 4 year period to test the hypothesis that cell transplantation regulates endogenous progenitor activity. We assessed the regenerative properties of a purified bone marrow-derived cell population (lineage⁻/c-kit⁺ or c-kit⁺ cells) previously reported to improve cardiac function (Figure 1A; Orlic et al., 2001; Rota et al., 2007). *MerCreMer-ZEG* female mice were pulsed with 4-OH-tamoxifen to induce cardiomyocyte-specific GFP expression, after which they were subjected to myocardial infarction by coronary ligation. Mice were randomized to receive vehicle control or c-kit⁺ cells (6×10^5) freshly isolated from a wild-type male mouse (Figure S1 available online) in two divided 5 μL intramyocardial injections to the medial and lateral infarct borders of the left ventricle. After an 8-week chase, histologic sections were stained for GFP and β-galactosidase as previously described (Hsieh et al., 2007). An observer unaware of treatment group captured photographs from the infarct border

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The CAT is an open-minded scientific player

PERSPECTIVES

OPINION

Challenges with advanced therapy medicinal products and how to meet them

The Committee for Advanced Therapies (CAT) and the CAT Scientific Secretariat

Abstract | Advanced therapy medicinal products (ATMPs), which include gene therapy medicinal products, somatic cell therapy medicinal products and tissue-engineered products, are at the cutting edge of innovation and offer a major hope for various diseases for which there are limited or no therapeutic options. They have therefore been subject to considerable interest and debate. Following the European regulation on ATMPs, a consolidated regulatory framework for these innovative medicines has recently been established. Central to this framework is the Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA), comprising a multidisciplinary scientific expert committee, representing all EU member states and European Free Trade Association countries, as well as patient and medical associations. In this article, the CAT discusses some of the typical issues raised by developers of ATMPs, and highlights the opportunities for such companies and research groups to approach the EMA and the CAT as a regulatory advisor during development.

Advanced therapy medicinal products (ATMPs) comprise gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products and tissue-engineered products (for legal definitions see BOX 1 and REFS 1,2). They are at the forefront of innovation, offering potential treatment opportunities for diseases that currently have limited or no effective therapeutic options. ATMPs have therefore been subject to considerable interest, but have generated both positive and negative outcomes.

For example, recent publications have suggested that gene therapy for monogenetic diseases could result in long-term beneficial results and may prove to be an effective treatment strategy[3–6]. In addition, cell-based skin substitutes and cartilage products have already been used for more than a decade, and upcoming somatic cell therapy medicinal products and tissue-engineered products might also become efficacious treatment modalities. However, despite their promise and the progress made, ATMPs have sometimes caused clinical problems, which have led to reports in the lay press. For example, although rare, fatalities following gene therapy have been reported, including a lethal systemic inflammatory immune reaction and leukaemia due to insertional oncogenesis[6,7]. Recently, fetal stem cells were reported to cause a brain tumour, suggesting that cell-based medicinal products (CBMPs) also have intrinsic risks that need to be addressed[8].

With the new European regulation on ATMPs[9], a consolidated regulatory framework for these innovative medicines has recently been assembled. Central to this new legislation is the establishment of the Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA) in London, UK. The CAT is a multidisciplinary scientific committee of experts representing all member states of the European Union and countries from the European Economic Area and the European Free Trade Association (Iceland and Norway are currently represented in the CAT), as well as representatives from patient and medical associations (BOX 2). This independent committee, with a high degree of expertise in both the scientific and regulatory aspects of ATMPs, started its work in January 2009. The CAT gathers dedicated European experts to review the quality, safety and efficacy of ATMPs according to standards established by regulatory authorities, and to debate scientific developments in the field. Information on the declared scientific expertise of the CAT members and alternates (reflecting the expertise required by the regulation on ATMPs) can be found in FIG. 1.

The CAT is responsible for the primary evaluation of ATMP marketing authorization applications (MAAs) for the EMA's Committee for Medicinal Products for Human Use (CHMP). The CAT operates two new regulatory procedures for companies developing ATMPs — the classification procedure and the certification procedure — which are both discussed further below. The CAT aims to foster innovative medicines while maintaining a high standard of regulatory responsibility. Guidance had already been developed by various EMA and CHMP regulatory groups (for example, the Biologics Working Party, the Gene Therapy Working Party or the Cell-based Products Working Party) before the establishment of the CAT, and through the Scientific Advice Working Party. However, the CAT now combines and complements these activities within a single committee to support the development of ATMPs in Europe.

Marketing authorization of ATMPs requires, as for all medicinal products, that the applicant demonstrates that the product is consistently manufactured to a predefined quality, and that it is safe and efficacious in patients. The CAT recognizes that some ATMPs will require new strategies for their development and scientific assessment. For example, the clinical performance of many types of CBMPs strongly depends on the final performance of the cell preparation administered. Success depends on the rigorous control of the manufacturing process and specifications, which has

Nat Rev Drug Discov 9(3):195-201.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 June 2010
EMA/CAT/235374/2010
Patient Health Protection

Committee for Advanced Therapies (CAT) Work Programme 2010 - 2015

Introduction – Problem statement

New and emerging science has been identified as an important driver for progress and change in the European Medicine Agency's (EMA) Road Map to 2015[1].

It is generally well recognised in the international scientific arena and by regulators that advanced therapies are at the forefront of scientific innovation in medicine, offering potential groundbreaking new treatments for diseases and injuries of the human body.

The continuous scientific progress, for example in the field of cellular and molecular biology, has boosted the hope for highly innovative and improved therapies and has led in the last decade to intensive research and development in the field of gene therapy and regenerative medicine (including tissue engineering and somatic cell therapy). However, whilst science has revealed the potential, only a limited number of these research projects managed to translate into products that are able to further progress to the late stage of clinical development and eventually to reach the market. Surveys performed by European operators in the sector depict a very lively sector that has not managed to unlock its potential due to a variety of hurdles, including lack of access to funding and changed regulatory environment (e.g. need for further guidance to improve predictability of registration, complex regulatory system not easily accessible by SMEs and Academia, regulatory package requiring high investment in terms of human and financial resources).

The negative effect of the hurdles, both real and perceived, is consistent with the limited number of products that are seen by the Committee for Advanced Therapies (CAT) (3 MAA, 1 certification application in 2009) and a very limited number of products heading for a MAA in 2010-2015. Some products appear to be in a more mature state but lack the resources to be brought up to regulatory standards. In addition, the CAT acknowledges messages received from interested parties and patients' organisations that such hurdles are limiting the timely access by patients to potential effective treatments[2].

The traditional regulatory framework for medicines is structured as an applicant-driven system, which involves regulators responding only upon receipt of applications from developers. In view of the demonstrated potential of ATMPs but lack of progress to the market, the CAT is investigating

[1] The European Medicines Agency Road Map to 2015: The Agency's Contribution to Science, Medicines, Health
[2] E.g. conclusions from 'World Conference on Regenerative Medicine - Leipzig, 28-31 October 2009' sessions 'Funding in Regenerative Medicine Ventures' and 'Policy and Legal Issues in Regenerative Medicine'

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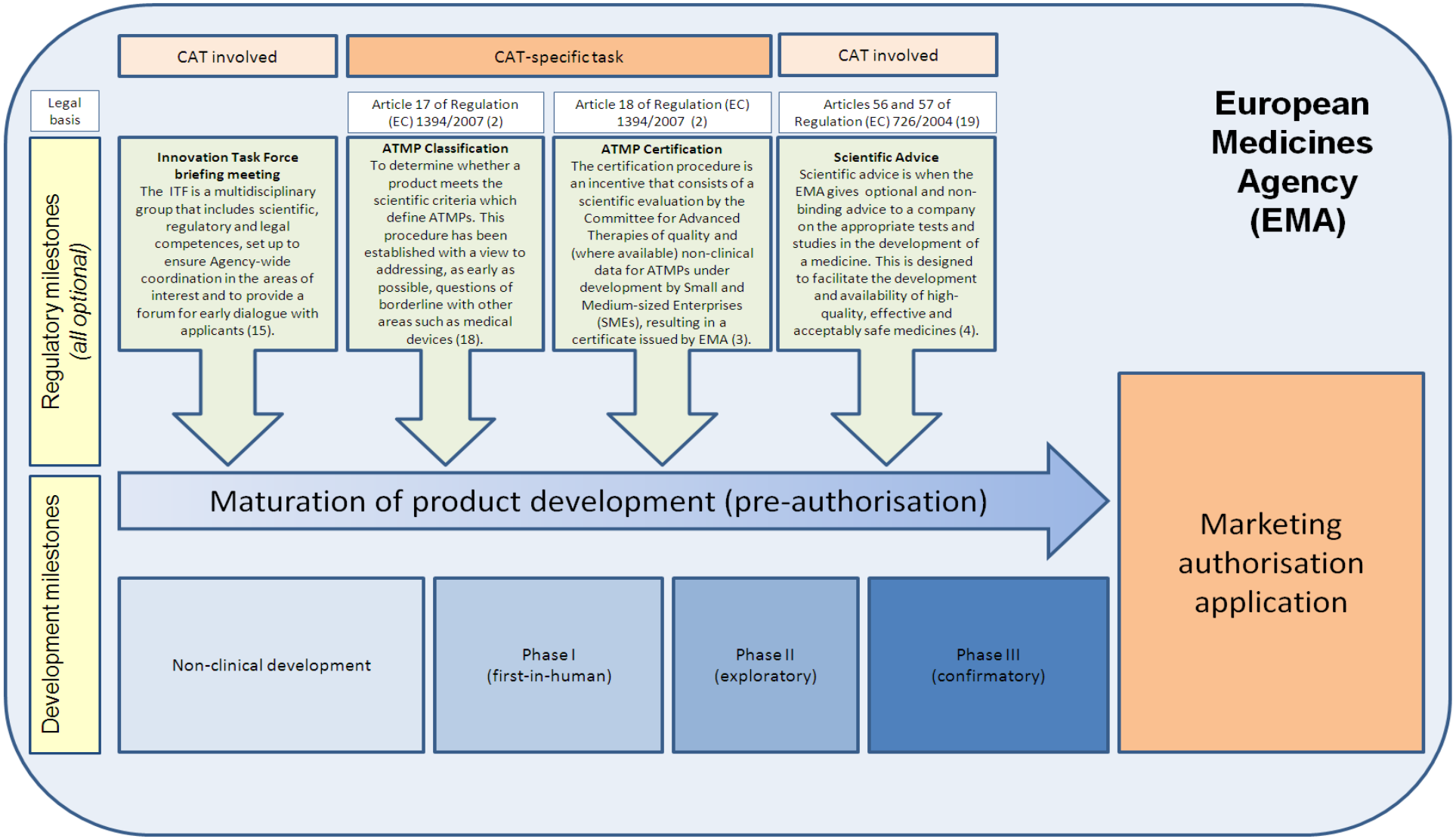
”The Committee with only one product”?



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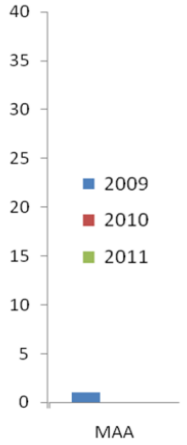

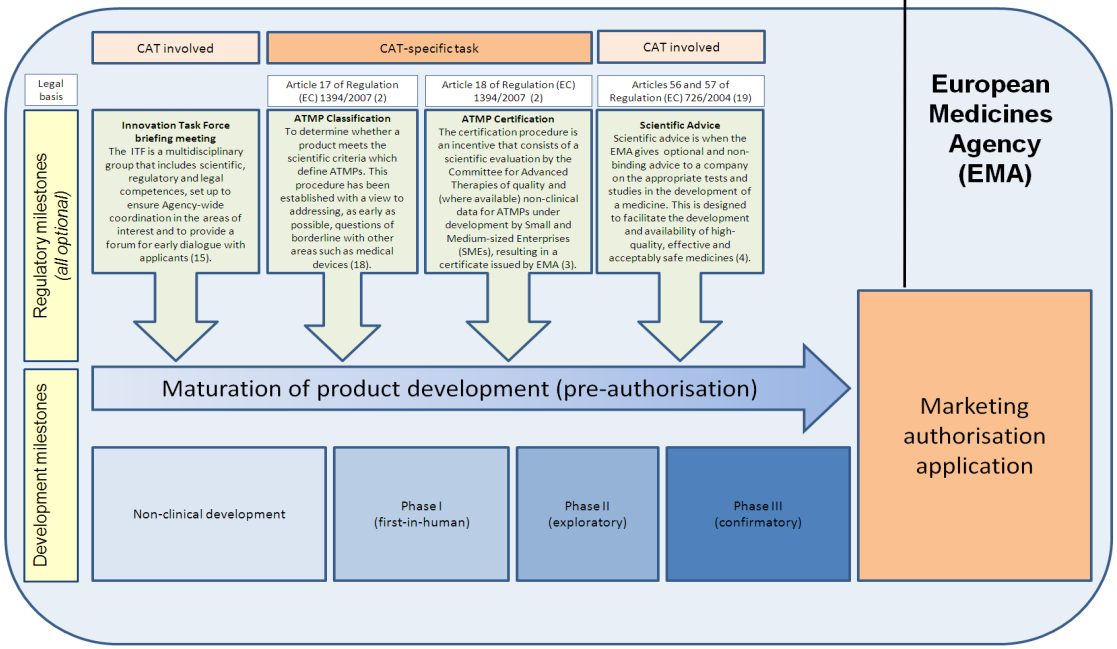

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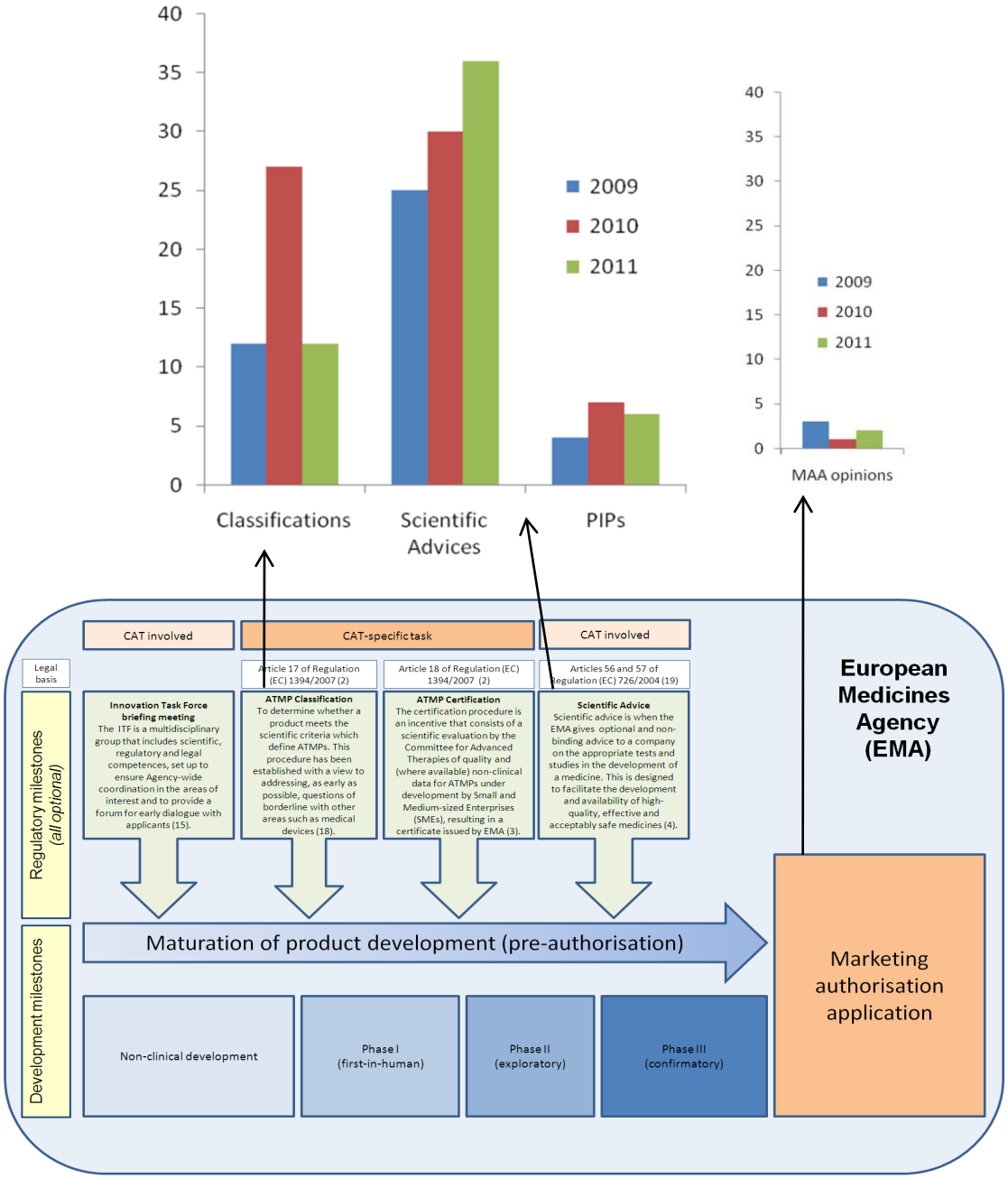
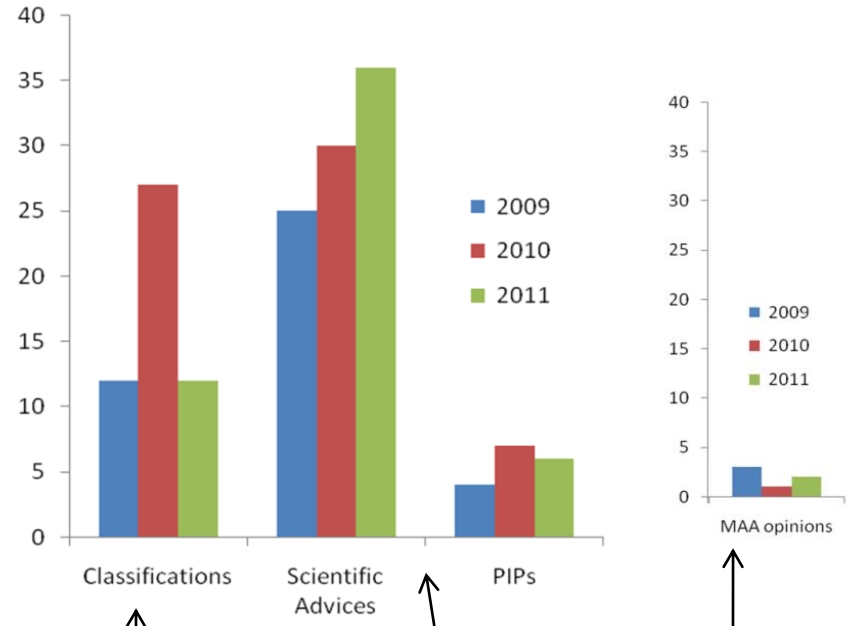
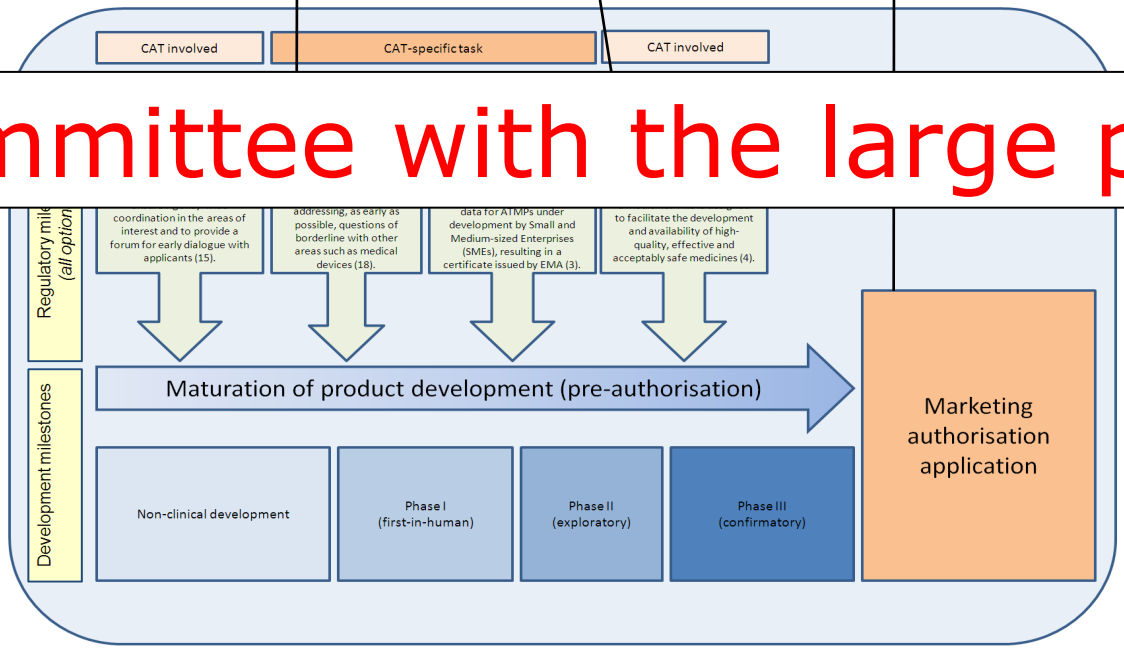


Source: CAT monthly report, EMA website

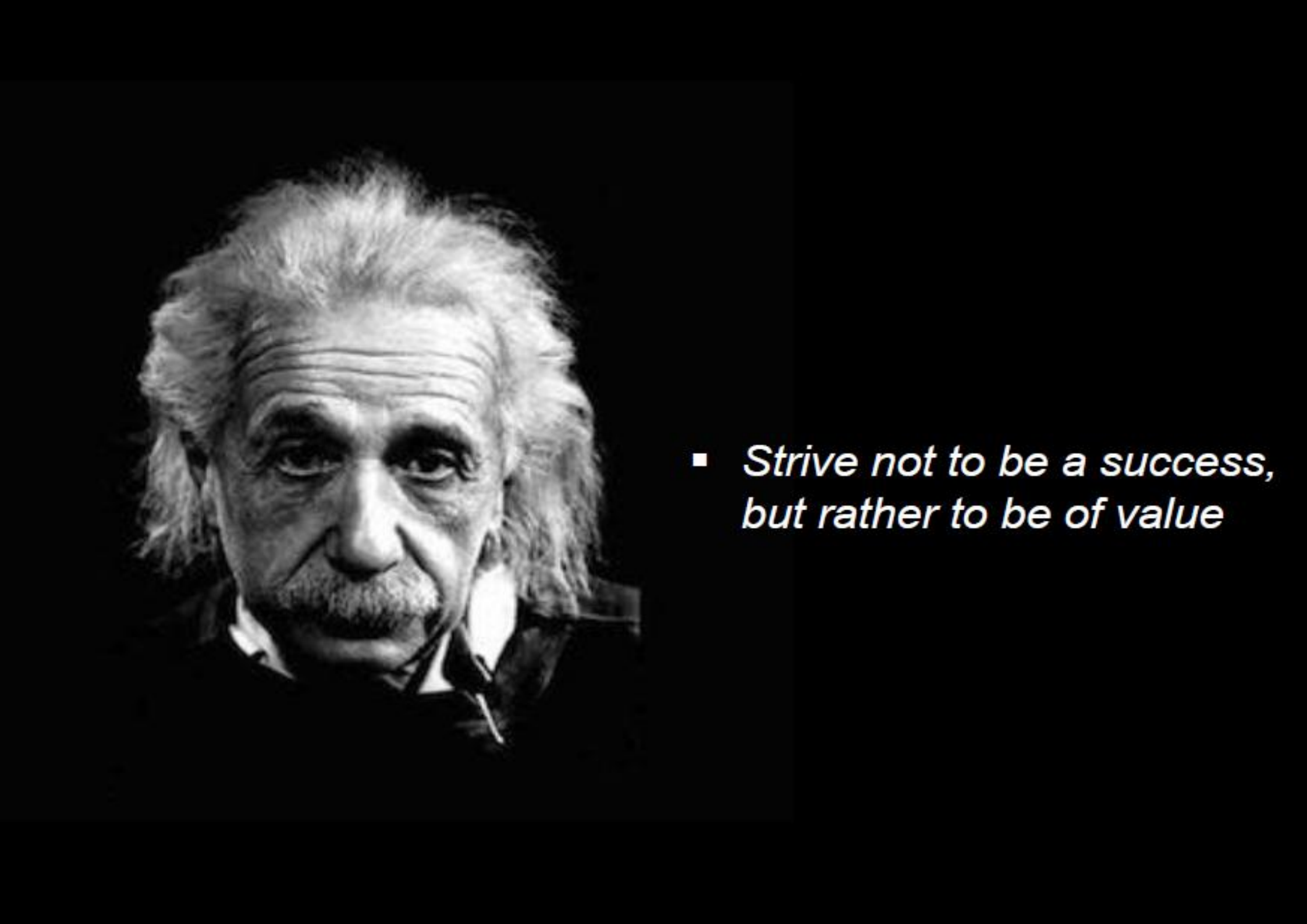
~~"The Committee with only one product"?~~





The committee with the large pipeline!

Source: CAT monthly report, EMA website


Strive not to be a success,
but rather to be of value