



European Medicines Agency, CAT Secretariat & US Food and Drug Administration

We speak to EMA/CAT and US FDA about the current state of stem cell regulation

The **European Medicines Agency (EMA)** and the **Committee for Advanced Therapies (CAT)** are responsible for reviewing applications for marketing authorization for Advanced Therapy Medicinal Products (ATMP), which include (stem) cell-based medicines, for the ATMP classification and certification procedure, and to provide scientific advice to developers of ATMPs. The CAT, an expert committee dedicated to ATMPs, was established by the Regulation (EC) No 1394/2007 on Advanced Therapies. The CAT came into operation in January 2009. ATMPs are defined in this Regulation as gene therapy and cell therapy medicinal products, and tissue-engineered products.

The **US FDA's** Center for Biologics Evaluation and Research is responsible for ensuring the safety, purity, potency and effectiveness of many biologically derived products, including blood intended for transfusion, blood components and derivatives, vaccines and allergenic extracts, and cell, tissue and gene therapy products for the prevention, diagnosis and treatment of human diseases, conditions or injury. Human cells or tissue intended for implantation, transplantation, infusion or transfer into a human recipient are regulated as human cells, tissues, and cellular and tissue-based products (HCT/PS).

How has the number of applications for stem cell therapies increased over the past 10 years?

EMA/CAT: The field of advanced therapies, which include cell-based therapies, is relatively new. Most of the development is still in preclinical and early clinical investigations. EMA and CAT (which has only been in existence since the beginning of 2009) have seen a number of products – most of them via Advanced Therapy Medicinal Products (ATMP) classifications (see later), informal meetings with companies (briefing meetings of EMA Innovation Task Force) and scientific advice questions. Some Member State authorities have a slightly higher exposure to this new field, via the

review of clinical trial applications for ATMPs, but the number of ATMPs in confirmatory (Phase III) clinical trials is limited. It is therefore difficult to make any valid statements on any trend in cell therapies over the last 10 years.

Looking at the last 3 years (since the CAT has been operational), the following information can be provided:

- The number of applications for marketing authorization (licensing) for ATMPs is for the moment limited (only five applications submitted so far). No stem cell-derived product has been approved so far;
- Based on the number of applications for ATMP classification, Scientific Advice, Orphan Drug Designation and briefing meetings with developers, it can be deduced that a

substantial number of ATMPs are currently under development or in early clinical trials;

- 45 scientific recommendations for ATMP classification and one application for ATMP certification have already been finalized;
- For the ATMP classification, 30 out of 45 classifications related to cell-based products (somatic cell therapy product or tissue-engineered products). About 30% of these are adult stem cell-derived products. No product derived from embryonic stem cells has been classified;
- The one product for which an ATMP certification procedure has been finalized contains autologous bone marrow-derived progenitor cells;
- CAT discusses approximately two new scientific advice requests for ATMPs every month; the majority of these advices are related to cell-based therapies.

Orphan designations (are the responsibility of the Committee for Orphan Medicinal Products [COMP]). COMP has designated 13 stem cell-derived products as orphans, 12 of which are adult stem cell-derived products, and one is a product derived from an embryonic stem cell line (human embryonic stem-cell-derived retinal pigment epithelial cells for the treatment of Stargardt's disease).

The number of clinical trials in the EU with cell-based therapies (somatic cell therapy and tissue-engineered products) is about 200. One quarter of these involve stem cell-derived products, based on a preliminary analysis of the EudraCT database. These numbers should be considered with caution for a variety of reasons, including the recent introduction of the ATMP Regulation. Prior to this legislative change, some cell-based products, for example, tissue-engineered products or minimally manipulated cell-based products for nonhomologous use, were not

considered as medicinal products and, therefore, not included in the clinical trial database.

FDA: Stem cells proposed for clinical use are categorized by FDA as cellular therapies. While there is currently much interest in stem cells, cellular therapies are a broad category, and there are many types of cellular therapy products that do not involve stem cells.

Federal regulations prohibit FDA from acknowledging the existence of, or disclosing information contained in an Investigational New Drug Application (IND), unless that information has been made public by the sponsor. Having said that, we have seen a steady increase in the number of clinical trials in the cell therapy area. For example, our database shows that there were 86 active cell-therapy IND/Investigational Device Exemptions 10 years ago, 446 5 years ago, and 764 active currently in 2011.

How has the agency developed its approach to stem cell-derived products?

EMA/CAT: Stem cell products fall within the definition of Advanced Therapy Products, and hence all the procedures in place for ATMPs apply to stem cell-derived products.

From a scientific perspective, EMA follows research into stem cells in medicines closely. CAT, together with its cell-products working party, has developed a guidance document (reflection paper) on quality, non-clinical and clinical aspects specific to stem cell-derived products [101] and organized a public workshop in May 2010 [102].

EMA/CAT also issued a Public Statement on concerns over unregulated medicinal products containing stem cells [103].

FDA: FDA has extensive experience

(more than two decades) with the oversight of early clinical trials for cellular therapies. The Agency has implemented a risk-based approach to the regulation of human cells, tissues and cellular and tissue-based products (HCT/Ps). Regulation focuses on three general areas: limiting the risk of transmission of communicable disease from donors to recipients; establishing manufacturing practices that minimize the risk of contamination; requiring an appropriate demonstration of safety and effectiveness for cells and tissues that present greater risks due to their processing or their use.

HCT/Ps are regulated by the Center for Biologics Evaluation and Research (CBER) under the authority of Section 361 of the Public Health Service (PHS) Act as well as Title 21 of the Code of Federal Regulations (CFR) Part 1271. HCT/Ps that meet all of the criteria in 1271.10(a) are regulated solely under Section 361 of the PHS Act [104].

Owing to their biological complexity, many HCT/Ps need to be evaluated on a case-by-case basis to determine the appropriate regulatory pathway. In many cases, cellular therapies administered to patients as a means of therapeutic intervention for a disease or medical condition do not meet the criteria in 1271.10(a) that constitutes the basis for their regulation as tissues under Section 361 of the PHS Act. HCT/Ps that do not meet all of the criteria listed in 1271.10(a) are also regulated under Section 351 of the PHS Act and/or the Federal Food, Drug and Cosmetic Act as drugs, devices and/or biological products requiring premarket approval for demonstration of safety and effectiveness. An IND application is required to be in effect before clinical studies involving '351' products can be initiated. Eventually, a Biologic License Application will need to be approved before commercial marketing is permitted. An IND is a request for authorization from FDA to administer an investigational drug or biological product to humans. A Biologic

License Application is an application for approval to market and distribute a product in interstate commerce.

What are the priorities FDA would consider when reviewing an application to start clinical trials of a new stem cell-based therapy?

FDA: Facilitating the development of innovative therapies to address unmet medical needs is a high priority for the Agency. Product safety and human subject protection are FDA's primary concern.

As a regulatory agency, FDA makes judgments based on the evaluation of scientific data submitted with each individual application, and does not prejudge classes of products. For investigational human clinical trials involving any cellular products including stem cells, we consider on a case-by-case basis whether the risks of the proposed study are reasonable and acceptable in light of the potential benefits that may be provided to patients.

It is not possible to anticipate all the potential risks and safety issues that may be associated with an investigational cellular therapy product. However, it is possible for sponsors to mitigate risk by performing detailed product characterization and conducting adequate preclinical testing in appropriate animal models. In addition, FDA participates in many outreach activities, including presentations and panel participation at scientific meetings and workshops in which these potential risks and the need to mitigate them through comprehensive product and preclinical testing are conveyed.

Some of the potential safety concerns include: administration site reactions; adverse reactions due to the cell administration procedure;

potential unwanted inflammatory and/or immune responses to the cells; the ability of the cells to migrate from the site of administration and differentiate into inappropriate cell types; adverse effects on physiologic function; risk associated with administration procedures, especially when there is lack of evidence to show that cells function as anticipated in the target tissue of the body; excessive proliferation of the cells in the body; and the development of tumors in the body.

In assessing risks and benefits, FDA takes many factors into account, including, for example, results derived from analytical assessment of product characteristics as well as preclinical proof-of-concept and safety testing submitted with each individual application. One of FDA's responsibilities is to assess potential risks and benefits, and to take steps to reduce potential risks to subjects enrolled in investigational clinical trials for those studies conducted under an IND filed with FDA. For investigational human clinical trials, we consider whether the risks of the study are acceptable in light of the potential benefits. Safety assessment is based in part on the preclinical safety studies performed by a sponsor, and the design and conduct of the studies are critical to evaluating whether it is reasonably safe to conduct the proposed clinical investigations.

Additionally, a clinical investigation to study a product in pediatric populations must offer the enrolled child a sufficient prospect of direct benefit to justify that risk (21 CFR 50.52). FDA is very interested in this issue, and held a public workshop on cell and gene therapy clinical trials in pediatric populations on 2 November, 2010. Information on the best practices related to cell and gene therapy clinical trials in pediatric populations, as well as challenges and considerations in the review of these clinical studies, is

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available in the background materials and the link to the webcast from this meeting posted at FDA website [105].

How long does a stem cell therapy application take to approve compared with a drug?

EMA/CAT: ATMPs, including stem cell-derived products, will be reviewed by the centralized procedure. The evaluation takes a maximum of 210 days active review time (not including the time required by the applicant to respond to questions put to them by the Committee). This review time is the same as for other medicinal products that are reviewed by the centralized procedure (e.g., recombinant proteins, new chemical entities).

A shorter review time is possible once the products/technologies become more established.

FDA: For products under Section 351 of the PHS Act and/or the Federal Food, Drug and Cosmetic Act, the timelines and process for review of cellular therapies are the same as for other drugs and biologics. However, the specific review concerns can vary greatly from product to product.

There are no stem cell-based cellular therapies approved by FDA for use in the USA. FDA is unable to offer projections as to the timeframe for approval of any particular investigational cellular therapy. The agency is actively involved in overseeing the approval process for cellular products, including those comprised of stem cells.

What would be your advice to companies developing a stem cell-based therapy?

EMA/CAT: As we are dealing here with a novel class of products, it is very important that the developers of such products get in contact with the Regulators (EMA, national authorities) as early as possible, via informal or formal meetings, scientific advice requests, etc, to discuss the development of their product and ensure that the application for marketing authorization is to the highest standard possible.

FDA: Early communication is important. FDA encourages applicants to take advantage of informal communications between the Agency and the sponsor/applicant prior to the submission of an IND. These discussions provide a forum for the Agency to provide guidance to firms during product development and facility design, and to facilitate their compliance with the regulations governing development and post-approval marketing of products. The sponsor/applicant can request a meeting without an IND to discuss general product issues. Additionally, they may request a meeting with FDA to obtain advice on their proposed bench/animal testing as well as on the design of their clinical trials. This type of regulatory discussion is referred to as a pre-IND meeting. The purpose is to reach agreement on the format for the IND, the scope and design of planned Phase I clinical studies, design of animal studies needed to support human clinical testing and product characterization issues. Pre-IND meetings are informal, and the feedback is nonbinding for either party.

What are the most common misconceptions regarding the role of the Regulator in this area?

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promising/novel product on the market. Nevertheless, it is the duty of the Regulators to make sure that all medicinal products are safe and efficacious, and of adequate quality. Regulators have to balance carefully the benefits of early access of the products to the patients versus the negative consequences from unsafe or ineffective medicines.

In general, Regulators tend to be cautious, especially for novel products/technologies, asking the developers for a more elaborate proof of quality, safety and efficacy.

However, in the EU, we have some regulatory tools that could speed up the approval process without jeopardizing patients safety. Most notable are, specifically for ATMPs: the application of a risk-based approach, which allows for a more 'tailor-made' development program (taking into account the published experience with the type of products) and the possibility to request postauthorization efficacy follow-up studies (alongside postauthorization safety studies, which can be requested for all medicines), to further substantiate the efficacy findings after the product is on the market.

FDA: One of the most common misconceptions is that FDA has a bias either for or against certain therapies. In fact, FDA's reviews are based solely on the scientific data provided by the sponsor. The Agency reviews applications to evaluate safety, product quality and effectiveness.

How successful do you think regulators have been in communicating with researchers and companies in the stem cell field to date? Where do think communication could be improved?

EMA/CAT: The developers of ATMPs are in many case different from those of other medicinal products, with a very high proportion of ATMPs developed by academia/hospitals and small companies, and an almost complete absence of big pharma. It is acknowledged that academia/hospitals might not be aware of the regulatory requirements for medicinal products, and will most likely not consult the websites of EMA or the National Competent Authorities for Medicines to find the guidelines or procedures related to the products they are developing.

Therefore, very early in its existence, the CAT took a couple of initiatives to find alternative means to establish contacts, especially with the academic/hospital researchers and the small (spin-off) companies developing ATMPs. These include publications in scientific journals [1], attendance and presentations at scientific conferences/meetings, joint meetings with international societies [106], and active dialogue with stakeholders in the field of ATMPs via regular meetings with interested parties [107].

Notwithstanding these initiatives, communications with developers can certainly still be improved. Further interaction with international societies on (stem) cell/gene therapies might be very helpful in this respect.

FDA: FDA believes that it can always improve communication and welcomes input as to how best to achieve this goal, within our statutory limits regarding disclosure. FDA uses many outreach mechanisms to communicate with stakeholders, including guidance documents and public meetings, such as advisory committee meetings, workshops and outreach talks. For example, FDA advisory committee meetings serve as a forum to publicly discuss potential safety issues related to the stem cell field as well as other product classes. Examples of recent

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advisory committee meetings include the meeting held on 18–19 March, 2004 to discuss safety concerns for cellular products for the treatment of cardiovascular diseases and the testing that should be performed to ensure administration of a safe product [108]. There was also an advisory committee meeting held on 10 April, 2008 to discuss safety issues related to the use of the cell therapy products derived from human embryonic stem cells [109].

A recent NIH–FDA public workshop entitled Pluripotent Stem Cells in Translation: Early Decisions took place March 21 and 22 2011. A videocast of this meeting is available at the NIH website [110].

FDA also periodically issues guidance documents to explain FDA's current thinking on various topics. The guidance documents relating to cellular and gene therapy can be found on FDA's website [111].

Additionally, the Office of Cellular, Tissue and Gene Therapies has developed a website (OCTGT Learn) specifically designated for industry education. This site provides useful information to help manufacturers develop quality cellular and gene therapy products – including the preparation of an IND application [112].

What steps are you taking towards harmonization (adoption of standards worldwide) and how can industry help speed this process?

EMA/CAT: International harmonization activities are earmarked as a very important next step. Already for 4 years, EMA/CAT and US FDA have held regular teleconference calls (every 2 months) to discuss ATMP-related issues and to build a common understanding of the technical and

scientific requirements.

More recently, a further initiative has been taken at the international level to explore potential areas for future harmonization and/or other approaches leading to regulatory convergence for cell therapies (including stem cell therapies) [113]. This initiative involves regulatory authorities from Europe, USA, Canada, Japan and Asian countries, and an initial fact-finding exercise is ongoing. Any future harmonization activities will likely take place under the International Conference for Harmonization umbrella, whereby industry will be involved.

FDA: While countries around the world have their own regulatory authorities, there is no one uniform global safety standard for the evaluation and regulation of stem cell-based products. The International Society for Stem Cell Research has published recommendations for the clinical translation of stem cell-based products [114]. The recommendations were developed by a task force consisting of a multidisciplinary group of stem cell researchers, clinicians, ethicists and regulatory officials from 13 countries. Liaisons from FDA worked with this group. The recommendations, many of which address safety, targeted for an international community, highlight issues that should be addressed so that basic research involving stem cells is translated responsibly into appropriate clinical applications.

FDA is currently undertaking an exploratory effort with other regulators, including EMA, to assess opportunities for harmonization in this arena. That effort is taking place within a Regulators Forum that meets in conjunction with biannual meetings of the International Conference for Harmonization. In a complementary approach, FDA is working within the Asian–Pacific Economic Community (APEC) Life Sciences Innovation Forum (LSIF) to discuss and further develop regulatory frameworks for stem cell therapy

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products. FDA participated in the APEC/LSIF Stem Cell Workshop held in July, 2011 and hosted by the Thai Ministry of Health and Thai FDA. The outcomes of the Workshop will be discussed within the Global Regulators Forum in an effort to identify potential areas of harmonization for cellular therapies, including stem cells.

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