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Meeting report

Extent and content of data for regulatory submissions: First-in-human and marketing authorization – Viewpoint of US industry

Ian Ross Harris*

Janssen Research & Development LLC, USA

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ABSTRACT

The amount and type of data in regulatory submissions increases dramatically from the first-in-human clinical trials application through to the extensive dossier that is required for marketing authorization. The Pharmaceuticals and Biotechnology industries are very familiar with the requirements and expectations of Health Authorities for small molecule and biologics, but have limited experience for cell-based therapies. Fortunately, the United States Food and Drug Administration (FDA) and European Medicines agency (EMA) Committee for Advanced Therapies (CAT) have considerable experience in regulating cell therapies and have provided extensive Guidance documents for developers. The Agencies offers advice to Sponsors through a variety of meetings. However, it is incumbent on the Sponsor to understand the regulations, interpret the Guidance documents and formulate clear company positions to enable the Agency to provide clear feedback.

It is important for Sponsors to understand the factors that are critical for the safety and efficacy of their product and to demonstrate to the Health Authorities that they have a control strategy that ensures safety and efficacy during all stages of development. The focus of this paper is to describe some of the challenges for the chemistry manufacturing and controls (CMC) for cell therapies being development internationally.

1. Background

US FDA has developed regulations and provided Guidance for the regulatory submissions required for first in human studies and for licensure of cell-based products [1–7]. Similarly the EMA has provided Guidance for cell and tissues as well as advanced medicinal products derived from cells [8–17]. Some of these Guidance documents are for specific therapeutic applications such as cartilage repair or cardiac disease [18,19]. These documents should always be the starting point for developing the regulatory submission. However, due to the large diversity of products these documents cannot provide Guidance for every specific question the Sponsor may have for the extent and content of the regulatory submission for their specific product. The focus of the paper is on the information required for the Chemistry Manufacturing and Controls (CMC) and Quality sections of regulatory submissions and what additional Guidance Health Authorities can provide to support the development of cell-based products. This article can only highlight some specific areas that should be addressed and does not attempt to be comprehensive.

1.1. Scientific advice

Sponsors have the opportunity to request scientific advice to prepare regulatory submission. However, depending on the framing of questions that a Sponsor asks during Pre-IND meetings with FDA and Scientific Advice meetings with EMA and/or National Competent Authorities the answers may only pertain to the current state of development and not future development or Market Authorization. Health Authorities can remain silent on these discrepancies or sometimes provide cautionary comment. In some Health Authorities there will be different reviewers for clinical development and Market Authorization. Therefore, in certain circumstances it is advisable to ask questions that address both the

Abbreviations: CAT, Committee for Advanced Therapies; CCIT, container closure integrity test; CFR, Code of Federal Regulations; CLIA, Clinical Laboratory Improvement Amendments; CMC, Chemistry Manufacturing and Controls; CPMP, Committee for Proprietary Medicinal Products; CTD, Common Technical Document; EMA, European Medicines Agency; ESC, embryonic stem cell; FDA, Food and Drug Administration; GMP, good manufacturing practice; GTP, good tissue practice; LAF, Laminar air flow; iPS cell, induced pluripotent stem cell; Ph. Eur., European Pharmacopoeia; TSE, Transmissible Spongiform encephalopathy; USP, United States Pharmacopeia; WCB, working cell bank.

* 1400 McKean Road, PO Box 776, Spring House, PA 19477, USA. Tel.: +1 215 628 5829.

E-mail address: Iharris@its.jnj.com.

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near term and long-term particularly if issues cannot be corrected and impacts are long-lasting, such as donor eligibility or testing for an allogeneic cell bank.

Good and clear communication with Health Authorities through the Common Technical Document (CTD) is hampered by the lack of a commonly defined Drug Substance and Drug Product for cell-based products so each Sponsor will put information in different sections. There is guidance to help Sponsors but it is not specific for cell therapies [20].

Due to the wide variety of cell-based products it is critical that Sponsors clearly describe their cell type and product to avoid confusion with other cell therapies and clearly define what the critical quality attributes of their product are. The communication of the criticality analysis and risk assessments, which are routinely performed, is also not clearly defined in the CTD format.

1.2. Donor eligibility

There are key items that are required to enable the development, manufacture and distribution of cell therapies to patients around the world so we would like to have clarity in Guidance documents, and if possible, harmonization on these topics. One of the most fundamental and important is the donor eligibility and testing requirements for allogeneic products. 21 CFR 1271 [5] (also known as Good Tissue Practice or GTP) Subpart C – Donor Eligibility, does not make a distinction between materials used for clinical studies and commercial distribution. This topic has been most challenging for some of the embryonic stem cell (ESC) lines that were derived before the donor eligibility requirements were established. It may not be known what the donor health history was for both the male and female donors. In the United States, 21 CFR §1271.155 allows a Sponsor to request an exemption from or alternative to the donor eligibility requirements. But the regulatory pathway in other jurisdictions is not clear. A separate, but related topic is the importation of cellular products into countries for investigational or marketed products that were procured, manufactured and tested outside of that country.

The use of donors from other countries/regions may be restricted due to the risk of transmission of pathogens. For example the use of European donor cells in the USA is highly restricted due to the potential for Transmissible Spongiform encephalopathies (TSEs) [21]. Testing of the donors could be standardized in terms of the type of test to be performed, the equivalency of approval status of test kits and equivalency of test laboratories. The US FDA required FDA licensed, approved or cleared donor screening tests and Clinical Laboratory Improvement Amendments (CLIA) certified laboratories or must meet equivalent requirements as determined by the Centers for Medicare and Medicaid Services [22]. However EMA follows Directive 2006/17/EC [9], Annex II "*The tests must be carried out by a qualified laboratory, authorised as a testing centre by the competent authority in the Member State, using EC-marked testing kits where appropriate. The type of test used must be validated for the purpose in accordance with current scientific knowledge.*". It is not clear if it is acceptable for the donor test sites to be ISO 15189 Medical laboratories certified, but not GMP or CLIA certified. According to EudraLex, Volume 4, Annex 2, Table 1 [22], procurement and testing of donor tissue/cells are not within the scope of GMP for biologics. The donor testing should follow the GTP requirements [5] and EU requirements laid out in Directive 2004/23/EC [10] but not GMP. Also that some tests may not be both CE marked and FDA licensed. The issue may be even more complicated if the donor tests need to comply with regulations from additional Health Authorities. Therefore, it would be advantageous for Health Authorities to establish and recognize harmonized standards for test and testing laboratories.

When cell banks for allogeneic products are established there is a considerable investment. If new donor testing is required it may not be possible or practical to retest the donor or perform testing on retained samples so provisions need to exist to "grandfather" in cell banks that have been tested or used without evidence of transmissible agents.

To provide assurance that Sponsors can comply with 21 CFR 1271 [5] or the EU cell & tissue directives 2004/23/EC [10], 2006/17/EC [9], 2006/86/EC [8], Sponsors may be asked to have contingency plans for the transfer and archiving of records from third parties if they are no longer operational. This type of contingency should be written into supply and quality agreements with third parties.

1.3. Application of Good Manufacturing Practice

Another fundamental issue is how Good Manufacturing Practice (GMP) will be applied to cell-based products. Although GMP is not explicitly part of the regulatory submission the control strategy is an important aspect. It is recognized by Sponsors that Health Authorities want to promote access to new medicinal products through regulatory flexibility, provided that there are adequate and appropriate controls in place and that the Sponsors can provide suitable justification for the approaches being taken. This is especially so in early clinical development where there is greater flexibility. However, it may not be clear to Sponsors at Market Authorization what items are required (sometimes legally) and therefore not negotiable and present potential "landmines" for developers. Although this is not unique to cell therapies it is likely to occur in a relatively new field and could be proactively addressed. In addition, the interpretation and application of GMP by auditors performing inspections on behalf of the Health Authorities needs to be aligned. The control strategy that can be applied to other biologics such as monoclonal antibodies may not be technically feasible or appropriate for cell-based therapies. The control strategy should be clearly described and justified in the regulatory submission to try and reduce the risk of auditors having alternative interpretations of how GMP should be applied.

1.4. Intermediate cell banks

The nomenclature of two-tiered master and working cell banks, which are used in biologics manufacture as seed pools, may not be appropriate for cell therapies from diploid cells with finite *in vitro* lifespan as these banks are cryopreserved process intermediates, but have been widely adopted. For some cell therapies banks of cells will be made from multiple donors and exhausted each year. The Health Authorities should have mechanisms to approve the use of new cell banks that would not legally require extensive regulatory submissions (e.g. variation procedure) to be given so long as pre-defined specifications are met for the new banks.

Initial stability data for cell banks requires a formal stability plan, but routine manufacture in-process data can be used in the Market Authorization according to ICHQ5D [23]. Viral testing of the WCB may not be appropriate due to limited cell expansion and amount of samples and so an exception may be justified.

1.5. Variability in the starting cellular materials

Autologous products are a challenge for the Sponsor to develop a control strategy that allows for the consistent manufacture of product during clinical development and marketed product. A key variable is the cellular starting material. This is especially so for cells coming from patients who have different states of disease and concomitant medications such as leukopheresis from oncology patients. There is a question of how you qualify the process on

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