International Society for Cellular Therapy ISCT

Cytotherapy (2008) Vol. 10, No. 3, 312–316

informa healthcare

Investigational new drugs submitted to the Food and Drug Administration that are placed on clinical hold: the experience of the Office of Cellular, Tissue and Gene Therapy

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Background

Cell and gene therapies are medical products regulated by the U.S. Food and Drug Administration (FDA) within its Center of Biologics Evaluation and Research (CBER) in the Office of Cellular, Tissue, and Gene Therapy (OCTGT). Clinical research using cell and gene therapies in the United States must be conducted under an Investigational New Drug (IND) application. After an initial, 30-day review FDA either places an IND on clinical hold or allows the IND to proceed.

Methods

We reviewed letters sent by OCTGT to IND sponsors that were placed on clinical hold. We categorized each deficiency and determined its frequency.

Results

We found that similar deficiencies existed across IND applications and we tabulated the most common deficiencies.

Discussion

We discussed the deficiencies and the resources that can help individuals avoid those deficiencies. We believe that awareness of the common deficiencies along with the applicable resources can reduce the frequency of clinical holds and allow clinical studies to proceed without delay. We also believe that this information will guide the FDA as to how to facilitate development of safe and effective cell and gene therapies.

Keywords

cell therapy, clinical, chemistry, manufacturing and controls (CMC), Food and Drug Administration (FDA), gene therapy, hold, investigational new drugs (IND), Office of Cellular, Tissue and Gene Therapy (OCTGT), pre-clinical.

Introduction

Cell and gene therapy products hold the potential to treat many diseases, including many with no current therapeutic options. These products are regulated in the USA by the US Food and Drug Administration (FDA) as biologic drugs and must meet standards of safety and efficacy before they can be marketed. Clinical testing to determine the safety and efficacy of therapeutic products must be performed under an investigational new drug (IND) application submitted to and reviewed by the FDA. Therefore, sponsors who plan to conduct clinical trials with cell or gene therapy products must submit an IND to the FDA prior to beginning their clinical trial [see Code of Federal Regulations Title 21 Part 312.2 (21 CFR 312.2) for additional details on when an IND is required for clinical studies].

This paper uses the term 'cell therapy' to describe somatic cell therapies regulated under section 351 of the Public Health Service (PHS) Act. It does not include products regulated solely as HCT/Ps under section 361 of

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DOI: 10.1080/14653240801910905

the PHS Act. For more information see 21 CFR Part 1271 and http://www.fda.gov/cber/tiss.htm (42 USC 262).

The IND process is guided by federal regulations, primarily published in the Code of Federal Regulations (CFR) Title 21 Part 312 (21 CFR 312). The major objectives of the FDA during the review of an IND application for early phase clinical studies are to ensure the safety and rights of the subjects who participate in the clinical trials. In addition, for later phase studies, FDA must ensure that the clinical trials are adequately designed and controlled to allow an evaluation of the product's safety and effectiveness [21 CFR 312.22(a)].

Each IND is reviewed within 30 days of arriving at the FDA. Upon arrival, FDA assigns an IND number, issues an acknowledgement letter, and forms a review team. The review team includes a project manager and expert reviewers. The review includes an evaluation of clinical, pre-clinical, and chemistry, manufacturing and control (CMC) information. Typically, one reviewer is assigned for each discipline and he or she reviews the relevant portion of the IND application. As needed, other reviewers or review disciplines are added to the review team (for example biostatisticians and device engineers).

The review is based on scientific and regulatory principles. According to FDA regulations (21 CFR 312.42), an IND may not be allowed to proceed if the proposed investigation presents an unreasonable risk; insufficient information has been provided to assess the risk; the investigators are found to be unqualified; the investigator's brochure is erroneous or misleading; gender discrimination exists for a disease or condition occurring in both men and women. If no deficiencies are identified, the IND becomes active and the study may proceed; FDA is not required to issue a letter when no deficiencies are identified. If deficiencies are identified, the sponsor is informed that the proposed study may not proceed and the IND is placed on clinical hold. The IND sponsor is sent a letter describing the nature of the deficiencies and what must be done to correct them. The clinical hold status can be removed, allowing the study to proceed, once the deficiencies are corrected by the sponsor and submitted to and reviewed by the FDA. There are many resources available providing more information about the IND review process, such as those on the FDA website [1,2].

Methods

We reviewed and identified the deficiencies in original IND applications for early phase clinical trials as documented in letters to cell and gene therapy IND sponsors. We reviewed all of the nearly 100 hold letters that were issued by Office of Cellular, Tissue and Gene Therapy (OCTGT) between 2002 and 2005. We found that similar deficiencies existed across IND applications and we categorized and tabulated the deficiencies. We did not include deficiencies that represented less than 5% of the respective discipline's reasons for hold. In addition, we discussed additional resources that may be helpful to sponsors when they fill in their IND application. We believe that this information may help individuals who plan to submit a cell or gene therapy IND to the FDA, thus avoiding a clinical hold.

Results

Clinical reasons why cell and gene therapies were placed on hold

The common clinical reasons for INDs being placed on clinical hold could be classified into various categories, as listed in Table 1. The major categories were patient

Table 1. Common clinical reasons for hold

Patient population deficiencies
Eligibility and/or exclusion criteria inappropriate
Number of subjects not specified or unreasonable
Starting dose deficiencies
Insufficient data to support the intended starting dose
Product preparation or formulation inadequately described
Dose regimen deficiencies
Administration of product risky or inadequately described
Proposed dose escalation scheme too aggressive
Failure to stagger enrollment of patients in trials using a new product with unknown risks
Dose modification plan unreasonable
Repeat treatment plan unreasonable or not supported
Safety monitoring deficiencies
Anticipated toxicities inadequately monitored
Lack of appropriate toxicity scale
Individual patient treatment discontinuation criteria absent or unreasonable
Study stopping rules absent or unreasonable
Withdrawn subjects not adequately followed
Long-term follow-up for patients absent or inadequately described
Adverse event reporting procedures inadequate