ついて

・CHMP から国を重複せずに 5 名が参加

・EU 各国から 25 名の代表が参加

・医師代表が 2 名

・患者代表が 2 名

・Advanced Therapies の科学的側面と倫理的側面の双方について、CHMP にアドバイスをおこなう

Guideline on cell-based medicinal products について

- 本 Guideline は、Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products を改正する目的で策定中である
- 対象は、細胞の由来、その分化度、製剤の形状の面で様々である。したがって、自家、同種を問わず、また遺伝子修飾されたものも含む
- 内容は Risk Management、Quality and Manufacturing Aspects、Non-Clinical Development、Clinical Development に章立てされている

Technical requirement について

- リスクに応じて、相応の動物実験を行うこととし、Points to Consider を記載
- 承認後のビジランス、特に Traceability について規定
- Risk management について規定

Risk Management について

ICH E2E に基づいて、2005 年 11 月から Risk Management System of Medicinal Products for Human Use が開始。ICH E2E が Safety Specification と Pharmacovigilance Plan を提言しているのに加えて、EU として Risk Minimization Activities の必要性も検討することにしている。

現在検討中の内容として、Traceability system、Pharmacovigilance system、Risk management Plan、Efficacy Follow-up Plan の 4 項目がある。また安全性確認の視点(案)として、1) 製剤の物流、2) ドナーへのリスク、3) 患者へのリスクとして、製剤の質、保存、流通面での検討、4) 患者へのリスクとして投与方法に関するもの、5) 患者体内での製剤の反応性に関するリスク、6) 患者体内での製剤の動向に関するリスク、7)患者体内での製剤の安定性に関するリスク、8) 製剤取扱者や患者の周辺に居る人々にとってのリスク、が挙げられている。

Stem cell Therapy に関する考え方

Stem cell therapy については、Embryonic Stem cell として特別に規制を作成するのではなく、Cell Therapy の一環として捉えている。一方で、Cell Therapy を包括的に管轄する Regulation の策定が難しいことも承知している。

EC No 1394/2007 によって、Cell Therapy を含む Advanced Therapies の法的根拠が出来たため、今後 Scientific Requirement に関して細かく詰めていく予定である。しかし、米国 FDA 同様、十分な研究がなされていない状況での審査基準の設定は不可能という前提であり、Advisory Committee の開催などによって随時対応する予定、とのことであった。

EU 加盟国毎の ES 細胞の臨床応用の可否など、Ethical な判断は、各国の判断に任せている。

日本への Implication

EMEA では、ES、iPS に関連した指針等を特に切り出すのではなく、先進医療技術(Advanced Therapies)として、これまでと異なる管理体制の構築、規制の改正を行うことにしている。例えば、iPS 細胞の技術と遺伝子治療の技術との共通性に配慮して、それぞれを別々の技術指針にするのではなく、統一した指針として扱う、という方針である。

先進医療に対して統一的な指針を作成する、という方針は、日本でも同様の取り組みが可能であり、ヒト幹細胞指針の改正に含めて取り組むのが良いと思われる。また、その他の基本的な認識としては、先進医療技術には、これまでと異なるパラダイムでのリスク管理が必要との認識があり、特に細胞治療においては、Pre-Pharmacovigilance として臨床試験のフェーズから Traceability の確保すべき、と述べていた。

臨床研究に関する指針の策定を、Scientific Regulation としては EU 内で統一する一方で、Ethical Regulation は各国にゆだねる方法は、異文化国家の集合体である EU では合理的であると同時に、日進月歩の技術へ速やかに対応する方法としても優れている。日本の指針のように、両者を内包している場合、改定に際して、一方が足を引っ張ることで、対応が遅くなる可能性がある。このため、規則、指針を科学面と倫理面で切り分けることが今後の目標となりうる。

C-3

MHRA（英国医薬品庁）調査報告

山本雄士（独）科学技術振興機構　研究開発戦略センター・フェロー

日時：2008年3月7日

場所：The Medicines and Healthcare products Regulatory Agency (MHRA) Headquarters at London

出席者

石井哲也、山本雄士(科学技術振興機構　研究開発戦略センター)、梅垣（厚生労働省医政局研究開発振興課)

対応者

Dr. Ian Hudson, Director, Licensing Division (Medicines)

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Dr. Andrew M French, Group Manager, Licensing Division

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Mr. Ian Rees, GMP Operations Manager & Senior Medicines Inspector

英国の審査機関であるMHRAでは、既に幹細胞を用いた臨床試験の問い合わせを受けており、2007年11月に策定されたAdvanced Therapy Medical Productsに関するRegulation (EC No1394/2007)に合わせて国内法の改定を進めている。MHRAは、科学面での審査を担当しており、特にTraceabilityの確保に注目した規定の策定を強調していた。

背景

MHRAは英国の審査・承認機関であり、年間約1200件の臨床試験申請を取り扱っている。EU Clinical Trial Directive (2001/20/EC)発効以降、英国では、臨床試験の科学面の審査はMHRAが行い、倫理面では別のEthical Committeeが行っている。

MHRAの審査のうち、特に免疫系や生物製剤を扱う臨床研究の審査には、外部のAdvisory boardを招集して妥当性を問うなど、慎重な対応を取っている。

（参考）Cell tharapy に対する英国における規制

細胞治療とその開発を、その精製、保存、探索的医療用品(Investigational Medicinal Products；IMP)、販売承認、という流れに沿って俯瞰し、それぞれの根拠法と所轄機関を図１に示す。

１．　UK での The human tissue and cells directive　(2004/23/EC) に対応した、donation から保存、利用に関する法律として２００４年 the Human Tissue Act が制定され、提供される細胞組織の安全性・品質の確保が規定されている。また、この法律に基づいて the Human Tissue Authority (HTA) が監督省庁として設置され、tissue banks の審査・認定などを行っている。

２．　この法律の制定以前から UK では、ＥＳ細胞等ヒト胚や生殖細胞に関しては The Human Fertilisation and Embryology (HFE) Act (1990) および the HFE (Research Purposes) Regulations, 2001 によって、提供卵子、精子、体外受精卵の扱い、保存等が規定されている。英国内におけるあらゆる体外受精卵の作成・研究は同法に基づいた license が必要。限られた利用目的のみに限定されている（2001 年、使用目的規定が若干拡大され、「難治性疾患の理解」等も目的に加えられた)。

Embryo の研究目的の容認範囲を治療研究にまで広げるかどうかの議論の中で、2003 年１月 NIBSC(National Institute for Biological Standards and Control；国立生物学的製剤研究所) の元に、the National UK Stem Cell Bank が設置された。基礎研究や先進医療研究のために quality-control された cell line の登録・提供を行うものである。Bank への細胞の登録・Bank からの提供は、Stem Cell Steering Committee (SCSC) により" The Code of Practice for the Use of Stem Cell Lines 2005" にしたがって行われる（輸入 cell line の管理もこのルールによっている)。Bank の ES 細胞や cell line を利用する側の研究者も、この Code に従う。

３．　英国内の Clinical trial の監督省庁は MHRA であり、国内における clinical trial の regulation としては、The clinical trial directive (2001/20/EC) などの EU directive に基づいて制定された英国内の医薬品 clinical trial の GCP、" UK Statutory Instrument 2004 No. 1031 (The Medicines for human use clinical trials regulations)" があり、stem cell を用いるものも含め、臨床試験を行うものは、すべてこれらの

regulationへの適合性につきMHRAのadviseを受けねばならない。

4. Medicinal productの製造品質管理基準(GMP)はClinical trial、marketing authorizationのいずれかを問わず、GMP directive (2003/94/EC)に基づく、EudraLex Volume 4におけるEU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use、Part I, IIで基本的な要件が、さらにAnnexesで各論が記されている(cell therapyが関係するのはAnnex 2 : Manufacture of Biological Medicinal Products for Human Use)。

また、UK内のregulationとしては、stem cell clinical trialで用いられるstem cellのGMP基準を含んだtechnical requirementsは、stem cell linedでは前述のSCSC the Code of Practice for the Use of Stem Cell Lines 2005によりカバーされている。また、一般的なcell therapy clinical trialで使用される細胞製品はMHRAの査察を受け、かつThe Code of Practice for the Production of Human-derived Therapeutic Products, MHRA, 2002に適合したclinical facilityで採取・調製されたものでなければならず、適切な品質管理システムを備え、さらに実施計画書はformal risk assessmentを受ける必要がある(ただし、EMEAのGuideline on human cell-based medicinal productsが正式発効後は、こちらに移行するものと見られる)。

5. marketing authorizationに関してはRegulation (EC) No 1394/2007に基づくEMEAによる中央審査体制を構築中(EMEA調査報告を参照)。

EU域内では、臨床試験と販売承認ともに各国で行われるのが基本ではあるが、生物製剤においては、臨床試験の実施に関して各国の担当機関が管理し、販売承認に関してはEMEAが中央管理する、という仕組みになっている。

EUではAdvanced Therapies Medicinal Productsとして、Tissue Engineering、Cell Therapy、Gene Therapyが取り上げられている。これまでに、体細胞を用いた臨床試験の申請は2007年第三四半期までで112件(昨年、一昨年の同期間ではそれぞれ40件、13件)あり、対象疾患として、がん治療が45件、心臓血管系が31件、皮膚が28件の順で多い。また遺伝子治療に関しては、2004年～2007年の間で33件(うち15件が2007年)、生物製剤に関しては5,977件の取り扱いがあった。

最近、MHRAに対して、幹細胞を用いた臨床試験に関する問い合わせがあり、MHRAも規則作りを行っている最中である。EMEAの認識と

同様に、MHRA でも、現状の規制が新たな医療技術をカバーしきれていないことは認めている。

Cell therapy に関する英国の実状

すでに述べたように、英国での細胞治療に関する法規制と管轄は図１のようになっている。

細胞の精製および保存において、UK Human Tissue Act、UK Fertility & Embryology Act があり、これらの所轄機関として Human Tissue Agency、Human Fertility & Embryology Agency が設置されている。これらの細胞はNIBSC(National Institute for Biological Standards and Control; 国立生物学的製剤研究所)の管轄する Cell Bank にて一元的に管理されている。これらの過程では、ドナーの同意の上で細胞を採取、保存しているが、細胞の用途として臨床応用を念頭に置いて説明および同意が得られているかは不明である、とのことであった(MHRA としては、臨床応用する場合には、当然その旨を採取前に説明すべき、との姿勢は明確であった)。

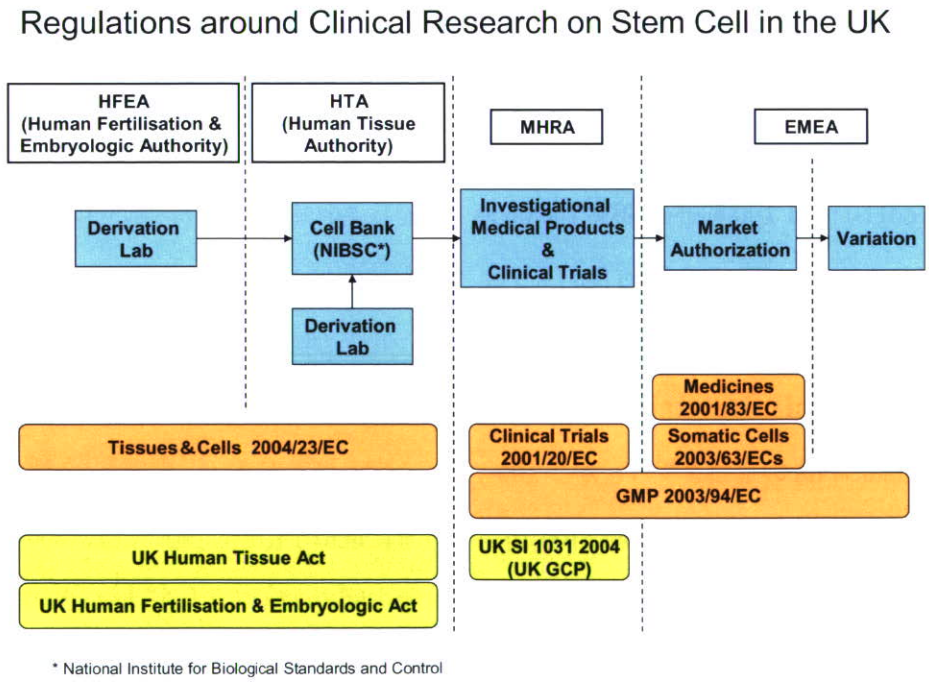

図１　英国における細胞を用いた研究のプロセスと管轄法(改訂中のものも含む)

臨床研究の申請である Investigational medicinal product(IMP; 探索的医療用品)の申請後に適用される GMP に関しては、2003/94/EC の Annex2 において、生物製剤に関するより詳細な要件が記載されている。この Annex も、EC No1394/2007 の発令後は、改正が必要となっており、現在作業中である。Annex 2 は、一般的な指針を述べた Part A と、製剤ごとの用件を述べた Part B に分類される。幹細胞を含めた細胞治療に関しては、Somatic and Xenogeneic cell Therapy に分類され、フィーダー細胞に関する規定や、ドナーの健康情報に関する規定が定められている。しかし、未知の部分が多いのも事実で、例えば腫瘍原性に関しても観察期間として12ヶ月が良いのか、あるいは2年が必要十分なのか、また、実験動物として何を用いるのか、まだ定まっていない、とのことである。

臨床研究に際しては、特に Traceability の確保が重要であり、一定期間の観察による臨床試験という概念が根本から変わる可能性がある、とも述べていた。

英国の医学研究の実績を背景に、MHRA が EMEA での発言力が強いことを自負している。そのため、幹細胞研究に関しても結局 MHRA が主導して、EMEA の規則を作っていくことになるだろう、という思惑も見て取れた。

日本への Implication

MHRA に対し、幹細胞を用いた臨床試験に関する問い合わせがあったために、急ピッチでルールを作ろうとしている感がある。一方で、TGN1412 事件以降、First in Man の研究には慎重な姿勢を崩せない、という姿勢も見せている。日本でも、規制の確立と平行して、社会対応を十分にしなくてはいけないことは明らかである。

科学的には、細胞治療の経年における影響を十分観察する必要があり、Pharmacovigilance のための Traceability 確保は必須である。MHRA の指摘のように、従来のような一時的な観察に過ぎない臨床試験では、細胞製剤の審査・管理に対応できない、と考えるのが妥当である。従って、実際の治験に際しては、GCP、GVP の改正を視野に入れた検討も必要となる可能性もある。

また EMEA、FDA 同様に MHRA でも、iPS のような細胞技術を独立して切り出すのではなく、細胞治療と遺伝子治療の双方の観点から考慮されるであろう、というスタンスであった。

（参考）幹細胞を用いた臨床研究関連資料、政府機関のリンク先

①米国関係

FDA http://www.fda.gov/default.htm

FDA/CBER http://www.fda.gov/cber/index.html

FDA Cellular & Gene Therapy Publications

http://www.fda.gov/cber/genetherapy/gtpubs.htm

1） Tissue Rules

・Title 21 Code of Federal Regulations / Sec 1271 (21CFR 1271)

http://www.access.gpo.gov/nara/cfr/waisidx_07/21cfr1271_07.html

・Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products - 8/8/2007

http://www.fda.gov/cber/gdlns/tissdonor.htm

2） Cellular & Gene Therapy Rules

・Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs) - 4/9/2008

http://www.fda.gov/cber/gdlns/cmcsomcell.htm

・Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) - 4/9/2008

http://www.fda.gov/cber/gdlns/gtindcmc.htm

3） その他（考え方等）

・Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals – 7/12/1993

http://www.fda.gov/cber/gdlns/ptccell.pdf

・Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products; Notice - 10/14/1993

http://www.fda.gov/cber/genadmin/fr101493.pdf

・Proposed Approach to Regulation of Cellular and Tissue-Based Products - 2/28/1997

http://www.fda.gov/cber/gdlns/celltissue.pdf

・Reinventing the Regulation of Human Tissue

http://www.fda.gov/cber/tissue/rego.htm

http://www.fda.gov/cber/tissue/regotab.pdf (Table)

②欧州（ＥＵ）関係

EMEA　http://www.emea.europa.eu/

EMEA / Committee for Medicinal Products for Human Use (CHMP)

http://www.emea.europa.eu/htms/general/contacts/CHMP/CHMP.html

EudraLex / The Rules Governing Medicinal Products in the European Union

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm

1) Tissue Rule

・The tissues and cells directive　(2004/23/EC)

http://www.who.int/ethics/en/ETH_EU_Directive_2004_23_EC.pdf

2) GCP Rules

・The clinical trials directive (2001/20/EC、2005/28/EC)

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf

3) Authorization Rules

・the medicinal products directive (2001/83/EC, 2003/63/EC)

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_83/dir_2001_83_en.pdf

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2003_63/dir_2003_63_en.pdf

・the medical devices directive (93/42/EEC)

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31993L0042:EN:HTML

・ Regulation on Advanced therapy medicinal products (Regulation (EC) No 726/2004)

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf

4) GMP Rules

・GMP directives (2003/94/EC)

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2003_94/dir_2003_94_en.pdf

・EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev4.htm

5) Guideline on human cell-based medicinal products (EMEA/CHMP)

http://www.emea.europa.eu/pdfs/human/cpwp/41086906en.pdf

6) Pharmacovigilance Rules

・EudraLex Volume 9A (Pharmacovigilance for medicinal products for Human use)

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9_2007-07_upd07.pdf

③英国関係

MHRA http://www.mhra.gov.uk/index.htm

HTA (Human Tissue Authority) http://www.hta.gov.uk/

HFEA (Human Fertilisation & Embryology Authority) http://www.hfea.gov.uk/

National Institute for Biological Standards and Control http://www.nibsc.ac.uk/

UK Stem cell Bank http://www.ukstemcellbank.org.uk/

1) Tissue Rules

・the Human Tissue Act (2004)

http://www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_1

2) ES cells Rules

・The Human Fertilisation and Embryology (HFE) Act (1990)

http://www.opsi.gov.uk/acts/acts1990/Ukpga_19900037_en_1.htm

· Code of practice for the use of human stem cell lines (UK stem cell Bank, 2005)

http://www.ukstemcellbank.org.uk/documents/Code%20of%20Practice%20for%20the%20Use%20of%20Human%20Stem%20Cell%20Lines.pdf

3) GCP Rules

· UK Statutory Instrument 2004 No.1031(The Medicines for human use clinical trials regulations)

http://www.opsi.gov.uk/si/si2004/20041031.htm

4) GMP Rules

· The Code of Practice for the Production of Human-derived Therapeutic Products (MHRA, 2002)

http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007432&RevisionSelectionMethod=LatestReleased

Guidance for FDA Reviewers and Sponsors

Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)

Additional copies of this guidance are available from the Office of Communication, Training, and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Office of Cellular, Tissue, and Gene Therapies at 301-827-5102.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
April 2008

Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Guidance for FDA Reviewers and Sponsors

Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance document provides to you, sponsors of a human somatic cell therapy investigational new drug application (IND), recommendations on the chemistry, manufacturing, and control (CMC) information to include in an original IND. This guidance also applies to combination products that contain a human somatic cell therapy biological product in combination with a drug or device as part of the final product. Also, this guidance instructs FDA CMC reviewers about the information to record and assess as part of an IND review, taking into consideration the various manufacturing challenges for these products.

In order to deliver a safe and effective product, human somatic cell therapies present many manufacturing challenges. Some of these challenges include the variability and complexity inherent in the components used to generate the final product, such as the source of cells (i.e., autologous or allogeneic), the potential for adventitious agent contamination, the need for aseptic processing, and the inability to "sterilize" the final product because it contains living cells. Distribution of these products can also be a challenge due to stability issues and the frequently short dating period of many cellular products, which may necessitate release of the final product for administration to a patient before certain test results are available.

This guidance finalizes the draft guidance entitled, "Guidance for Reviewers: Instructions and Template for Chemistry Manufacturing, and Control Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications" dated August 2003 (68 FR 49488; August 18, 2003).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

A. How will FDA Reviewers and Sponsors Use this Guidance?

FDA's primary objectives in the review of INDs are to help ensure the safety and rights of human subjects in all phases of an investigation and, in Phases 2 and 3, to help ensure that the quality of the scientific evaluation of the investigational product is adequate to permit an evaluation of its safety and effectiveness (21 CFR 312.22(a)). This guidance will help sponsors and FDA reviewers to assess, given the phase of the investigation, whether sufficient information is provided to assure the proper identification (identity testing), quality, purity, and strength (one aspect of potency) of the investigational product (21 CFR 312.23(a)(7)(i)). These principles apply to investigational biological products and drugs; however, specific terms, such as safety, identity, purity, and potency, are generally understood to be applicable to biological products and are used throughout this document.

If you are a FDA reviewer, you will use this guidance as you assess the safety, identity, purity, and potency of an investigational product and you will use the format of the human somatic cell therapy CMC review template (Appendix A) in preparing your reviews. Because of the wide variability of the contents of IND amendments, you are only expected to use the attached template during review of original IND submissions. However, you should consult this document for guidance throughout the investigational new drug development process.

The human somatic cellular therapy CMC review instructions and template described in this guidance are tools to assist FDA in the review of human somatic cellular therapy INDs. They are designed to serve as a guide to help ensure that all applicable regulatory requirements are reviewed at the appropriate stage of product development. In addition to the CMC review instructions and template, some general considerations are discussed in Appendix B that should be helpful in assessing proposed release criteria testing and specifications. Section 10.70 (21 CFR 10.70) provides further instruction to FDA reviewers regarding documentation of review decisions.

If you are a sponsor of a human somatic cell therapy IND, you may use this guidance in developing an IND submission that will be adequate to permit FDA reviewers to make an assessment of the safety, identity, purity, and potency of your investigational product. Other regulatory documents that may be relevant are listed in the references (see Section XII below).

B. How is this Guidance Organized?

This guidance is organized in a format that generally corresponds to the sections in the CMC review template provided in Appendix A. In each section, where necessary, we (FDA) provide recommendations as to the information you may submit in your original IND submission. As necessary throughout this document, we give specific instructions

to FDA reviewers concerning their documentation and assessment of an IND submission during the CMC review. Many of the instructions for FDA reviewers provided in this guidance are distinguished by the designation "Note to FDA Reviewers."

II. ADMINISTRATIVE INFORMATION TO BE DOCUMENTED BY FDA REVIEWERS

Note to FDA Reviewers: Document in your review all of the IND information listed below. Most of this information should be available on Form FDA 1571, the sponsor's cover letter, or the reviewer assignment notice from the Regulatory Project Manager (RPM) of the application division.

- BB-IND Number (assigned by Center for Biologics Evaluation and Research (CBER) after receipt);
- Date of submission;
- 30-day review due date;
- Sponsor – name, address, title, phone, fax;
- Sponsor point of contact (sponsor's authorized representative) – name, address, title, phone, fax;
- Title of IND;
- Proposed use;
- Product description;
- Phase of study;
- Cross-referenced INDs, investigational device exemptions (IDEs), and master files (MFs): List all regulatory files (IND, IDE, MF) that the sponsor has obtained permission to cross-reference in support of this file. The file under review must contain a letter signed by the person who submitted the cross-referenced file (21 CFR 312.23(b)), giving FDA permission to cross-reference the file. This letter should identify the nature of the information being cross-referenced (e.g., pre-clinical, product manufacturing, and/or clinical) and where it is located within the file being cross-referenced. You should verify that the cross-referenced information satisfies the IND requirement for which the information is cited. If the letter of cross-reference is absent or inadequate, or the cross-referenced information is inadequate for the purpose cited, the RPM or the reviewer should notify the sponsor to obtain additional information;
- Key words: Include three to four words that can be used to identify the product, indication, and any materials, components, or devices that may be part of the final product or used in the manufacturing process. These key words should be general enough to be used in a database search;
- Introduction/rationale: Summarize relevant information on the development of the product if the sponsor provides this information. In addition, document and assess, as appropriate, the sponsor's scientific rationale and justification for using the product for the indication under review; and
- Study objectives.

III. PRODUCT MANUFACTURING AND CHARACTERIZATION INFORMATION TO BE SUBMITTED BY SPONSORS AND DOCUMENTED BY FDA REVIEWERS

As described in the following sections, you should provide a detailed description of where and how the cell therapy product is manufactured. You should include all of the components and materials used during the manufacture of the cellular product, such as cells, cell bank systems, and any reagents or excipients. In addition, you should describe all procedures used during the manufacturing process. Examples of these procedures may include recovery and processing of tissues or cells, purification, and other preparation of cells, donor screening and testing, including final formulation of the product. This information will allow us to assess the identity, quality, purity, and potency of your product. For further information, refer to the "Guidance for Human Somatic Cell Therapy and Gene Therapy" (Ref. 1) and the guidance on "Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products" (Ref. 2). In addition, you may refer to the other documents listed in the references (see Section XII below).

We also encourage sponsors to use the format and headings described in Appendix A to facilitate an efficient review by FDA.

Note to FDA Reviewers: Document and assess product manufacturing and characterization information in your IND reviews. Organize the CMC review using the format and headings described in Appendix A and below, as appropriate.

A. Product Manufacturing – Components and Materials

Note to FDA Reviewers: Document the source of all materials and components and summarize the testing performed on those materials and components, and review the specific instructions and recommendations set out below.

Your IND must include a list of all components used in manufacturing of your product (21 CFR 312.23(a)(7)(iv)(*b*)). The sections below detail the information on manufacturing components that we recommend you submit in an IND.

1. Cells

   a. Allogeneic and/or Autologous Cell Components

   You should describe the following information in your IND:

   - Cell source: tissue and cell type (e.g., colon, hematopoietic, neuronal, T-cells);
   - Mobilization protocol: document whether or not donor cells are mobilized or activated in vivo in the donor;

- Collection or recovery method: state the procedure used to obtain cells (e.g., surgery or leukapheresis indicating the device used if possible), the name and location of the collection facility, and transport conditions if shipped to a processing facility for further manufacturing; and
- Donor screening and testing: the donor screening and testing that is performed to determine donor eligibility. Requirements for screening and testing donors of human cells and tissues are described in 21 CFR Part 1271 (see final rule, "Eligibility Determination for Donors of Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps)") (Ref. 3). When appropriate, you should document the donor safety testing that is performed. In addition, FDA has published a final "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" (Ref. 4). We recommend that you review this guidance to ensure that the donor qualification criteria described in your IND are consistent with current recommendations.

  1) Autologous

  You are not required to make a donor eligibility determination or to perform donor screening for cells and tissues for autologous use (21 CFR 1271.90(a)(1)). However, you should determine whether your manufacturing procedures increase the risk of propagation of pathogenic agents that may be present in the donor. If so, you should document whether the donor is reactive for specific pathogens. Also, you should describe precautions to prevent the spread of viruses or other adventitious agents to persons other than the autologous recipient (see Ref. 3).

  2) Allogeneic

  You must perform donor screening and testing as required in 21 CFR Part 1271 for all allogeneic cells or tissues except those that meet the exceptions in 21 CFR 1271.90(a). Donors of all types of cells and tissues must be screened and tested for HIV-1, HIV-2, hepatitis B virus (HBV, surface and core antigen), hepatitis C virus (HCV), *Treponema pallidum* (syphilis), and CJD (screening only). Donors of viable leukocyte-rich cells or tissues should be screened and tested for human T-lymphotropic virus types 1 and 2 (HTLV-1, HTLV-2) and CMV. In addition, you should document whether FDA-licensed, cleared, or approved test kits are used in these detection assays and document which tests are used. Include a description of the type of serological, diagnostic, and clinical history data obtained from the donor. You should consider other issues such as typing for polymorphisms and human leukocyte antigen (HLA) matching, where appropriate. If cord blood or other maternally derived tissue is used, you should describe testing and screening performed on birth mothers.

Note to FDA Reviewers: Communicate with the clinical reviewer regarding any issues or concerns relating to the screening or testing of the donor cells.

b. Cell Bank System

You should describe pertinent information, as described in sections 1) and 2) below, relating to the cell bank system (i.e., master cell bank (MCB), and working cell bank (WCB)) used in product manufacture. In addition, you should describe the history, source, derivation, characterization of each cell bank (both MCB and WCB), and the frequency at which testing is performed. For further information, refer to the document on "Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals" (Ref. 5). See also ICH document Q5D, "Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products" (Ref. 6), and, where applicable, "Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans" (Ref. 7) and the "PHS Guideline on Infectious Disease Issues in Xenotransplantation" (Ref. 8).[1]

Note to FDA Reviewers: Document and assess the testing that is performed on each cell bank. Determine if the most relevant and critical testing for the particular cellular product has been performed. Appropriate tests should be performed depending on the species of origin used to derive the cell bank.

1) Master Cell Bank (MCB)

You should include in the IND information regarding MCB history, source, derivation and characterization, including testing to adequately establish the safety, identity, purity, and stability of the cells. This section will likely address:

- Product microbiologic characteristics, including sterility, mycoplasma, in vivo and in vitro testing for adventitious viral agents, as appropriate (see Section IV below);
- Freedom from the presence of specific pathogens, including, for human cells, testing for CMV, HIV-1 & 2, HTLV-1 & 2, EBV, B19, HBV, and HCV, as appropriate. For cell lines that are exposed to bovine or porcine components (e.g., serum, serum components, trypsin), appropriate testing would include testing for bovine and/or porcine adventitious agents. See further discussion of bovine components and reagents in Section III.A.2.a;
- Identity of the cells, including tests to distinguish the specified cells through physical or chemical characteristics of the cell line (i.e., phenotype, genotype, or other markers);

[1] If a feeder cell line of animal origin is used to propagate human cells (i.e., human and non-human animal cells are co-cultivated), the final product falls within the definition of a xenotransplantation product (see both Refs. 8 and 9).