第９回　再生医療における制度的枠組みに関する検討会

議事次第

日時：平成２２年８月２５日（水）　１５：００～１７：００

場所：はあといん乃木坂

１．開会

２．第８回主な議論のまとめ

３．関係者からのヒアリング

- Dr. Steven R Bauer
  FDA（米国食品薬品庁）
- Prof. Dr. Jean Hugues Trouvin
  AFSSAPS（仏国保健製品衛生安全庁）
- Dr. Bettina Klug, MSc
  Paul-Ehrlich-Institut
  （独国ポールエールリッヒ研究所）

４．意見交換

- 確認申請　他

５．閉会

（配布資料）

議事次第、座席表、委員名簿、開催要項

資料１　　第８回主な議論のまとめ

資料２　　第８回検討会での確認事項

資料３－１　ヒアリング資料（Prof. Dr. Jean Hugues Trouvin）

資料３－２　ヒアリング資料（Dr. Bettina Klug, MSc）

資料３－３　ヒアリング資料（Dr. Steven R Bauer）

資料４　　今後のスケジュール

（参考資料）

参考資料１　薬事法、薬事法施行規則抜粋

参考資料２　医薬品の臨床試験の実施の基準に関する省令（GCP 省令）

参考資料３　ヒト（自己）由来細胞や組織を加工した医薬品又は医療機器の品質及び安全性の確保について

参考資料４　ヒト（同種）由来細胞や組織を加工した医薬品又は医療機器の品質及び安全性の確保について

参考資料５　細胞・組織を利用した医療用具又は医薬品の品質及び安全性の確保について

参考資料６　確認申請と治験届について（前回資料）

参考資料７　第７回主な議論のまとめ（前回資料）

「再生医療における制度的枠組みに関する検討会」開催要項

1　開催の趣旨等

ライフサイエンスは、我が国のものづくりと科学技術の先進性を兼ね備えた分野であり、世界をリードできる先端科学技術の進歩の恩恵を国民が受けることができるよう、また我が国の優れた技術を国際的な舞台で活かしていけるよう、その発展に寄与する施策を講じていく必要がある。

この中で、再生医療といった新たな分野について、再生医療における共同での診療を行うためには、医療機関の間でどのような条件の下に行うことが望ましいか検討していくこととする。

また、再生医療製品を広く患者に提供するためには、どのような制度的枠組みがふさわしいか、その特性を踏まえつつ、検討していくこととする。

2　検討事項

①　医療機関が患者から採取した細胞について、別の医療機関において培養・加工を行った上で患者の診療に用いることが現行の医療法の下で可能であること及びその条件を明示し、周知徹底すること。　（２１年度中）

②　再生医療にふさわしい制度を実現するため、自家細胞と他家細胞の違いや、皮膚・角膜・軟骨・免疫細胞など用途の違いを踏まえながら、現行の法制度にとらわれることなく、臨床研究から実用化への切れ目ない移行を可能とする最適な制度的枠組みについて、産学官の緊密な連携のもとに検討する場を設け、結論を得ること。　（２２年度中）

3　構成員（別紙）

4　運営

本会議の庶務は、厚生労働省医政局及び医薬食品局で行う。

議事は公開とする。

資料１

第８回検討会主な議論のまとめ

１．有効性・安全性の評価、管理のあり方について

○　自家細胞の加工について、安全性・有効性を十分に担保するために、医療法の枠内で施設認定する、又は、薬事法の枠内で新たなカテゴリーを創設して加工プロセスを認可する制度とし、事後チェックを十分に行う体制とすべき。

○　事前に確認すべきことは確認すべきであり、事後評価が先行するのは危険。

○　GCP に則った試験でのエビデンスに基づき評価を行っていくべき。

２．質の高い製品を迅速に開発する方策について

（１）相談料等について

○　国の予算で PMDA に補助を行い、相談料を安くするシステムが必要なのではないか。

○　相談料の割引だけではなく、開発コストに関しても、先端的なものに関しては国レベルで補助していくというような方針も検討すべきではないか。

（２）確認申請について

○　確認する項目について、細胞組織等の特性に合わせて柔軟に取り扱うべき。

○　ヒト幹細胞臨床研究から治験への速やかな移行のため、ヒト幹指針に基づき確認された場合は、確認申請を不要とすべき。

（３）臨床研究・治験促進策

○　医師主導治験の活用を進めていくべき。

（４）審査の迅速化・質の向上、評価の指針の明確化等

○　日本版 HUD 的審査基準の導入を検討すべき。

○　審査体制の強化を進めるべき（人員の確保、人材育成・人事交流）。

○　承認審査の国際化。

（５）その他

○　承認取得がゴールではなく保険収載までがパッケージであることを認識すべき。

○　様々な企業関係者からの意見を聴取すべき。

資料２

第８回再生検討会における平成22年度結論分についての確認事項

１．再生医療・細胞治療製品の品質、安全性、有効性の確保のあり方

再生医療・細胞治療製品の品質、安全性、有効性を確認し、市販後の安全対策及び製造管理・品質管理を行う必要があることから、品目毎に行政による承認及び安全対策が必要。

２．迅速かつ適切な開発・審査を行うための施策

○　再生医療・細胞治療製品の開発促進、審査の迅速化のためには、PMDAが開発初期から、開発者に必要なデータの範囲を含めた相談を行うことが有用。

○　特に、再生医療・細胞治療製品の分野では開発初期段階は研究者やベンチャー企業が関わることが多いことから、研究者、ベンチャー企業がPMDAの相談を受けやすい制度設計が求められる。

３．今後の検討

引き続き、再生医療・細胞治療製品の迅速かつ適切な開発・審査を行うための制度的枠組みについて上記内容を含め柔軟に検討。今後の検討内容についても適宜上記確認事項に反映。

資料3－1

cell/tissue engineered products

- French experience
- European experience

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Chair BWP, CAT member, EMA, London

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Disclaimer

- *I attend this conference as an individual expert* and, although being a member of the CAT and BWP, my presentation might not be the view of the EMA and any of their Committees or working parties and neither of the French Medicines Agency (Afssaps).

- *The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the EMA or Afssaps* and binds in no way the organisations mentioned before.

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Presentation outlook

- ✓ The two regulatory status in Europe for « cell/tissue [engineered] products »
  - Tissues and cells directive
  - Advanced therapy medicinal products
- ✓ French experience and organisation
- ✓ European approach for ATMP
- ✓ CAT activities
  - Dossier evaluation
  - Classification
  - Scientific advice
  - Technical guidelines
  - Certification
- ✓ Conclusion

« cell/tissues [engineered] products » What are we speaking about?

- ✓ In Europe, two distinct regulatory systems:
  - Human tissue and cells → Directive 2004/23
  - Advanced Therapy Medicinal products → Regulation 1394/2007

Human tissues and cells Directive -1-

DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 31 March 2004
on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

And subsequent directives

- DIRECTIVE 2006/17/EC on technical requirements for the donation, procurement and testing of human tissues and cells
- DIRECTIVE 2006/86/EC on traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells

This Directive shall apply to the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications.

Human tissues and cells Directive - 2-

The main chapters of Tissues and cells directive:

Article 3 : Definitions

- Tissue establishment: means a tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells;

Human tissues and cells Directive - 3-

The main chapters of Tissues and cells directive:

- Article 4 : National competent authorities responsible for implementing the requirements
- Article 5 : Supervision of human tissue and cell procurement
- Article 6 : Accreditation, designation, authorisation or licensing of
  - tissue establishments
  - tissue and cell preparation processes
- Article 7 : Inspections and control measures
- Article 8 :Traceability: from the donor to the recipient and vice versa.
- Article 9: Import/export of human tissues and cells
- Article 10: Register of tissue establishments and reporting obligations:
  - record of activities by tissues establishments
  - competent authorities to maintain a publicly accessible register of tissue establishments
- Article 11: Notification of serious adverse events and reactions:
  - Member States shall ensure that there is a system in place to report, investigate, register and transmit information about serious adverse events and reactions

→ It is the Member States responsibilities to put in place the necessary regulatory framework to authorise, follow-up and monitor activities in the field of "tissues and cells".... Which are not considered as "medicinal products".

Human tissues and cells Directive - 4-

- The « Human tissues and cells » directive
  - Covers tissues and cells obtained from donation (autologous or allogeneic), intended for human application
  - Introduce the notion of
    - donation and procurment
    - testing and processing
    - preservation, storage
    - distribution of human tissues and cells
  - Introduce the definition and concept of
    - « tissue Establishment » authorised by National Competent Authorities,
    - National competent authorities responsible for accreditation, inspection, of the establishment(s) on their territory and vigilance → National duties for implementation of the Directive
- Human tissues and cells are not considered as medicinal products (and thus not all pharmaceutical requirements are applicable)
- However, « manufactured products » can be derived from those tissues and cells collected in « tissue establishments » and will be regulated by other regulation
- Human Tissues and Cells are under the responsibilities of tissue establishments and the "market" is relatively limited to national territory and use.... More for hospital use and for "conventional application".
- This contrast with the other types of "medicinal products" which may be derived from Human Tissues and Cells, designated as "advanced therapy medicinal products" (ATMPs) and covered now by the pharmaceutical legislation

Advanced Therapy Medicinal Products (ATMP)

✓ Second regulatory status possible in Europe for « cell/tissue [engineered] products »

✓ Regulation 1394/2007

EN Official Journal of the European Union

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

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF

Regulation 1394/2007

Article 1

Subject matter

This Regulation lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.

Article 2

Definitions

1. In addition to the definitions laid down in Article 1 of Directive 2001/83/EC and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:

(a) 'Advanced therapy medicinal product' means any of the following medicinal products for human use:

— a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a tissue engineered product as defined in point (b).

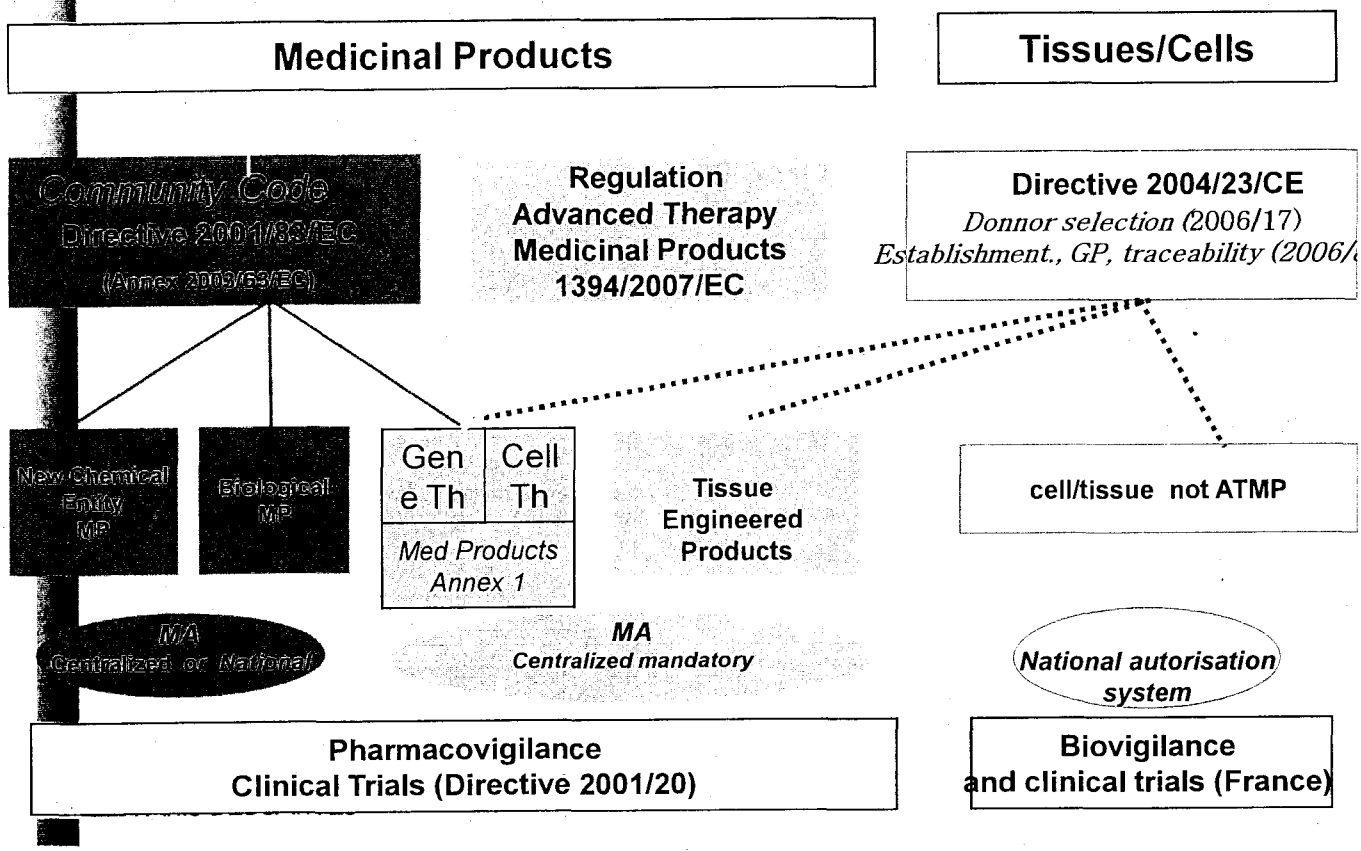
✓ Classifying tissue-based or cell-based products as medicinal products → pharmaceutical legislation applies in all aspects of the product life cycle:
- Development and Clinical trials
- GMP for the production/quality control
- Pharmacovigilance
- With additional requirements (long term follow up –art.14)

✓ EMA responsible for the regulatory framework

✓ One centralised Marketing Authorisation

✓ One scientific Committee to deal with the submission : CAT

European Regulatory Framework for tissues and cells products



The two regulatory status

	Dir. 2004/23 → National responsibilities	Reg. 1394/2007 → European framework
Product	Not considered as « medicinal product » but - Cell preparations - Tissues	Medicinal products: ATMP
Authorisation	National Authorisation(s)	EU centralised Marketing Authorisation
Establishment	« Tissue establishment » National accreditation (for France Tissues or cells establishment)	Pharmaceutical establishment Authorisation by National competent Authorities
Manufacturing practice	Based on the principles of cGMP with adaptation for Tissues and Cells (Dir. 2006/86) At the discretion of National authorities	GMP mandatory ATMP production covered in annex 2 of the EU cGMP (public consultation on going)
Dossier	National decision (in France adaptation of the CTD)	CTD format
Vigilance	National decision (in France « Biovigilance » is mandatory)	Pharmacovigilance + long term follow up
Clinical trials and GCPs	National decision (in France case by case, well established use or clinical trial evidence)	Mandatory to establish the risk-benefit profile and claimed indication(s)

Importance of classifying those products

- Importance of the definition /classification chosen, examples given:
  - T2c001™: Autologous bone marrow-derived mononuclear cells
    - a bone marrow aspirate followed by a ficoll centrifugation,
    - Acute myocardial infarction: cardiac re-injection in the left ventricle
    - → considered as ATMP, cell therapy
  - Chondroselect ™:
    - autologous chondrocytes, expanded from a cartilage biopsy
    - reimplanted in the cartilage defect
    - → ATMP, cell therapy
  - freeze-dried thrombocytes,
    - for application is any wound healing (orthopedics, dental surgery)
    - → not considered as medicinal product, to be regulated by Dir. 2004/23

- The « process » and final product and its claim(s) → qualify or not as « medicinal products »
- The autologous origin of the cells is not the only criteria to justify not being classified as medicinal product and not being imposed clinical trials and clinical evidence

Presentation outlook

- French experience and organisation

French organisation for « tissues and cells »

- In France, Afssaps is the Competent Authorities for regulating the two status

- The same department in Afssaps is in charge of dealing with the two types of products

Afssaps mandates and responsabilities

- Afssaps is in charge of authorising or accrediting
  - Tissues or cells Establishments
    - Private or Public organisations
  - Pharmaceutical establishment for ATMP

- Products to be authorised by Afssaps
  - Tissues or cells preparations (according to Dir. 2004/23): authorisation for a "preparation" (cells) or a "process" (tissues)
  - ATMP under the "hospital exemption" status

- Clinical trials
  - During the development of ATMPs
  - For qualification of the "tissue" or "cell preparation" to be authorised for use in France

- Other Responsabilities:
  - Inspection
    - Manufacturing sites for medicinal products (including ATMPs)
    - Tissue establishments
    - Academic/hospital labs involved in preparation of tissues or cell preparations used in clinical trials
  - Vigilance
    - Pharmacovigilance for medicinal products
    - Biovigilance for tissues and cells
- Quality controls of the products on the market

Cell "Preparation" Authorizations

- Cell establishments : 36
  50% public establisments (EFS) – 50% hospital
- Dossiers : around 140 applications for hematopoietic stem cells
  - Peripheral blood (majority)
    - Autologous
    - Allogeneic
  - Bone marrow
    - Autologous
    - Allogeneic
  - Umbilical cord blood (30 % but increasing number)
    - Allogeneic
  - CD 34+ (allogeneic peripheral HSC) only few
- Scientific data required for Quality, Safety, Efficacy (mainly well established use)

Tissue "Process" Authorizations

- Tissue establishments : 41
  50% held by the state establishment (EFS)
  40% hospital
  10% Private
- Dossiers : around 210 dossiers
  - Bones cryopreserved or viro inactivated
    - massive bone
    - femoral head
    - Others : iliac crest, skull bone flap...
  - Corneas
    - Keratoplasty
    - Cornea stopper
  - Skin
  - Amniotic membranes
  - Arteries, veins, valves
- Scientific data required for Quality, Safety, Efficacy (mainly well established use)

Clinical Trials in France
Cell Therapy

- ✓ Haematopoietic stem cells :marrow, peripheral, placental
  - Hematology : lymphoma, leukemia (ALL, AML...)
  - Cardiomyoplasty, lower limb arteriopathy
- ✓ Immune cells : Macrophages, dendritic, dexosomes, T cells
  - Immunotherapy of cancers (melanoma, lung, kidney, ovarian...) and infectious diseases
- ✓ Chondrocytes
  - Knee articular cartilage injuries
- ✓ Keratinocytes/ Fibroblasts
  - Veinous ulcer, diabetic forefoot ulcer, second and third degree burns
- ✓ Nervous cells
  - Parkinson, huntington diseases
- ✓ Myoblasts
  - Severe postinfarction left ventricular dysfunction
- ✓ Pancreatic islets
  - Diabetes mellitus

Clinical Trials in France
Tissues

- ✓ Amniotic membrane in corneal ulcer
- ✓ Trachea replacing aorta
- ✓ Ovarian tissue auto-transplant (chimotherapy situation)
- ✓ Face transplantation
- ✓ Forearm transplantation

French activities for ATMPs

- Essentially during the development stage of those « candidate » medicinal products
  - Authorisation for Clinical trials
  - Assistance for innovation development and Scientific advice
- Contribution to EMA and CAT activities for centralised authorisations
- Other contributions
  - joint discussion with official labs, inspectors,
  - « hospital exemption » autorisation → National competences

Presentation outlook

- European approach for ATMP

Consequence of the regulation -1-

- For products fulfilling the definitions (Gene therapy, cell therapy, tissue engineered):
  - Marketing authorisation before launching
  - Assessment of the Quality, Safety & Efficacy
  - Post-authorisation vigilance; specific obligation for safety and for efficacy
- Authorisation via the centralised procedure
- Same dossier as for a medicinal product (CTD) with technical adaptations)

Consequence of the regulation -2-

- Technical requirements:
  - Pre-authorisation:
    - Compliance with 'Essential Requirements' for combined products incorporating medical devices
    - Specific guidelines on
      - GMP (Good Manufacturing Practice)
      - GCP (Good Clinical Practice)
    - Specific rules for labelling/packaging
  - Post-authorisation requirements
    - Follow-up of efficacy and adverse reactions, and risk management: long term follow up → art. 14
    - Traceability

Regulation 1394/2007: the "hospital exemption" – Art. 28

- ✓ Excluded from the scope of the regulation
  - ATMP prepared in a non-routine basis (Art. 28(2))
    - Used within the same member state, in a hospital, for an individual patient
    - In that case : manufacturing is authorized by the MS. Traceability, pharmacovigilance requirements, specific quality standards at national level should be equivalent to the regulation
- ✓ "Hospital exempted products"
  - are still considered as medicinal products
  - Still considered as ATMP
  - Should be authorised by the National Competent authority
  - Following the same standards and criteria as for a marketing authorisation: *"Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards are equivalent to those provided for at Community level in respect of advanced therapy medicinal products*" (art. 28, Regulation)

Committee for Advanced Therapies (CAT)

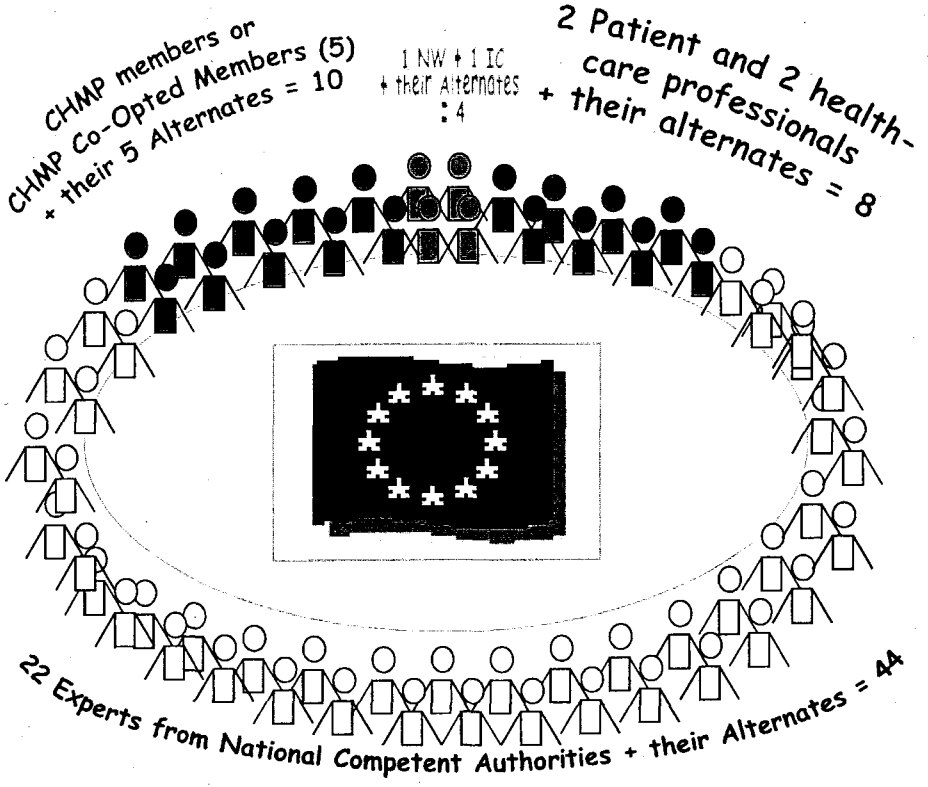
- ✓ New Committee within the EMEA
  - pooling of Community expertise
  - multidisciplinary nature:
    - biotechnology
    - medical devices
    - risk management
    - ethics
    - …
  - representation of Civil Society and Research Community

CAT COMPOSITION

CAT should covers the scientific areas relevant to advanced therapies, including:

- Medical devices [2+2 at least],
- Tissue engineering,
- Gene therapy,
- Cell therapy,
- Biotechnology,
- Surgery,
- Pharmacovigilance,
- Risk management and
- Ethics.

[Recital 9 & Art.21 of ATM Reg]



Presentation outlook

✓ CAT activities

- Dossier evaluation
- Classification
- Scientific advice
- Technical guidelines
- Certification

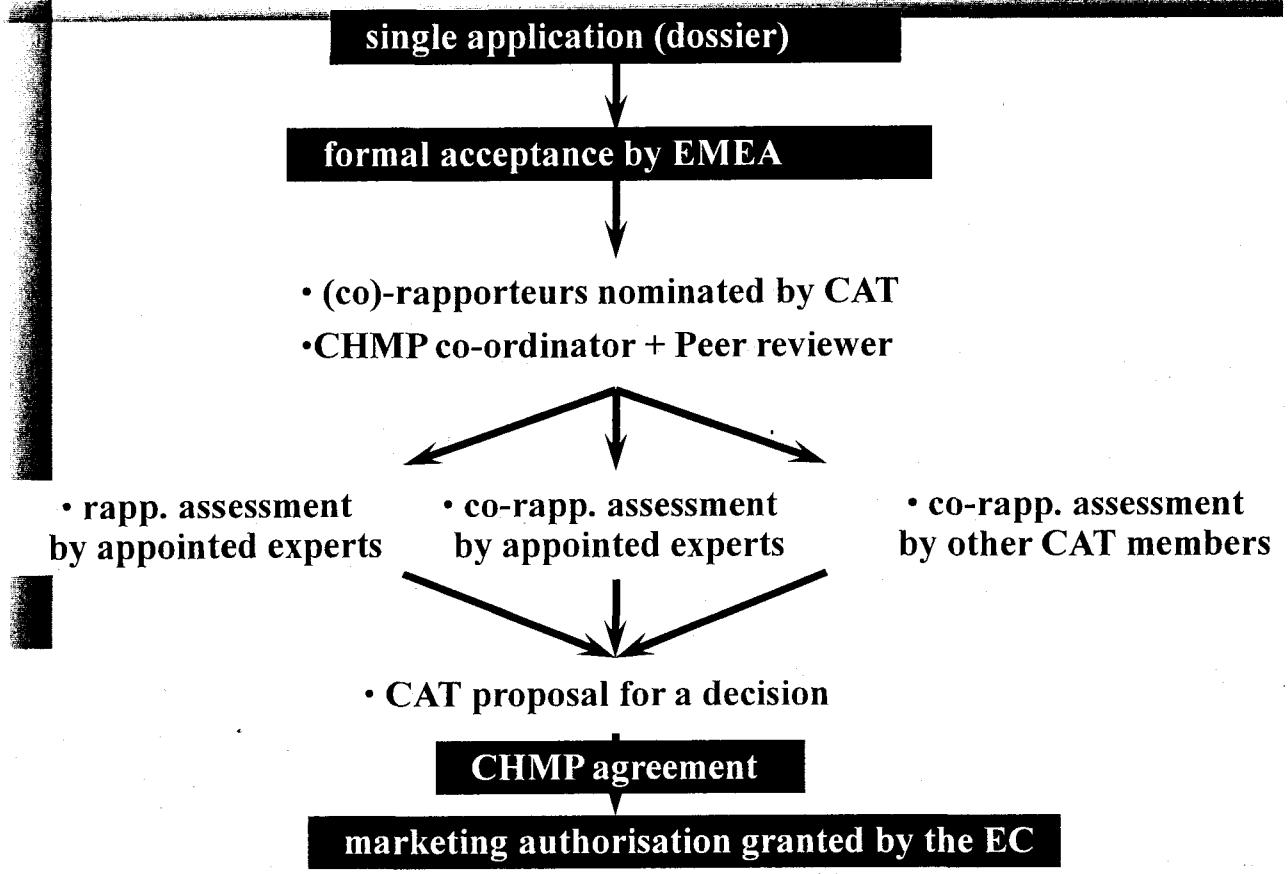
Tasks of the Committee for Advanced Therapies (art. 23)

- ✓ to formulate a draft opinion on the quality, safety and efficacy of an advanced therapy medicinal product for final approval by the CHMP → dossier evaluation
- ✓ to provide advice, on whether a product falls within the definition of an advanced therapy medicinal product → classification
- ✓ to advise on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in one of the scientific areas → Scientific advice
- ✓ to assist scientifically in the elaboration of any documents related to the fulfilment of the objectives of this Regulation → criteria and guidelines

Tasks of the Committee for Advanced Therapies (art. 23)

- ✓ to formulate a draft opinion on the quality, safety and efficacy of an advanced therapy medicinal product for final approval by the CHMP → dossier evaluation

Assessment and draft opinion for authorisation



Tasks of the Committee for Advanced Therapies (art. 23)

- to provide advice, on whether a product falls within the definition of an advanced therapy medicinal product → classification

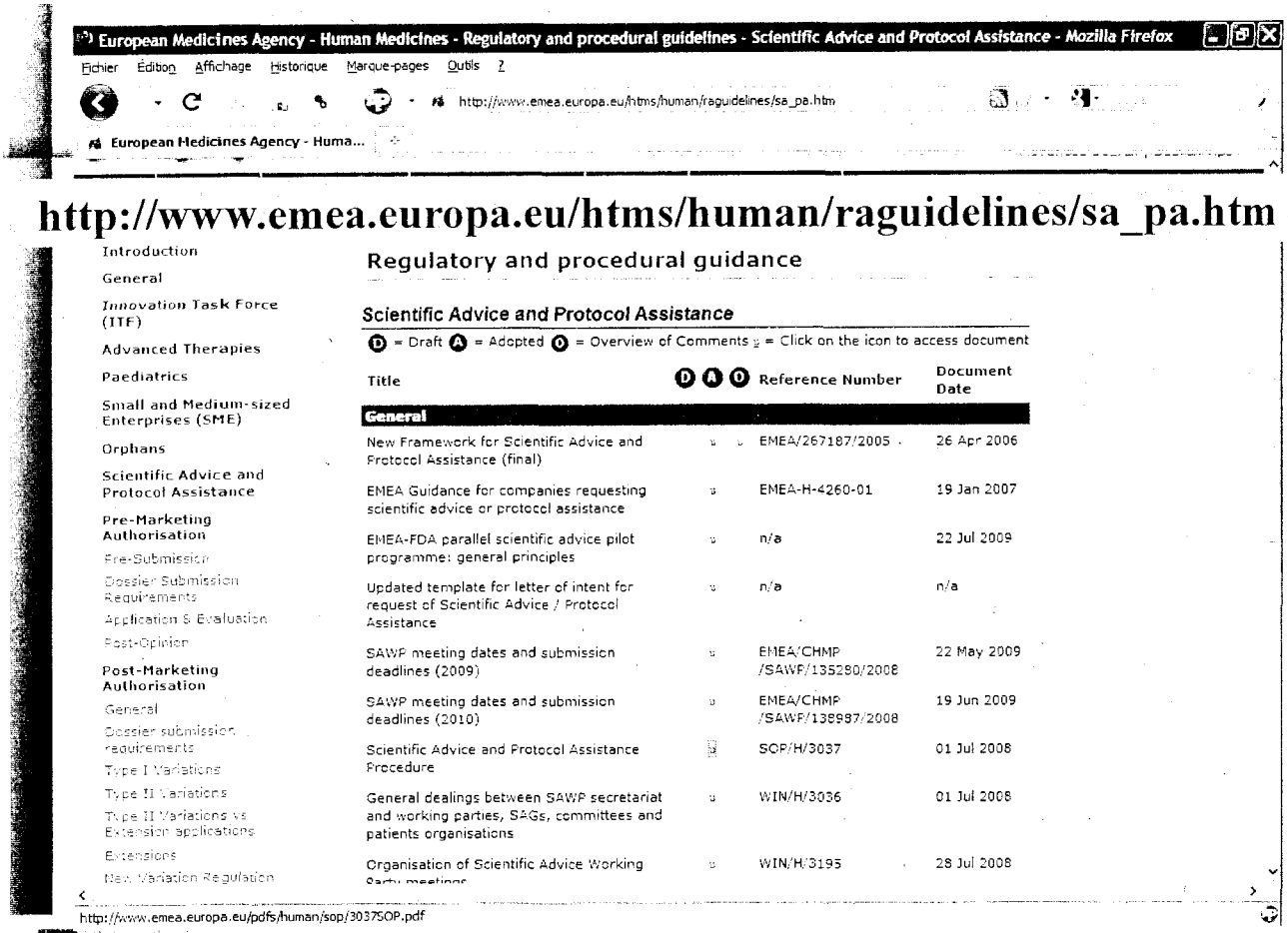
Scientific recommendation on advanced therapy classification (art. 17)

(b) to provide advice, pursuant to Article 17, on whether a product falls within the definition of an advanced therapy medicinal product;

- The CAT will answer the following questions for a given product submitted for classification:
  - Is it a biological ?
  - Is it a medicinal product
  - Is it an ATMP
  - What ATMP ?
- Within 60 calendar days following receipt of a valid request for scientific recommendation classification, the EMEA with involvement of the CAT, shall deliver its recommendation after consultation with the European Commission (EC).

Tasks of the Committee for Advanced Therapies (art. 23)

- to advise on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in one of the scientific areas
  → Scientific advice



Tasks of the Committee for Advanced Therapies (art. 23)

to assist scientifically in the elaboration of any documents related to the fulfilment of the objectives of this Regulation → criteria and guidelines

New criteria and Guidelines

- Multidisciplinary approach
- Specific questions due to the nature of the products (Ethics, methodology, long term follow up, …)
- New concept and mechanisms to take onboard
- Adaptation of the current approaches both for the scientific criteria and production processes

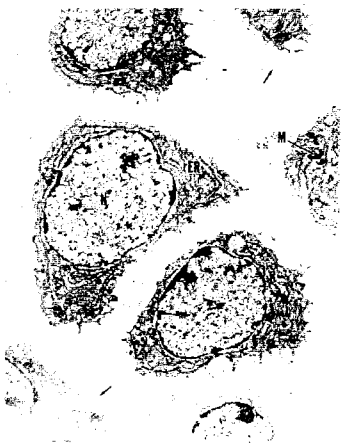
Examples of specific questions

- Quality
  - Impurities
  - Cells: Culture conditions and their impact on differentiation
  - Bioassay, characterisation and definition of the product
  - …..
- Safety
  - tissue cross-reactivity?
  - unwanted biodistribution?
  - toxicity studies: relevance of the experimental models (animal or in silico) ?
- Efficacy
  - Relevance of the clinical endpoints
  - additional safety measures required?
  - Immunogenicity
  - Long term follow-up
- Regulatory
  - How to find the correct regulatory routes for guidance documents (e.g. cell-based tumour vaccines)
  - How to deal with products that have already been used without evidence?
  - Regulation of long-term follow-up of efficacy
- Ethics
  - How to perform first-in-human trials?
  - How to deal e.g. with the risk of insertional mutagenesis?

Challenges with cell-based products

✓ Cells are complex systems

- Cells are dependent on their (micro-)environment
  - Species-specificity
  - Disease-specificity
- Cells are reactive to their environment
- Cell cultures can become heterogeneous
- Cells might de-differentiate (e.g. during longer cell culture)
- Cells might migrate („biodistribution")
- Cells are fragile and (sometimes) mortal



➢ **Regulatory consequences:**

√ Need for adequate characterization

√ but also necessity to accept limitations

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Need for a "risk-based" approach

✓ The following general risk criteria can be used in the estimation of the overall risk of the product:

- origin (autologous - allogeneic);
- ability to proliferate and differentiate;
- ability to initiate an immune response (as target or effector);
- level of cell manipulation (in vitro/ex vivo expansion / activation / genetic manipulation);
- mode of administration (ex vivo perfusion, local, systemic);
- duration of exposure (short to permanent);
- combination product (cells + bioactive molecules or structural materials)
- availability of clinical data on or experience with similar products.

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Tissues/cells [engineered] products – Tokyo – 25th August 2010

Technical Guidances available: Gene therapy

- Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products CPMP/BWP/3088/99 Apr 2001 Oct 2001
- Development and Manufacture of Lentiviral Vectors CHMP/BWP/2458/03
- Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer EMEA/273974/05
- Development of a guideline on the quality, pre-clinical and clinical aspects of medicinal products containing genetically modified cells CHMP/GTWP/405681/06
- Non-clinical studies required before first clinical use of gene therapy medicinal products CHMP/GTWP/125459/06
- Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products CHMP/GTWP/125491/06
- Environmental Risk Assessments for Medicinal Products containing, or consisting of, Genetically Modified Organisms (GMOs) (EMEA/CHMP/473191/06)
- Quality, non-clinical and clinical issues relating specifically to recombinat adeno-associated viral vectors CHMP/GTWP/587488/07
- Follow-up of patients administered with gene therapy medicinal products CHMP/GTWP/60436/07
- ICH Oncolytic Viruses CHMP/GTWP/607698/08
- ICH General Principles to Address Virus and Vector Shedding CHMP/ICH/449035/09

www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm

Technical Guidances available: Cell therapy

- Human cell-based medicinal products CHMP/410869/06
- Points to Consider on Xenogeneic Cell Therapy CHMP/1199/02
- Potency testing of cell based immunotherapy medicinal products for the treatment of cancer CHMP/BWP/271475/06
- Revision of the Points to Consider on Xenogeneic Cell Therapy Medicinal Products CHMP/165085/07
- Xenogeneic Cell-based medicinal products CHMP/CPWP/83508/09
- Reflection paper on *In-Vitro* cultured chondrocyte containing products for cartilage repair of the knee CAT/CPWP/288934/09

www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm

Certification of quality and non-clinical data (art. 18)

- ✓ Specific provision in the ATMP regulation (recital 25 and article 18)
- ✓ Incentive measure for small and medium-sized enterprises developing an advanced therapy medicinal product.
- ✓ submission to the Agency all relevant quality and, where available, non-clinical data required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC, for scientific evaluation and certification.
- ✓ Speci

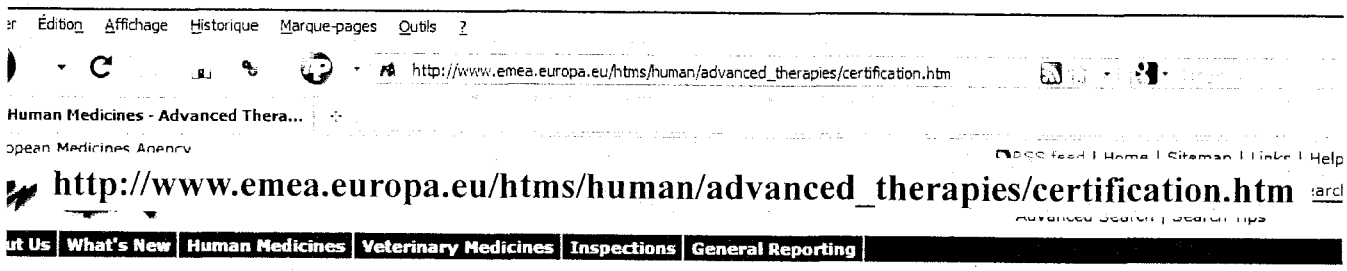
COMMISSION REGULATION (EC) No 668/2009

of 24 July 2009

implementing Regulation (EC) No 1394/2007 of the European Parliament and of the Council with regard to the evaluation and certification of quality and non-clinical data relating to advanced therapy medicinal products developed by micro, small and medium-sized enterprises

Objective of Certification Procedure

- ✓ Stand alone evaluation procedure
- ✓ Not directly binding for future MAA or Clinical trial application (CTA): Certificate will not replace any data to be submitted in MAA or CTA
- ✓ No Assessment of benefit/risk
- ✓ No Statements on appropriateness to enter into clinical trials
- ✓ No Prospective statements pertaining to the further development of the product: that is the role of Scientific Advice



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http://www.emea.europa.eu/htms/human/advanced_therapies/certification.htm

Human Medicines - Advanced Thera...

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ntroduction
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egulatory and Procedural uidance
pecial procedures esigned for ATMPs
ATMP Classificaton
Certification Procedure
cientific guidelines
ow to get support from he EMEA
nterested parties

ee also:
ommittee for Advanced herapies
AT Monthly Report

Certification procedure

The certification procedure is one of the new procedures provided for Advanced Therapy Medicinal Products (ATMPs) in the Regulation on Advanced Therapies (Article 18 of Regulation (EC) No 1394/2007). Commission Regulation (EC) No 668/2009 provides for implementing provisions for the certification procedure.

The certification procedure is the scientific evaluation by the CAT of quality and (where available) non-clinical data for ATMPs under development by Small and Medium-sized Enterprises (SMEs). Further to the scientific evaluation, EMEA will issue a certificate. A 90-day procedure has been developed for the evaluation and certification.

For more information on the procedure for certification and on the content of an application for ATMP certification, please consult following documents:

- Procedural advice on the Certification of quality and non-clinical data for small and medium-sized enterprises developing advanced therapy medicinal products (corr. 1 (23/09/09))
- Scientific Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products (corr. 1 (23/09/09))

Templates for the letter of intent to submit an application for ATMP certification and for the certification application form will be published shortly.

SMEs planning to submit an application for certification in the next months should contact

Contact Point

Questions relating specifically to the authorisation of advanced therapy medicinal products may be submitted to: AdvancedTherapies@emea.europa.eu

Conclusions

- ✓ Tissues and cells [engineered] products: two possible regulatory status in Europe, medicinal products or not
- ✓ New « advanced » products are now classified as medicinal products by EU regulation:
  - European centralised procedure for their authorisation prior marketing
  - European Scientific committee dedicated for their evaluation and proposal for authorisation
- ✓ For Tissues or Cells products, which are not classified as ATMP, considering their characteristics, not only in terms of benefit but also in terms of potential risk, it is important to regulate them, so that the patients, in the EU community, are offered reliable products and services.
  - EU Directive foresees the contribution of the National competent authorities at the various stages of the life cycle of those products

Acknowledgment

Afssaps

- Sandrine Jacob
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EMEA

- Patrick Celis
- Lucia d'Apote
- Veronika Jekerle
- Elisa Pedone
- Marie-Hélène Pinheiro
- Christian Schneider (CAT Chair)
- Paula Salmikangas (CAT Vice Chair)

資料3－2

Regulatory requirements for cell based medicinal products

Committee

25 August 2010

Dr. Bettina Klug, MSc
Paul-Ehrlich-Institut, Langen

klube@pei.de

Paul-Ehrlich-Institut
Federal Institute for Vaccines and Biomedicines

Centralised Procedure

Rapid and EU-wide authorisation for innovative medicines (210 days)

1 **evaluation**

1 **authorisation**

1 **product information (SPC, Labelling, PL)**

22 **languages!**

Regulatory framework

Regulation (EC) No 726/2004

Scope

- Biotechnology Products (Art 3 (1) and point 1 of the Annex)
  - Controlled gene expression (e.g. "transgene")
  - r-DNA
  - MABs
  - Gene therapy
  - Somatic cell therapy
    (Not Tissue engineered products)
- New active substance
- Orphan medicinal products

Regulation (EC) No 1394/2007

- ✓ Amendment to Annex 1 (Directive 2003/63/EC)
- ✓ Traceability
- ✓ Long-term follow up of safety and efficacy
- ✓ Incentives
  - ✓ Scientific Advice on PhV and RMP
  - ✓ Fee Reductions (SMEs)
  - ✓ Scientific recommendation on ATMP classification
  - ✓ Certification of quality and non-clinical data
- ✓ Establishment of CAT
- ✓ Transitional Period
  - Until 30 December 2011
  - Until December 2012 (TEPs)

Regulation (EC) No 1394/2007
Chapter 1 Article 2

(b) Tissue engineered products

- engineered cells or tissues, and
- regenerating, repairing or replacing a human tissue

Î **A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices**

Regulation (EC) No 1394/2007
Chapter 1 Article 2

Î **(c) Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:**

- the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,

- the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor

Regulation (EC) No 1394/2007
Annex 1

Manipulations not considered as substantial manipulations:

- Cutting
- Grinding
- Shaping
- Centrifugation
- Sterilization / irradiation
- Filtering / lyophilisation
- Cell separation, purification, concentration
- Freezing / cryopreservation
- Soaking in antibiotic /antimicrobial solutions

Directive 2001/83/EC
Annex 1

Part IV Advanced Therapy Medicinal Products

Somatic cell therapy medicinal products

For the purposes of this Annex, somatic cell therapy medicinal products shall mean the use in humans of autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. This manipulation includes the expansion or activation of autologous cell populations ex vivo (e.g., adoptive immuno-therapy), the use of allogeneic and xenogeneic cells associated with medical devices used ex vivo or in vivo (e.g., micro-capsules, intrinsic matrix scaffolds, bio-degradable or not).

Regulatory framework
-Cells and Tissues-

- **Directive 2004/23/EC**
  Standards of quality and safety for donation, procurement, testing, processing, preservation, storage and distribution of human tissue/cells

- **Directive 2006/17/EC**
  Technical requirements for donation, procurement testing

- **Directive 2006/86/EC**
  Traceability, notification of serious adverse reactions and events, technical requirements for coding, processing, preservation, storage distribution

Regulatory framework
-Cells and Tissues-

- **Guideline on human cell-based medicinal products (EMEA/CHMP/410896/2006)**

- **Concept paper on the development of a guideline on the risk-based approach according to annex I, part IV of directive 2001/83/EC applied to advanced therapy medicinal products (CHMP/CPWP)708420/09)**

- **Reflection paper on stem cell-based medicinal products (CAT/571134/09)**

GCP legislation

🕮 Directive 2001/20/EC

- The applicant has provided a statement that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC

🕮 Directive 2005/28/EC

- ✓ Art 1 (1) The rights, safety and well being of the trial subjects shall prevail over the interest of science and society

GCP Definition (ICH)

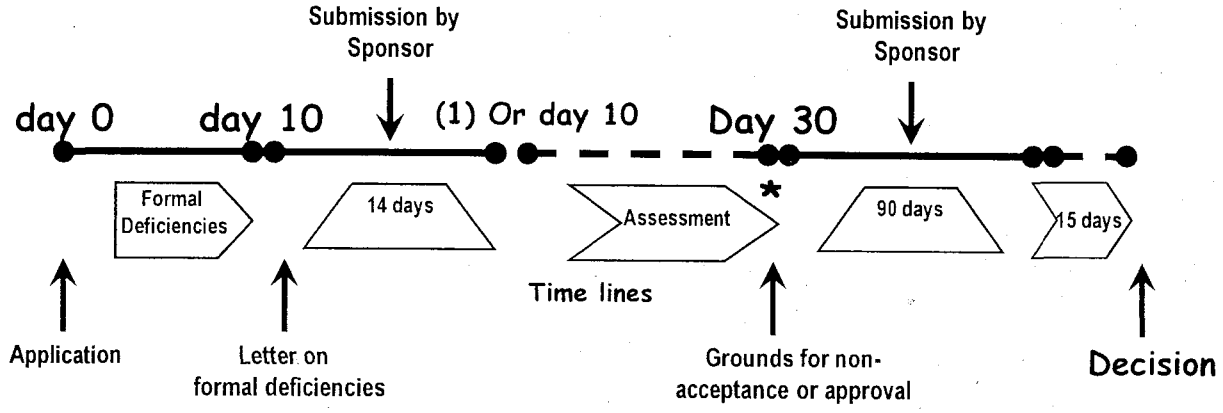
An international ethical and scientific quality standard for designing, conducting and reporting clinical trials ..... to ensure the rights, safety and well-being of trial subjects are protected

- **Rights, integrity and confidentiality of trial subjects are protected**

and

- **Data and reported results are credible, and accurate**

Clinical trial application (DE)



Biological Products (human or animal origin)	60 Days
Somatic Cell-Therapeutics; Gene Therapy Products Genetically modified Organisms (GMO)	90 Days
Xenogene Cell-Therapeutics	No time-limit

* Vaccines; Allergens; Biotech. acc. Reg. 726/2004/EC

Voluntary Harmonisation Procedure (VHP) for clinical trials

VHP

- ✓ **Clinical trial is planned to be carried out in three or more Members States**
- ✓ **Subsequent substantial amendments will also be handled by the VHP**

  - ➢ **Single application**
  - ➢ **Single evaluation (written in english)**
  - ➢ **Single list of questions (protocol, IMP)**

→Clinical trial authorisation (NCA) within 10 days

Voluntary Harmonisation Procedure (VHP) for clinical trials

Eligibility criteria

- ✓ Clinical trial is planned to be carried out in three or more Members States
- ✓ Subsequent substantial amendments will also be handled by the VHP
- ✓ The harmonized scientific assessment will start immediately following submission of a single application (written in English)

Clinical trial requirements Quality, non-clinical

- Quality
  - ✓ Manufacturing procedure (GMP certificate)
  - ✓ Impurities / Specifications
  - ✓ Excipients, adventitious agents
- Non-clinical
  - ✓ Proof of concept
  - ✓ Safety / toxicity (GLP)

Support

EMA

- **Briefing meetings**
- **Scientific Advice / Protocol Assistance**
- **Regulatory Advice**
- **Certification**

- **SME**

www.ema.europa.eu

Support

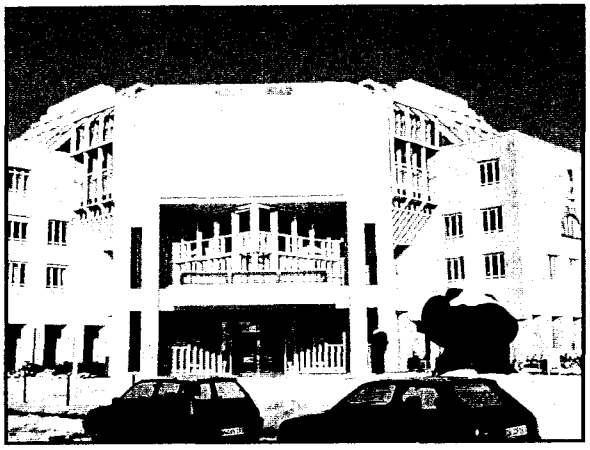
PEI - Innovation Office

- **Coordination of national Scientific Advice**
- **Regulatory Advice**
- **Preparation of SME status**

innovation@pei.de

www.pei.de

Thank you for your attention



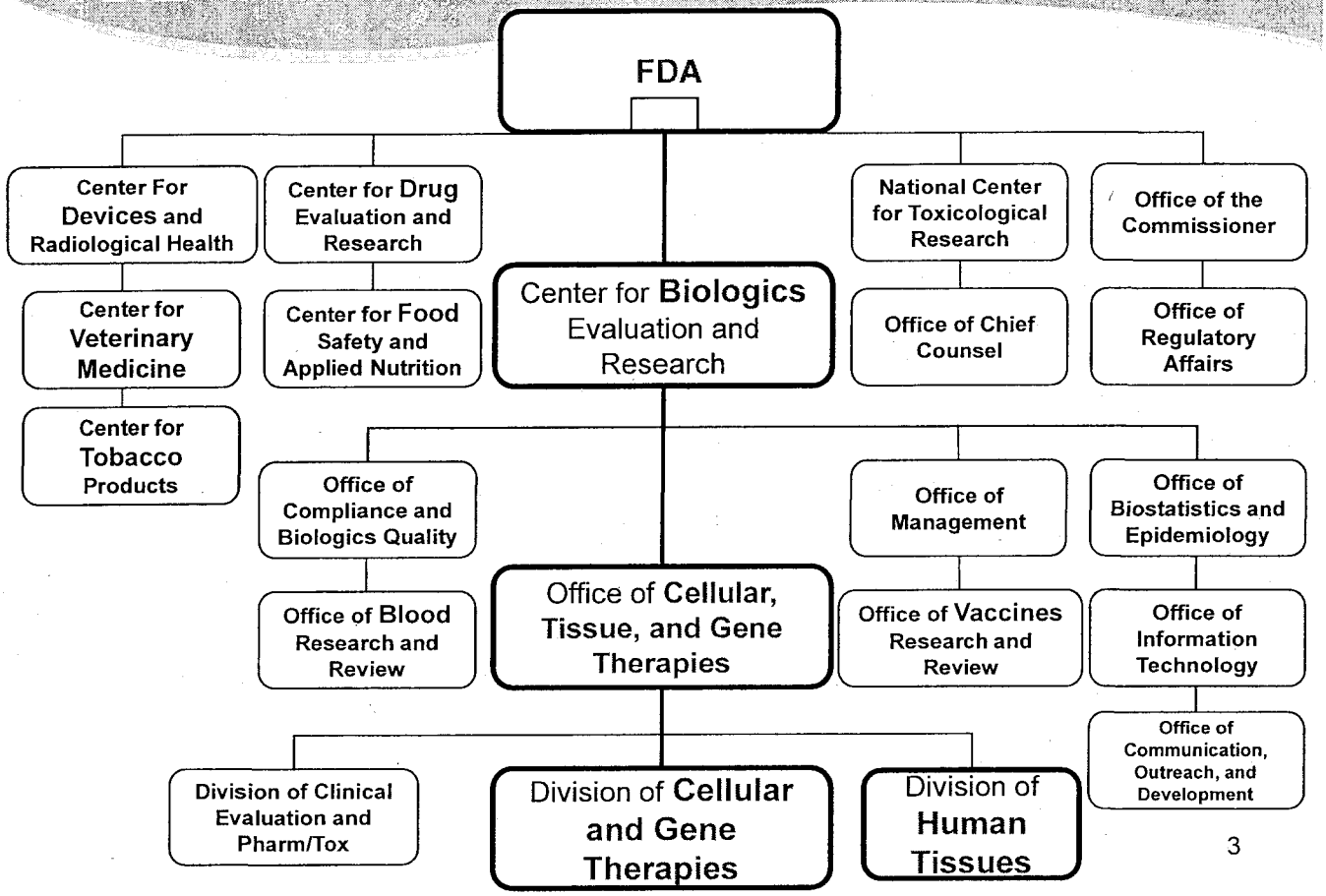
Development of Regenerative Medicine Products: FDA Perspectives

Steven R. Bauer, Ph.D.
Chief, Cellular and Tissue Therapies Branch
Office of Cellular, Tissue and Gene Therapies
Center for Biologics Evaluation and Research
US Food and Drug Administration

Regulatory Framework: 3-Tiered System

- Statutes (Laws):
  Passed by Congress and signed by the President
  - Food, Drug & Cosmetic Act (FD&C Act)
  - Public Health Service Act (PHS Act)
- Regulations (details of the law):
  Written by FDA and approved by the Executive Branch
  - 21 CFR (Code of Federal Regulations)
- Guidance (the FDA's interpretation of the Regulations):
  Written and approved within FDA
  - Advice non-binding on FDA or sponsor

2



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What is and is not an HCT/P

Regulated as HCT/Ps

- Musculoskeletal tissue
- Skin
- Ocular tissue
- Human heart valves; vascular graft
- Dura mater
- Reproductive tissue/cells
- Hematopoietic stem/progenitor cells; other cellular therapies
- Combination products (e.g., cells or tissue + device)

Not regulated as HCT/P's

- Vascularized human organs
- Minimally manipulated unrelated donor bone marrow
- Xenografts-separate regulatory pathway
- Blood and blood products - separate regulatory pathway
- Blood vessels recovered with organs and used for organ transplantation only
- Autologous cells recovered and used in same surgical procedure

HCT/Ps – Two Regulatory Tiers

Risk determines the level of regulation:

- Tissue ("361 HCT/P") – *lower risk*
  - Section 361 of PHS Act
  - Premarket review and approval not required; Product regulated solely under Tissue Regulations to control communicable disease (21 CRF 1271)
  - The Establishment Registration, Donor Eligibility and Good Tissue Practice (GTP) final rules comprise 21 CFR Part 1271
- Therapeutic ("351 HCT/P") – *higher risk*
  - Sections 351 & 361 of PHS Act, FD&C Act
  - Product regulated under Tissue Regulations and premarket review requirements (21 CFR Parts 1271, 600, 200, 312, 812)
  - Regulatory path: **Biologic** (IND/BLA) or **Device** (IDE/PMA)

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Cellular Therapies

- Regulated as HCT/P and subject to 1271 regulations
- Regulated as drugs and biologics and subject to premarket review requirements
- Clinical trials require an Investigational New Drug Application (IND)
  - A formal document with defined structure and content
  - Purpose is to request exemption from premarketing requirements and to allow lawful shipment of drug for clinical investigation.
  - Regulations (21 CFR 312) outline requirements for:
    - Use of investigational drug
    - Submission of application to FDA
    - Review by FDA

Regulation of Cell Therapies Under the 1271 Tissue Rules

HCT/P's regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 ONLY IF ALL FOUR of the following are met:

- Minimally Manipulated: Relevant biologic characteristic(s) are not altered by processing.
- Homologous Use Only: The HCT/P performs the same basic function in the recipient as in the donor.
- Production of the HCT/P does not involve combination of cells with another article (with limited exceptions and on the condition that addition of the excepted article does not raise new clinical safety concerns).
- Does not have a systemic effect, is not dependent upon the metabolic activity of living cells for primary function: exceptions for (a) autologous use, (b) first- or second-degree blood relatives, or (c) reproductive use.

More than Minimal Manipulation

- Risk of adventitious virus introduction during manufacturing
  - Reagents
  - Operators
  - Environment
- Risk of alteration of biological properties
  - Manufacturing is a novel, non physiological microenvironment

Risk/Benefit Considerations

- Protect patients from unreasonable risk
- Case-by-case
  - Patient population
    - Age
    - Medical condition
    - Availability of other treatment
    - Previous experience with similar products
  - Clinical Trial Design
  - Preclinical Information
  - Product Characteristics and Characterization

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Team Approach to Regulation of Regenerative Medicine Products

- Review Team
  - Product
  - Clinical
  - Pharm/Tox
  - Statistician
  - Regulatory Project Manager
  - Consult reviewer(s)
- CBER Research/Reviewer Model
  - Scientists/Clinicians: research-reviewers and full time review staff

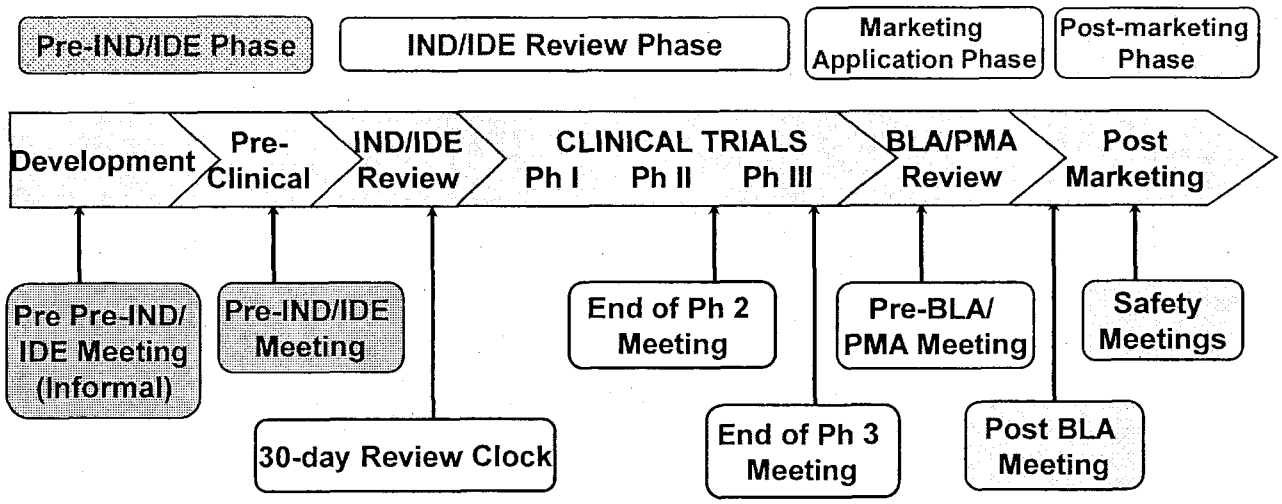
Reviewer Expertise

- Training
  - Education/Experience
  - On-the job
    - Scientific and regulatory meetings
    - Mentoring
    - Internal working group
    - Career development
      - clinical service, laboratory and clinical research
    - Research/Review model
      - Laboratory based review staff
        - » ~ 50% review, 50% research

Phases of Investigational Studies (21 CFR 312.21)

- Phase I Investigational Studies
  - Designed to evaluate safety and side effects
- Phase 2 Investigational Studies
  - Expanded safety; evaluates efficacy
- Phase 3 Investigational Studies
  - Emphasis efficacy, additional information on safety; expanded study

Interactions with FDA Throughout the Product Lifecycle



Product development is an iterative process, with frequent FDA and sponsor interaction

Combination Product

- A product composed of different categories of regulated articles:
  - Device-biologic, biologic-drug, drug-device, biologic-drug-device (not biologic-biologic, etc)
- Both components are:
  - intended for use together
  - required to mediate the intended therapeutic effect
- Can be:
  - Physically or chemically combined
  - Co-packaged; or packaged separately but cross-labeled
- Guidance:
  - Early Development Considerations for Innovative Combination Products (2006): http://www.fda.gov/RegulatoryInformation/Guidances/ucm126050.htm

Determining Classification and Lead Review Center for Combination Products

- Publically Available Resources
  - Meetings and workshops
  - Classification and Jurisdictional Information (FDA website): http://www.fda.gov/CombinationProducts/JurisdictionalInformation/default.htm
- Center Jurisdictional Officer
  - Informal jurisdictional inquiries
- Office of Combination Products (OCP)
  - OCP Jurisdictional Updates
  - Informal assignment requests
  - Request for Designation (RFD): classification and jurisdiction assignments made based on primary mode of action (PMOA) determination, inter-center agreements, most relevant expertise, and/or precedence

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Cell-Device Combination Products Regulated by OCTGT

- Tissue-engineered and regenerative medicine products (TEMPs): Cell-scaffold constructs
  - Tissue repair and replacement:
  - Orthopedic, cardiovascular, wound healing, musculoskeletal, ophthalmologic, osteogenic ..... indications
  - Bioartificial metabolic support system:
  - Hepatic, urinary, renal ..... indications
- Cells (and other biologics) + delivery device (catheters, injection/spray devices, etc):
  - Cardiovascular, orthopedic, musculoskeletal, wound healing..... indications

Chemistry, Manufacturing, & Controls

- CMC= Product manufacturing and testing
- How do you make the product?
  - Processing and manufacturing
- What do you use to make the product?
  - Cell or tissue source
  - Vector or genetically modified cell if gene therapy
  - Reagents and components
  - Equipment
- Product Safety and Quality testing
- Product Stability
- Other controls- product container labels, tracking
- Product comparability (when applicable)

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Product Characterization: Specifications-why you need them

- Demonstrate Product Consistency
- Control purity and impurity profiles of the final product.
  - Identify characteristics that predict safety and clinical effectiveness
  - Detect cells with undesired characteristics
- Demonstrate control of the Manufacturing Process.
  - Quality Assurance/Quality Control Program
- Ensure product integrity and stability.
- Identify product parameters that anticipate adverse events.

Biologic Product Specifications: Codified in Regulation *(CFR Specifications)*

Product should be characterized with reference to its:

- Safety (610.11, 610.12, 610.30, 610.40)
  - Sterility (bacterial and fungal sterility)
  - Endotoxin
  - Mycoplasma
  - Tests for opportunistic viruses
- Purity (610.13)
  - Free of extraneous materials
- Identity (610.14)
  - Specific test to distinguish it from others
- Constituent Materials (610.15)
  - Ingredients, Preservatives, Diluents, Adjuvants, Excipients
- Potency (610.10)
  - Assay for biological function

Potency

- Measured bio-activity: ability or capacity to achieve intended effect
  - Direct measure of biological activity
    - In vivo or in vitro assay
  - Indirect measure of biological activity
    - Analytical assay methods: non-bioassay method directly correlated to a unique and specific activity of the product
  - Multiple Assay Approach (Assay Matrix)
    - May not be possible or feasible to develop a single assay that encompasses all elements of an acceptable potency assay
- BLA: validated functional bioassay
- Relate data to appropriate Reference Standard
- A US regulatory requirement for biologics

Purpose of Potency Testing

- Demonstrate that each product "lot" manufactured has biological activity within established limits
- Demonstrate product consistency
  - Lot to lot, Patient to patient
- Demonstrate product stability
- Aid interpretation of clinical data

Challenges for testing cell therapy products

- Small lot size/limited sample volume
- Limited shelf life (due to cell viability)
- Limited availability of starting material for process, product, and test method development
- Lack of reference standards
- Patient to patient variability and cellular heterogeneity
- Multiple potential mechanisms of action

Advice on Preparing For Pivotal Studies-Product

- Understand critical product characteristics & have the controls in place to maintain consistency
- Have meaningful potency assay in place
- Lock down procedures and acceptance criteria based on development experience
- Protocol for stability of Phase 3 material in place, based on earlier stability data
- Shipping qualification

Lot Release Specifications- are you there?

- Guidance: ICH Q6B, Q6A
- Step-wise approach:
  - Phase 1: safety, quality manufacture
  - Phase 2: safety, tightening specifications
  - Phase 3: safety, specifications defined
  - BLA:
    - Validated assays
    - Statistical analyses
- Inability to understand critical product characteristics can impact ability to analyze clinical data

Pre-Clinical

- Scientific basis for conducting clinical trial
- Data to recommend initial safe dose & dose escalation scheme in humans
- Proof of Concept Studies in relevant animal models
- Toxicology Studies in relevant animal species
  - Identify, characterize, quantify the potential local and systemic toxicities

Clinical: Early Phase Considerations

- Optimal dose and administration
  - Starting dose level/dose escalation scheme
  - Route of administration
  - Dose schedule
- Define appropriate patient population
- Staggering of dose escalation
- Safety Monitoring plans
- Safety Reporting requirements

Planning Later Phase Clinical Studies

- End of phase 2 meeting with FDA
  - Justify dose, regimen for phase 3
  - Preliminary safety profile established
  - Target population
    - Specific proposed indication
    - Assays required for eligibility
    - Prior therapy
  - Proposed control arm
  - Statistical considerations
  - Assessments
  - Preliminary evidence of activity/effect size
- Estimate patient effect size for phase 3 planning
  - Interpretation of time to events is problematic in single arm studies
    - Leads to over optimistic interpretation of effect size

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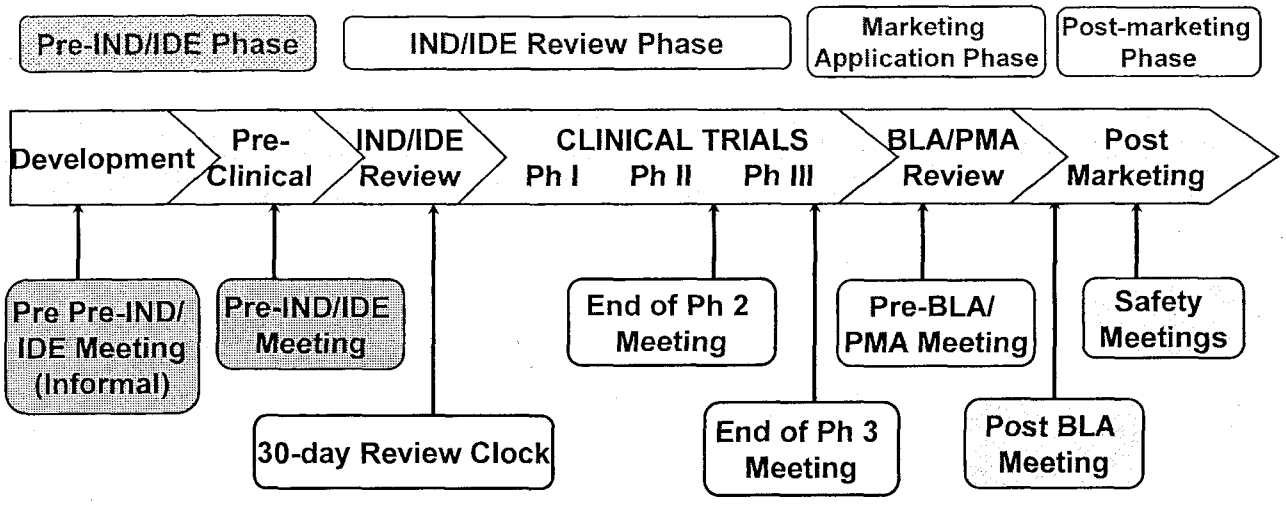
Interactions with FDA Throughout the Product Lifecycle



Product development is an iterative process, with frequent FDA and sponsor interaction

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Legal Standard for New Drug Approval

- Adequate tests of safety under the conditions prescribed, recommended or suggested in labeling
- Substantial evidence of effectiveness under the conditions prescribed, recommended or suggested in labeling
- Manufacturing, processing and packing is adequate to assure identity, strength [potency], quality and purity

-- Section 505(d)

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Examples of mechanisms for ensuring product safety and efficacy

- License application review
- Clinical data auditing and site inspections
- Pre-approval and biennial manufacturing facility inspections
- Appropriate product labeling
- Post marketing commitments and requirements
- Monitoring of adverse event and product deviation reporting

OCTGT Resources & Contact Information

- References for the Regulatory Process for OCTGT:
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm
- Guidance Documents for Cell and Gene Therapies:
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm
- OCTGT Regulatory and Administrative Contact:
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  steven.bauer@fda.hhs.gov / 301-827-0684

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資料４

今後のスケジュールについて（案）

平成 22 年

10 月 19 日　第 10 回検討会
　　関係者からヒアリング

12 月 20 日　第 11 回検討会
　　骨子案を提示

平成 23 年

2 月 18 日　第 12 回検討会
　　原案を提示

3 月 14 日　第 13 回検討会
　　結論