Navigating Uncertainty

Addressing ill-defined regulatory routes for novel biopharmaceuticals

Dr. Chris Holloway
Navigating Uncertainty

Scope of the presentation:

• Novel Biopharmaceuticals
  • Reasons for the Regulatory Challenges
• Case Studies
  • High risk medicinal products
  • Biosimilar monoclonal antibodies
  • ATMPs
• Minimising the Regulatory Uncertainty
  • Scientific Advice
  • Innovations Task Force
Emerging Biopharmaceuticals

Broadly covers:

- ATMPS (Somatic Cell therapies, Gene therapies and Tissue Engineered Products)
- Nanomedicines
- Biosimilar monoclonal antibodies
- High risk medicinal products
- Novel expression systems
- Novel targeting systems
- Novel routines of administration and delivery systems
Reasons for the Regulatory Challenges

- Rapidly moving scientific field
- Availability of experience commercially and by the Competent Authorities
- Availability of legislation in some cases
- Acceptability of new testing methods
- Availability of experts in the network
- Adequacy of existing guidelines (u = concept paper)

<table>
<thead>
<tr>
<th>Cell therapy and tissue engineering</th>
<th>CHMP/CPWP/708420/09</th>
<th>Release for consultation Dec 2009</th>
<th>Deadline for comments 31 Mar 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflective paper on In-Vitro cultured chondrocyte containing products for cartilage repair of the knee</td>
<td>u</td>
<td>CAT/CPWP/288934/09</td>
<td>Release for consultation Sep 2009</td>
</tr>
<tr>
<td>Biosimilar</td>
<td>CHMP/BINWP/632613/09</td>
<td>Release for consultation Oct 2009</td>
<td>Deadline for comments 31 Jan 2010</td>
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<tr>
<td>Development of a guideline on similar biological medicinal products containing monoclonal antibodies</td>
<td>u</td>
<td>CHMP/BINWP/632613/09</td>
<td>Release for consultation Oct 2009</td>
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</tbody>
</table>
High Risk Medicinal Products
TGN 1412

Two drug trial men critically ill

Two men remain critically ill and four others are in a serious condition after suffering a violent reaction while taking part in a clinical drugs trial.

Health

Drug trial creates 'Elephant Man'

LONDON, England -- Two men are in critical condition in a London hospital and four others are in serious condition after taking part in a clinical trial for a new drug.

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• Recombinant humanised monoclonal antibody that specifically targeted CD28

• Developed as a medicine to treat leukaemia / RA

• In terms of structure and manufacture, TGN1412 not unusual in any way
The Role of CD28 in the Immune System

- CD28 co-stimulatory receptor expressed on the cell surface of CD4+ and CD8+ T cells.
- Simultaneous triggering of the T cell antigen receptor (TCR) by antigen and of CD28 by its physiological membrane-bound ligands B7-1 (CD80) or B7-2 (CD86).
- CD28 promotes development of helper T cells.
- TGN1412 bypasses the requirement for TCR signalling and activates human T cells irrespective of their TCR specificity.
TGN1412 Nonclinical / Clinical

- Preclinical safety studies apparently showed no serious side effects (in primates) at a dose of 50 mg/kg/day over 4 weeks
  - No TGN1412 related toxicity, hypersensitivity or systemic immune system deviation observed
  - No adverse effects on cardiovascular system, respiratory system or central nervous system
- First-in-man dose 0.1 mg/kg

Catastrophic organ failure soon after administration of the product.
Press release

Date: 25th May 2006
Time: 1100 hrs
Subject: Clinical trial final report

Contact: Press Office 020 7084 3535 / 3564 press.office@mhra.nhs.uk
Out of hours 07770 446 189

Final report on TGN1412 clinical trial

Following on from an interim report published by the Medicines and Healthcare products Regulatory Agency (MHRA) on 5/4/06 into the adverse incidents which occurred on 13/3/06 during the clinical trial of TGN1412 a final report has today been issued on the matter (see below).

In addition to the various inspections carried out by MHRA inspectors and the German Regulatory Authorities, further tests have been conducted on the drug product. The product testing focused on the batch used in the original toxicology studies as well as the batch used in the trial. Although there were some ‘good clinical practice’ discrepancies identified (see below), the conclusions remain the same as reported in April 2006, that an unexpected biological effect is the most likely cause of the severe reactions in the six trial volunteers.

“This is a very complex scientific issue, which will be reviewed by the independent expert scientific group appointed by the Secretary of State for Health. We are satisfied that the adverse incidents which occurred were not as a result of any errors made in the manufacture of TGN1412, its formulation, dilution or administration to trial participants” said Professor Kent Woods, MHRA Chief Executive.

Notes to Editors:

1. Full details of the Expert working group are available from the Department of Health (020 7220 5375)
2. Full report below

Ends

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TGN 1412

Lessons to be learned

- Pre-clinical findings may be less relevant than originally thought
  - Important to validate animal models, e.g. through comparative in vitro testing using animal and human cells
- New paradigms required for establishing NOAEL or NOEL
  - Also reconsideration of the basis for establishing the MABEL (Minimum Anticipated Biological Effect Level)
- Mode of action to be considered more carefully e.g.:
  - Targets connected to multiple signalling pathways
  - Possible amplification of effects outside the control of physiological feedback mechanisms
  - Non-linear dose-response relationships (e.g. bell-shaped)
Note the final title of the guideline with the emphasis on: “Risk Mitigation” for first-in-man studies

States a medicinal product should be considered as high-risk when concerns exist that serious adverse reactions in first-in-man clinical trials may occur.

- Mode of Action
- Nature of the Target
- Relevance of Animal Models
Biosimilar Monoclonals
In Europe the term Similar Biological Medicinal Product (Biosimilar) has been adopted.

The European Medicine Agency (EMA) was the first jurisdiction to publish guidelines relating to such products.

The ‘over-arching’ biosimilar guideline was adopted in September 2005.

Guidelines specifically addressing quality issues and also nonclinical/clinical issues were adopted shortly after.
Additional Guidance in Europe

A guideline specifically addressing quality issues as well as a guideline specifically addressing nonclinical/clinical issues were adopted shortly after:


Product Specific Guidance

- Recombinant Granulocyte-Colony Stimulating Factor (2006)
- Recombinant human insulin (2006)
- Recombinant Erythropoietins (2006, 2009 revision)
- Recombinant Somatotropin (2006)
- Recombinant interferon alfa (2007 Draft, 2009 revision)
- Low Molecular Weight Heparins (October 2009)

European Medicines Agency

London, 22 October 2009
EMEA/CHMP/BMWP/632613/2009

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHIMP)

CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING MONOCLONAL ANTIBODIES

DRAFT AGREED BY BIOSIMILAR MEDICINAL PRODUCTS WORKING PARTY (BMWP) October 2009
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION October 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS) 31 January 2010

Comments should be provided electronically in word format using this template to BMWP.secretares@emea.europa.eu

KEYWORDS Biosimilars, monoclonal antibodies, similar biological medicinal products, relevant animal model, clinical use, clinical endpoints, extrapolation.

Concept Paper on the Development of a Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies
(EMEA/CHMP/BMWP/632613/2009)
Issues to be addressed in the envisaged guideline:

- Quality attributes: e.g. conformation, post-translational modification
- Extent of comparative toxicity and pharmacodynamics studies
- Value of comparative cross-reactivity studies
- Primary endpoint: most relevant or most sensitive
- Immunogenicity is addressed in a separate paper
- Extrapolation of clinical efficacy and safety
- Post-marketing follow-up
Biosimilar Monoclonal Antibodies

- No ‘biosimilar’ monoclonal antibody containing product has been approved in Europe, Canada, Japan or the United States to date
- No specific biosimilar monoclonal antibody product EU guidance note yet
- Some technical issues to consider:
  - Deamidation
  - Truncation
  - Oxidation
  - Aggregation
  - Glycosylation
  - Acetylation
Antibody Post-Translational Modifications -
*The Example of Glycosylation*

- Glycosylation is the major post-translational modification to which antibodies are subjected.
- Minor process fluctuations during manufacture can dramatically alter antibody glycosylation.
- Glycosylation is a key mediator of antibody effectors function (and mAb immunogenicity).
- Regulatory authorities view glycosylation as one of the most crucial issues for a biosimilar mAb (Christian K Schneider, Chairman of the BMWP).

An alpha carbon backbone representation of an IgG molecule:
- Oligosaccharide chains (white)
- Light chains (orange)
- Heavy chains (blue)
Typical Oligosaccharides Present on an Antibody Manufactured Using a Mammalian Expression Platform

OligoMan

G2

G2

G1\(_{(1-6)}\)

G1\(_{(1-3)}\)

G0

G0\((-\text{GlcNAc})\)

G0\((-\text{Fuc})\)

Asn297

Asn297

Asn297

Asn297

Asn297

Asn297

Asn297

Mannose (Man)  N-Acetylglucosamine (GlcNAc)  Galactose (Gal)  Fucose (Fuc)
Altered Antibody Glycosylation is Observed at Increased Manufacturing Scale
Requirements for Biosimilars in Europe

- Full CMC data package + comparative CMC data package
- Immunogenicity data crucial
- Robust potency/bioassay + clinical data
- Extrapolation (clinical data) between indications may not be possible
- Biosimilarity may not be possible for all monoclonal antibody products: Case-by-case basis
Requirements for Biosimilars in Europe (continued)

- Decide on appropriate development/registration route
- Comprehensive and conclusive CMC comparability programme
- Use of state of the art analytical techniques
- Discussion of the significance or otherwise of any observed CMC differences (impact assessment)
- Compliance with relevant regulatory guidelines (unless strong reason otherwise)
- Robust, well designed and powered comparative clinical studies
Advanced Therapy Medicinal Products
Regulatory Gap for Tissue Engineered Products

Dir 93/42/EEC

Regulatory Gap

Dir 2003/63/EC

EU Legislation

Dir 2001/83/EC

Reg (EC) 726/2004

Science

Medical Devices

Tissue Engineering

Cell Therapy

Gene Therapy

Biotech (e.g. insulin)

Chemical Medicines (e.g. aspirin)

Advanced Therapy Medicinal Products

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Regulatory Gap for Tissue Engineered Products

EU Legislation

Science

Advanced Therapy Medicinal Products

- Medical Devices
- Tissue Engineering
- Cell Therapy
- Gene Therapy
- Biotech (e.g. insulin)
- Chemical Medicines (e.g. aspirin)

- Dir 93/42/EEC
- Reg (EC) 1394/2007
- Dir 2003/63/EC
- Reg (EC) 726/2004
- Dir 2001/83/EC
Implementation of Legislation

- Technical requirements for quality, preclinical and clinical data for medicinal products are specified in Annex I to Directive 2001/83/EC
- The implementation of the ATMP Regulation required a revision of Part IV of Annex I to Directive 2001/83/EC
- Updated to include tissue engineered products
# Definitions

<table>
<thead>
<tr>
<th><strong>Somatic Cell Therapy Medicinal Product</strong></th>
<th><strong>Tissue Engineered Product (TEP)</strong></th>
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<tbody>
<tr>
<td>(a) Contains or consists of cells or tissues that have substantial manipulation, or</td>
<td>(a) Contains or consists of engineered cells or tissues, and</td>
</tr>
<tr>
<td>(b) Not intended to be used for the same essential function(s) in the recipient and the donor.</td>
<td>(b) To regenerating, repairing or replacing a human tissue.</td>
</tr>
<tr>
<td>(c) To treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.</td>
<td>(c) Cells or tissues ‘engineered’ if:</td>
</tr>
<tr>
<td></td>
<td>– Substantial manipulation, or</td>
</tr>
<tr>
<td></td>
<td>– Not intended to be used for the same essential function or functions in the recipient as in the donor.</td>
</tr>
</tbody>
</table>

**Note:**
A product which may fall within the definition of a TEP and a somatic cell therapy medicinal product shall be considered as a TEP
Definitions

**Gene Therapy Medicinal Product**

(a) Contains an active substance which contains or consists of a recombinant nucleic acid

(b) To treating, to regulating, repairing, replacing, adding or deleting a genetic

(c) Therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

**Note:**
Gene therapy medicinal products does not include vaccines against infectious diseases and synthetic nucleic acid sequences.
According to Article 17 of Regulation (EC) No 1394/2007:

“1. Any applicant developing a product based on genes, cells or tissues may request a scientific recommendation of the Agency with a view to determining whether the referred product falls, on scientific grounds, within the definition of an advanced therapy medicinal product. The Agency shall deliver this recommendation after consultation with the Commission and within 60 days after receipt of the request.

2. The Agency shall publish summaries of the recommendations delivered in accordance with paragraph 1, after deletion of all information of commercial confidential nature.”
## Classification of ATMPs

### Advanced Therapies

**Summaries of CAT scientific recommendations on ATMPs classification**

<table>
<thead>
<tr>
<th>No.</th>
<th>Product Description</th>
<th>Therapeutic Area</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Allogeneic T cells encoding an exogenous TK gene</td>
<td>Intended as adjunct treatment in haematopoietic stem cell transplantation</td>
<td>Somatic cell therapy medicinal product</td>
</tr>
<tr>
<td></td>
<td><em>Updated on 30 March 2010</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Autologous bone marrow containing hematopoietic and mesenchymal stem cells</td>
<td>Intended for the treatment of incomplete and complete chronic traumatic spinal cord injury</td>
<td>Advanced therapy medicinal product</td>
</tr>
<tr>
<td>3</td>
<td>Suspension of expanded autologous skeletal muscle derived cells (myoblasts)</td>
<td>Urology/Gynecology – Intended for regeneration of the external urethral sphincter muscle (rhabdosphincter) in patients suffering from various levels of stress urinary incontinence</td>
<td>Tissue engineered product. Not combined</td>
</tr>
<tr>
<td>4</td>
<td>Advanced Therapy Medicinal Product composed of substantially modified human allogeneic fibroblasts and keratinocytes administered in conjunction with fibrin as structural component</td>
<td>Dermatology - Treatment of chronic venous leg ulcers</td>
<td>Somatic cell therapy medicinal product.</td>
</tr>
</tbody>
</table>

### Product 2:

The following medicine was classified as an ATMP:

- Centrifuged autologous bone marrow containing hematopoietic and mesenchymal stem cells, intended for the treatment of incomplete and complete chronic traumatic spinal cord injury.

Based on the information submitted by the applicant, the CAT could at this point in time not classify this product in one of the ATMP subclasses (in this case somatic cell therapy medicinal products or tissue engineered product).
ATMP Guidelines

• Limited product specific guidelines
Minimising the Regulatory Uncertainty
Scientific Advice in Europe - National

- Benefit of a face-to-face meeting, so much more interactive than EMA procedure
- Able to discuss issues, rather than just posing questions and receiving responses
- Ideal to address difficult or contentious issues, prior to seeking central Scientific Advice through EMA
- National Scientific Advice Procedures available in some, but not all of the 27 Member States
- Procedural details vary considerably between agencies
- Member State authorities cannot speak on behalf of the EU authorities as a whole
- Timelines: ~ 2-6 weeks (sometimes longer)
- Fees: Free to ~ € 5,000
Scientific Advice in Europe - National

- **Status of Scientific Advice Received**
  - Not binding (on the agency)
  - However: Advice given is recorded and may be taken into account at a later date, e.g. in the Marketing Authorisation Application process
  - Advice at national level does not represent pan-EU view
- **An important consideration**
  - Do not ask a question if you are not prepared to follow the advice given.
Which National Agencies:

- Product already approved in that member state
- Proposed clinical trials in the jurisdiction of that national agency
- Particular expertise available in the concerned agency (e.g. Paul-Ehrlich-Institute (PEI), for gene therapy)
- Already Rapporteur or RMS, or clarification on possible role as RMS
- Preparing for (and refining) subsequent Scientific Advice through the formal EMA procedure
Scientific Advice in Europe - EMA

- Compared with FDA interactions, the EMEA formal Scientific Advice
- Procedure uncommonly involves dialogue between Company and Agency, as it is a written procedure
- Cost (€76,300)
  - Protocol assistance for Orphan Medicinal Products – Free
  - 90% fee reduction for SMEs
  - 65% fee reduction for companies developing Advanced Therapy Medicinal Products
- Organisationally very structured (requiring very careful preparation)
- A 40 or 60 day procedure.
- Provides “pan-European” view
Scientific Advice in Europe - EMA

• **Status of Scientific Advice Received**
  - Advice not necessarily binding
  - Advice given will be noted in the review of a Marketing Authorisation Application

• **Follow-up Procedure**
  - Any subsequent request falling within the same therapeutic indication and initial area(s) as the initial request, (area means quality, preclinical and/or clinical development including pharmacovigilance/risk management aspects).
  - Clarify initial Scientific Advice received
  - Present additional data to gain further advice
EMA Innovation Task Force

- Established as an inter-disciplinary group to provide a platform for regulatory issues associated with emerging therapies and technologies
- The scope of the ITF encompasses emerging therapies and technologies for which there is no established EMEA scientific, legal or regulatory guidance
- Opportunity for novel biopharmaceutical sponsors to meet informally with the ITF to pose questions not covered in existing guidance documents
- Not “Scientific Advice” as such, but rather an exchange of ideas (educational)
- Fees: Free of charge
EMA Working Parties

- It is not the prime function of the EMA Working Parties (i.e. GTWP, CPWP, BMWP) to offer “Scientific Advice” directly to the sponsors
  - This is within the mandate of the Scientific Advice Working Party

- Nevertheless, under certain circumstances there may be an opportunity to interact directly with the GTWP, CPWP, BMWP, e.g. on fundamental scientific issues of interest to the committee
  - This can be clarified with the EMA
Conclusions

- The regulator uncertainty associated with novel biopharmaceutical can be addressed by interactions with the regulatory authorities.
  - Scientific advice procedures are an important tool in Europe during the development of medicinal products, especially 'novel' products for which experience and guidelines are limited
  - Advice at the national level has its own place in the process, but a formal pan-EU opinion is only possible through the EMEA Scientific Advice Procedure

- Apart from the ‘standard’ routes for seeking and obtaining Scientific Advice in the EU, there are also other opportunities for sponsors, such as
  - Innovation Task Force (ITF)
  - Working Parties under certain circumstances
Thank you!

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