SME-Workshop
„Focus on Scientific and Regulatory Advice“, 26 May 2011

The Innovation Office
at the
Paul-Ehrlich-Institut

Bettina Ziegele, M.A., Head Innovation Office
Overview

- Framework
- Legal Basis
- Kinds of Advice and Focus
- Services
- Statistics
- Future Projects
- Challenges
Implementation of the Innovation Office

- February 2009 – August 2009: Setting of formal requirements together with the German Federal Ministry of Health
- August 2009 – October 2009: Preparations for implementing the Innovation Office
- Start of work November 2009: Press release, presentation at the website of the PEI
- December 2009: Opening workshop at the PEI
A marketing authorisation is required for industrially produced ATMP.

Those ATMP having legally been on the national market by 30 December 2008 need a marketing authorisation after a transition period:
- gene and cell therapy products starting 30 December 2011
- TEPs starting 30 December 2012

Marketing authorisation is provided via the centralised procedure co-ordinated by the European Medicines Agency (EMA).

A full dossier (Directive 2009/120/EC incl. Annex I, Part IV) will be reviewed by experts in the
- Committee for Advanced Therapies (CAT; PEI membership).

An opinion (MA yes or no) by the CAT has to be agreed by the
- Committee for Human Medicines (CHMP; PEI membership).

MA is granted by the European Commission.
Legal Provision and Starting Point

  Need for central marketing authorisation by end of 2012 at the latest

- Article 28 of the Regulation
  National Regulation „Hospital exemption“

- National Implementation in Germany
  Section 4 b (sub-section 3) of the German Medicinal Products Act
Section 4 b AMG introduced in July 2009

Non-routinely prepared ATMP having characteristics as in Section 4 b (1) require an authorisation by the PEI.

Continued use if marketed and used on 23 July 2009:

- application to PEI by 01 August 2010 for gene and cell therapy products
- application to PEI by 01 January 2011 for TEP.

A decision should be taken within 5 months (clock-stop for answering questions on possible grounds for non-acceptance).

Use of ATMP not having a marketing authorisation: Section 40 ff AMG

- Clinical trial authorisation by PEI and positive appraisal by ethics committee.
Decision Tree for Section 4b AMG
(German Medicinal Products Act)


Bundesinstitut für Impfstoffe
und biomedizinische Arzneimittel

Innovation Office
Tasks of the Innovation Office

Co-ordination of national advice, regulatory and scientific with focus on ATMP

Preparing and providing (up-dated) information on ATMP
Regulatory Advice

- Regulatory advice on technical/strategic questions
- Advice on licensing procedures, e.g. national / European
- Advice on specific regulations, guidelines etc.
FAQs - regulatory

- What are the regulatory requirements?
- What is a possible/best practice procedure — national/European; „hospital exemption“/clinical trial?
- When to ask for (national) scientific advice?
- How to apply for certification/classification with the EMA?
Stages for National Scientific Advice

Very early stage of development of the medicinal product

Preparing a clinical trial

Preparing an application of a clinical trial authorisation

Preparing an application for a national authorisation (Section 4b AMG)

Preparing an application for a centralised marketing authorisation
FAQs - scientific

- Provide advice on:
  - Identification of a risk-based approach
  - Development of medicinal product and proof of concept/first in man
  - Concept designs of clinical trials / definition of relevant endpoints
Points of Discussion and Requirements

**Quality**
- Characterisation of the cell type
- Final control
- In-process-control

**Non-Clinic**
- Proof of Principle
- Discussion of a clinically relevant animal model
- Validation of data
- Implementation of studies on the basis of GXP

**Clinic**
- Proof of safety of the medicinal product (first proofs of efficacy)
- Proof of concept
- Discussion of primary and secondary endpoints
Innovation Office

Summary

1) e.g. genetically modified cells as therapeutic vaccines
2) e.g. autologous haematopoietic bone marrow stem cells for the treatment of myocardial infarction
3) e.g. autologous chondrocyte-transplants for the treatment of cartilage defects
National Advice for ATMP by the Innovation Office of the PEI

Addressee: Academia (clinical research groups) and companies focused on ATMP

Provision of advice on general regulatory issues

- MAA, European
- Section 4b AMG*: national

Co-ordination of scientific advice:

- Scientific advice with regard to the requirements of the quality of ATMP
- Scientific advice with regard to preclinical development of ATMP
- Scientific advice with regard to applications for clinical trials of ATMP

Supportive process-related advice on the basis of first data throughout the development of the ATMP

- First application-oriented development and / or application
- non-clinical studies
- clinical trials

*) Arzneimittelgesetz = German Medicinal Products Act
Optional joint and/or resp. parallel advice together with G-BA*/IQWiG**/PEI

1. Workshop for discussion on common requirements (e.g. advice or product specific)
2. Consideration of specific requirements defined by IQWiG in PEI - advice procedures
3. Involvement of IQWiG / G-BA in commenting minutes of advice
4. Advice by G-BA
5. Consideration of the expertise of the PEI
6. Involvement of IQWiG / PEI in commenting minutes of advice

*Joint Federal Committee
**German Institute for Quality and Efficiency in Healthcare
In accordance with Regulation (EC) No. 1394/2007, Section 4b AMG,

Medicinal products in accordance with the AMNOG

Optional: involvement by G-BA + PEI

ATMP

IQWiG

G-BA

ATMP?
Demand on advice for scientific requirements of clinical trials (PEI)

Demand on advice for requirements of clinical trials with regard to (additional) health benefit (IQWiG)

Advice on the basis of § 35a SGB (social code) V (G-BA)

Advice on ATMP Basis? (IQWiG und G-BA + PEI?)

Applicant
Function of the Innovation Office

- Central contact point for requests for advice
- Co-ordination of advice across various expert areas
- Contact point for further information and queries on planned or completed advice
- „All-in-one service“:
  
  bridge to EMA, IQWiG and G-BA and as far as possible to clinical trial centres and non-clinical facilities
Service and Information

- General information on the website of the PEI
- Request form for national advice
- Booklet on ATMP as guide to applicants
- Guides for national applications for ATMP
- Register of useful guidelines and links
- Selection of FAQs
Some details on advice

2010

Applicant

Category of the ATMP

Type of Application of the ATMP

Stage of Development

Total

from Germany

from other countries

private enterprises

universities and public institutions

Gene therapy medicinal products

Somatic cell therapy medicinal products

Tissue engineered products

Gene therapy medicinal products without h. cells

autologous

allogen

nonclinical

clinical

in use

45

32

13

17

14

13

26

11

8

29

11

5
Main focuses of advice

2010

- Total: 45 = 100%
- Quality: 22%
- Nonclinical: 19%
- Clinical: 25%
- Approval of clinical trial: 9%
- Regulatory issues: 18%
Details of advice:
Quality

<table>
<thead>
<tr>
<th>Component</th>
<th>2010 Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>45%</td>
</tr>
<tr>
<td>In-process controls</td>
<td>20%</td>
</tr>
<tr>
<td>End product testing</td>
<td>56%</td>
</tr>
<tr>
<td>Release criteria</td>
<td>62%</td>
</tr>
<tr>
<td>Fluctuations in manufacturing</td>
<td>9%</td>
</tr>
<tr>
<td>Changes in manufacturing process</td>
<td>18%</td>
</tr>
<tr>
<td>Donor selection</td>
<td>9%</td>
</tr>
<tr>
<td>Manufacturing facility / licence</td>
<td>27%</td>
</tr>
<tr>
<td>Worst-case scenario</td>
<td>11%</td>
</tr>
<tr>
<td>Cryopreservation</td>
<td>22%</td>
</tr>
</tbody>
</table>
Details of advice: Non-clinic

2010

- Toxicology: 53%
- Viral safety: 44%
- Microbiology: 40%
- Specificity of species: 44%
- Proof of principle: 56%
- Validation of data: 36%
- Performance of trials on the basis of GXP: 24%

Total: 45%
Details of advice:
Clinic

<table>
<thead>
<tr>
<th>Category</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>45%</td>
</tr>
<tr>
<td>Phase of trial (safety of product or first proof of)</td>
<td>27%</td>
</tr>
<tr>
<td>Proof of concept: primary/secondary endpoints</td>
<td>33%</td>
</tr>
<tr>
<td>In-/exclusion criteria</td>
<td>47%</td>
</tr>
<tr>
<td>Dose finding</td>
<td>42%</td>
</tr>
<tr>
<td>Comparator</td>
<td>44%</td>
</tr>
<tr>
<td>Biostatistics</td>
<td>22%</td>
</tr>
<tr>
<td>Risk/Benefit (application form, invasive treatment)</td>
<td>18%</td>
</tr>
</tbody>
</table>
Details of advice:
Regulatory issues

<table>
<thead>
<tr>
<th>Category</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>45%</td>
</tr>
<tr>
<td>National authorization vs. centralized MAA</td>
<td>11%</td>
</tr>
<tr>
<td>New indication = new product?</td>
<td>4%</td>
</tr>
<tr>
<td>SME</td>
<td>4%</td>
</tr>
<tr>
<td>Orphan drug status</td>
<td>9%</td>
</tr>
<tr>
<td>Children/PIP</td>
<td>4%</td>
</tr>
<tr>
<td>VHP</td>
<td>9%</td>
</tr>
<tr>
<td>Medical device</td>
<td>16%</td>
</tr>
<tr>
<td>Import/export</td>
<td>9%</td>
</tr>
</tbody>
</table>
Advice with regard to product / type of cells

- 32 mesenchymal cells
- 8 gene therapy medicinal products without human cells
- 5 hematopoietic cells

2010
Advice:

Origin / Type of the cells with regard to indication

Mesenchymal Cells (in total) in 2010
- cancer therapy: 16 (50%)
- bone and cartilage defects: 45 (25%)
- skin reconstitution: 3 (19%)
- others: 2 (6%)

Hematopoietic cells (in total) in 2010
- cancer therapy: 45 (40%)
- bone and cartilage defects: 2 (8%)
- skin reconstitution: 8 (6%)
- others: 3 (60%)

Gene Therapy Medicinal Products without H. Cells (in total) in 2010
- cancer therapy: 45 (100%)
- bone and cartilage defects: 8 (0%)
- skin reconstitution: 0 (0%)
- others: 0 (0%)
Future Projects

- Communication with and feedback from stakeholders
- Organisation of target group-specific workshops
- Organisation of ATMP group-specific workshops
- Special workshops on important topics, e.g. special development, bottlenecks
- Production and publication of regular printed and/or electronic newsletters, providing overviews of current scientific issues, developments and trends
Challenges

- Risk-based approach
- From VHP to HP
- Networks and inclusion of HTAs
- Harmonisation of reimbursement
- Joint advice
- Parallel advice
Der Anfang ist die Hälfte des Ganzen

Aristoteles

Passion is the only orator who can always convince us.
Contact

- Dr. Lotte Dahl            Tel. 06103/77-2131
- Athalia Müller, B.Sc.     Tel. 06103/77-1038
- Bettina Ziegele, M.A., Head Tel: 06103/77-1012

E-mail: innovation@pei.de

For further information, please click on the following link:

http://www.pei.de/cln_092/nn_154420/DE/infos/pu/innovationsbuero/innovationsbuero-inhalt.html?__nnn=true
Thank you!
Decision Tree for ATMP


Bundesinstitut für Impfstoffe
und biomedizinische Arzneimittel
Guide for Application: Module 0

ANTRAG AUF GENEHMIGUNG
für Arzneimittel für neuartige Therapien
nach § 4 b Abs. 3 LVvE, § 21a Abs. 2 a des Arzneimittelgesetzes (AMG)

Modul 0
Einbringen des Arzneimittels als Arzneimittel für neuartige Therapien
unter Berücksichtigung der Vorgaben zur Genehmigung
nach § 4 b Arzneimittelgesetz

Hinweis:

Die Antragsunterlagen sind an folgende Adresse zu senden:
Paul-Ehrlich-Institut
Paul-Ehrlich-Str. 11-13
69254 Langen
GERMANY

E-mail: AMG@pei.de
Tel.: +49 6130 77-1214

Kosten:
Die für die Genehmigung von ATMP nach § 4 b AMG anfallenden Gebühren können Sie in Kürze der
Kostenunterlagen für Arzneimittel des Paul-Ehrlich-Instituts nach dem Arzneimittelgesetz
(AMG)1200D) abholen.

Guide for Application: Module 1

ANTRAG AUF GENEHMIGUNG
von Arzneimitteln für neuartige Therapien (ATMP)
mit § 4b Abs. 3 i.V.m. § 21a Abs. 2 B des Arzneimittelgesetzes (AMG)

Modul 1
Arzneimittelerfassung
Edition 2010 - PEI

 Hinweis:
Bitte senden Sie den Antrag mit den erforderlichen Unterlagen auf einem der nachfolgend genannten Verfahren:

- postlich an 1-facher Auslieferung + CO-Return an: Paul-Ehrlich-Institut, Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel, Paul-Ehrlich-Str. 58-60, D-69254 Langen,
- oder im Adobe Acrobat-Format als e-mail an: PEI-Offenlegung@bmi.de, bitte beachten Sie, dass die Sendezeit und Unterschriften im Original vorliegen müssen,
- oder als Fax an: +49-621-77 1334

Kosten
Die für die Genehmigung von ATMP mit § 4b AMG erforderlichen Gebühren können Sie nach Beantwortung der Online-Kostenanfrage für Arzneimittel bis Paul-Ehrlich-Institut nach dem Arzneimittelgesetz (PhKost) entnehmen.

http://www.pei.de/cln_170/nn_1946116/SharedDocs/Downloads/pu/innovationsbuero/modul-1-
arzneimittelerfassung,templateId=raw,property=publicationFile.pdf/modul-1-arzneimittelerfassung.pdf
Guide for Application: Modules 3A + 3B

Modul 3A
Qualitätsdaten
Edition 2011 – PEI

Modul 3B
Qualitätsdaten
Edition 2011 – PEI

Bundesinstitut für Impfstoffe
und biomedizinische Arzneimittel
Guide for Application: Module 4
Guide for Application: Module 5