

# Biotech Regulation in Key Markets

## *Keeping Your Cool in the European Union*

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## Topics to be covered

- Regulatory framework for biotech/advanced therapy product development in the EU
- Regulation of clinical trials
- Recent issues attracting attention
- Strategies to support expeditious clinical development

# Regulatory pathway for biotech products, as well as many new chemical entities, is defined in Regulation (EC) No 726/2004

## Centralised Procedure

- Recombinant products
- Products intended for gene therapy
- Hybridoma products
- Cell therapy products
- Vaccines from strains developed by means of recombinant DNA technology, including gene deletion
- Any medicinal product for which a monoclonal antibody is used at any stage in the manufacturing process.

## And .....any new active substance for

- Acquired immune deficiency syndrome
- Cancer
- Neurodegenerative disorders
- Diabetes
- Auto-immune diseases and other immune dysfunctions
- Viral diseases

## EU Regulations



- Regulations are passed by EU Parliament, Council and/or Commission and are **obligatory and automatically in force** in the Member States
- Another example:  
The regulatory framework for Advanced Therapy Medicinal Products (ATMPs) is established by **Regulation (EC) No 1394/2007**
  - ATMPs are medicinal products for human use based on gene therapy, somatic cell therapy or tissue engineering

## EU Directives

- Directives are passed by EU Parliament, Council and/or Commission and have to be adopted into National law to be effective
  - “Prime” Directive regarding medicinal products for human use: Directive **2001/83/EC**, as amended.....
  - The Clinical Trial Directive, **2001/20/EC**, mandated **GCP** for trials in the EU and **GMP** for investigational products, became effective April 2004, and is now fully implemented
- Thus, while biotech products are regulated at the EU level, clinical trials on biotech products are regulated at the National level

# National Competent Authorities



**Austria**



**Belgium**



**Bulgaria**



**Cyprus**



**Czech Republic**



**Denmark**



**Estonia**



**Finland**



**France**



**Germany**



**Greece**



**Hungary**



**Ireland**



**Italy**



**Latvia**



**Lithuania**



**Luxembourg**



**Malta**



**Netherlands**



**Poland**



**Portugal**



**Romania**



**Slovakia**



**Slovenia**



**Spain**



**Sweden**



**United Kingdom**

+EEA (Iceland, Norway, Liechtenstein)

## Clinical Trial Applications in the EU

- Parallel submission to the Competent Authority (Agency) and the Ethics Committee
  - Single ethics opinion required per country
  - For Phase 1 trials, CTAs may be processed in 14-30 days
  - CTAs for Phase 2/3 studies, or highly complex products, may require 60-180 days
  - CTA is protocol-specific
  - There are country-specific requirements regarding GMOs
  - Transparency is important in the EU

## Clinical Trial Applications in the EU

- GxP requirements in the EU
  - Mutual recognition of GMP within EU and with PIC/S countries
  - Requirement for release of investigational product by an EU Qualified Person (QP)
  - ICH+ GCP standards
- Beware deficiencies - responses to Agency questions may be required in very short time frames (e.g. 7 days)
  - Take account of the relevant Commission guidelines and ensure the latest revision is used

[http://ec.europa.eu/health/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm)

## EU Guidelines for Product Development

- There is a vast number of guidelines released from the European Medicines Agency (EMA) addressing specific cases (e.g. detailed CMC requirements, indications and clinical requirements, etc)
  - It is important to be aware of these specific cases, since failure to follow these, without sound justification, will almost certainly result in regulatory objections
- It is advisable to participate in **Scientific Advice** meetings if the product/technology is novel or complex, such that there is no/insufficient coverage in existing guidelines

## Some links.....

Inside EMA: <http://www.ema.europa.eu>

National Competent Authority Directory:

<http://www.hma.eu/index.php?id=11&showctr=6>

Guidelines for Human Biological Medicinal Products:

<http://www.ema.europa.eu/htms/human/humanguidelines/biologicals.htm>

Recent major developments regarding clinical trials:

[http://ec.europa.eu/health/human-use/clinical-trials/developments/index\\_en.htm](http://ec.europa.eu/health/human-use/clinical-trials/developments/index_en.htm)

Regulations, Directives and Notice to Applicants:

[http://ec.europa.eu/health/documents/eudralex/index\\_en.htm](http://ec.europa.eu/health/documents/eudralex/index_en.htm)

*Then there is always:*



## Points to Consider #1: Risk Mitigation

- TeGenero's TGN 1412 (anti-CD 28 mAb)
  - Humanized mAb binding to and strong agonist for the CD 28 receptor on human T cells, for treatment of B cell chronic lymphocytic leukemia (B-CLL)
  - Preclinical safety studies apparently showed no serious side effects (in non-human primates) at a dose of 50 mg/kg/day over 4 weeks, but with a first-in-man dose 0.1 mg/kg, multiple organ failure soon after administration of the product occurred due to cytokine storm reaction
  - What was the regulatory fall-out from this catastrophe?

## Points to Consider #1: Risk Mitigation

- Learnings from TGN 1412
  - Heightened caution amongst regulators and drug developers
  - Pre-clinical findings may be less relevant than originally thought, animal models should be validated, e.g. through comparative *in vitro* testing using animal and human cells
  - New paradigms are required for establishing NOAEL or NOEL, including reconsideration of the basis for establishing the MABEL (Minimum Anticipated Biological Effect Level)
  - Mode of action considerations
    - 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)

# Points to Consider #1: Risk Mitigation

- EMEA guidance
  - Original title of the draft guidance included the words “High-Risk Medicinal Products”
  - Amended to focus on “Risk Mitigation” for first-in-man studies



London, 19 July 2007  
Doc. Ref. EMEA/CHMP/SWP/28367/07

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
(CHMP)

GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

|   |                  |
|---|------------------|
| DRAFT AGREED BY CHMP EXPERT GROUP             | 6 March 2007     |
| ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION | 22 March 2007    |
| END OF CONSULTATION (DEADLINE FOR COMMENTS)   | 23 May 2007      |
| AGREED BY CHMP EXPERT GROUP                   | 4 July 2007      |
| ADOPTION BY CHMP                              | 19 July 2007     |
| DATE FOR COMING INTO EFFECT                   | 1 September 2007 |

## Points to Consider #2: Databases

- EudraCT Clinical Trial Registry
  - Pursuant to Directive 2001/20/EC, the EudraCT registry was created - numbers are assigned to all EU clinical trial protocols
  - A draft was released in June 2010 of the list of fields for result-related information to be submitted to the EudraCT database, and this has attracted much comment
- EU Medicinal Products Database
  - Pursuant to Regulation (EC) No 726/2004, a database is being created to contain all the labelling information on approved products, worded in a “comprehensible” manner
  - Certain data from the selected EudraCT fields will also be transferred into this database and thus be made public  
[http://ec.europa.eu/health/files/clinicaltrials/table\\_en.pdf](http://ec.europa.eu/health/files/clinicaltrials/table_en.pdf)

## Points to Consider #3: Orphan Attractions?

- Criteria for orphan designation: prevalence of **<5 per 10,000** persons or no potential for return on investment; no existing therapy or significant benefit expected/demonstrated
- Benefits during development include free Scientific Advice; eligibility for grants; 50% reduction in application fee (100% if small/medium enterprise)
- Market exclusivity for **10 years** in the EU
  - In July 2010 the Committee for Orphan Medicinal Products (COMP) released recommendations on elements required to support medical plausibility (including pre-clinical studies) as well as the assumption of significant benefit (built around improved efficacy, safety or contribution to patient care)



## Points to Consider #4: The Kids

- Regulation (EC) No 1901/2006 (Paediatric Regulation):  
*Not before time!*
  - Need paediatric studies at submission, or a waiver or deferral
- Applications for approval of a Paediatric Investigation Plan (PIP), including a deferral or waiver, should be submitted no later than the completion of relevant PK studies in adults, unless justified
  - If a product is beyond Phase 1, this legal deadline is not applicable

## Points to Consider #4: The Kids

- Class waivers - list of conditions for which treatments do not require studies is published by EMA

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2009/11/WC500011500.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500011500.pdf)

- *Example:* Lung carcinoma (small cell and non-small cell) - The mean age of diagnosis is above the age of 60, though rare cases occur in the 3rd decade of life

- EMA has validated 1000 PIP or waiver applications since July 2007

- Search for PIPs can provide valuable information :

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip\\_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d129](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d129)

## Points to Consider #5: SMEs

- In December 2005 the European Commission adopted provisions aimed at promoting innovation and development of new medicinal products by small/medium enterprises:
  - *Enterprises employing fewer than 250 persons and having an annual turnover not exceeding EUR 50 million, and/or an annual balance sheet total not exceeding EUR 43 million*
- SME status is obtained by application to the EMA, and may be renewed annually
  - Proof of establishment in the European Economic Area required
- Benefits include a **90% reduction** on a number of fees payable to the EMA, such as for Scientific Advice
  - Availability of benefits to entities outside the EU - an established SME can assist.....

## Strategies to Expedite Development

- The EU has developed a complex and comprehensive system of pharmaceutical legislation, founded numerous committees, and proactively implemented processes and procedures, many specifically for biotech products and advanced technologies
- Leveraging these resources is crucial to successful product development in the EU
- **Example 1:** the EMA Innovation Task Force (ITF) is a multidisciplinary group including scientific, regulatory and legal competences, and provides a forum for early dialogue with applicants
  - Briefing meetings are free and can cover regulatory, scientific and other issues relating to new therapies, such as the -omics, and nanotechnologies

## Strategies to Expedite Development

- **Example 2:** Scientific Advice with the Regulators
- National procedures are especially useful at the early clinical trial stage, to familiarise the Agency responsible for the CTA review with the product, and gain input on study design, etc
  - Informal advice from a Member State, free or with a modest cost, covering technical aspects (CMC, nonclinical and clinical)
- EMA Scientific Advice - accessing the pan-European view
  - Formal procedure with timelines, relatively expensive advice (up to EUR 75,000 unless an SME)
  - May be sought after National advice
  - Not legally binding but should be followed if advice remains relevant.....

## Conclusions

- During early stage development it is essential to establish any and all Regulatory Agencies that will have jurisdiction over the product, since this defines the legal framework and relevant guidelines
  - Clinical development in the EU has stabilised under the implemented provisions of the Clinical Trial Directive
  - With a novel or complex product, or should no relevant guidelines be available, advice should be sought
  - **Note:** All Microsoft Office documents submitted to the EMA must be in a format compatible with MS Office 2003 (not 2007 or 2010)!
- The EU has been very proactive in the area of biotech and innovative therapies

*Stay informed  
and stay cool!*



***Thank you for your attention!***