EU Perspective on Regulatory Issues for Biologics

Oncology Biologics Development Primer
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Disclosure

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- Disclaimer
  - The views expressed represent personal views. My goal is to present timely and accurate information. Errors brought to my attention will be corrected in a timely manner. However I accept no responsibility or liability whatsoever with regard to the information in this presentation.

Topics

- **Perspectives on the EU**
  - **Take Home: Europe is complex but it works**
- Regulatory Framework in the EU for Clinical Trials (Not about Marketing Authorisation)
  - Take Home: Standard Procedures of Clinical Trials Directive but be aware of differing interpretations
- Biologics in the EU
  - Take Home: Review times may be longer and separate processes may be followed

Perspectives on the EU

- “To understand European Regulatory Issues, you have to understand European Issues”.
  - Stephen Hill, 1997


Map of Europe

European Union is young and dynamic: it works well with its complexity

- 18 April 1951: European Coal & Steel community
- 7 February 1992: Treaty of Maastrich

- Currently
  - 27 Member States
  - 23 Official Languages (3 alphabets)
  - 16 currencies (Euro + 15 others)
  - 3 time zones
  - Composed of Republics, Kingdoms & a Duchy
  - 493 Million Inhabitants
  - Drive on the right side of the road, mostly
  - Brussels, Belgium - home of the Commission
  - Strasbourg, France - Home of EU Parliament
  - London, UK - home of the European Medicines Agency

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EU - many Drug Regulatory Agencies

- Health Authorities
  - 29 Agencies in all
  - 28 National Competent Authorities + EMEA
    - 26 Member States have one, Germany has two [Paul Ehrlich Institut and BfArM]

European Medicines Agency (EMEA) has a limited role in clinical trials

- Clinical Trials
  - EMEA does NOT review or approve clinical trials
  - Maintains EUDRACT (European Clinical Trials) Database
  - Coordinate pharmacovigilance on behalf of EU (Eudravigilance)
    - Ensures links between EUDRACT and Eudravigilance

National Competent Authorities (NCA)

- NCA usually the National Agency (but some exceptions e.g., Netherlands)
- Areas of responsibility include:
  - Clinical trials
  - Pharmacovigilance
  - Manufacturing authorisation
    - Inspection of pharmaceutical facilities and laboratories
- Separate and independent
  - Interpretations of Directives transposed into National Law
  - Each operates independently under National legislation, structure varies
  - Differing scientific experience/capabilities

Clinical Trials in EU conducted under Clinical Trial Directive 2001/20/EC

- Harmonized requirements to improve safety for clinical trial subjects
  - Requirements existed already in Member States
- Creation of European infrastructure for information exchange (Safety, Start and Termination Dates)
  - GMP for investigational Products.
- Be aware of national differences - delays and complications can occur

A Clinical Trial Application Has Standard Elements

- Standardized Forms Available
  - http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/11_ca_14-2005.pdf
- Requirements
  - Protocol
  - Investigators Brochure
  - Entry into EUDRACT database
  - Investigational Medicinal Product Dossier (IMPD)
  - GMP certification (manufacturing facility)
  - Ethics Committee Approval
  - Safety Reporting

MHRA Website has links to detailed instructions for CTAs

- Clinical Trials
- http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=101
- Applying for a Clinical Trial Application
- http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=723
- Maintaining a Clinical Trial Application
- http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=983
- Making clinical Trial Applications
- http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=1123
- Additional Information
- http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=1177
- Fees for Clinical Trials
- http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=1124
- Forms for Clinical Trials
- http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=1125
- Safety Reporting – Annual Safety Reports and SUSARs
- http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=993

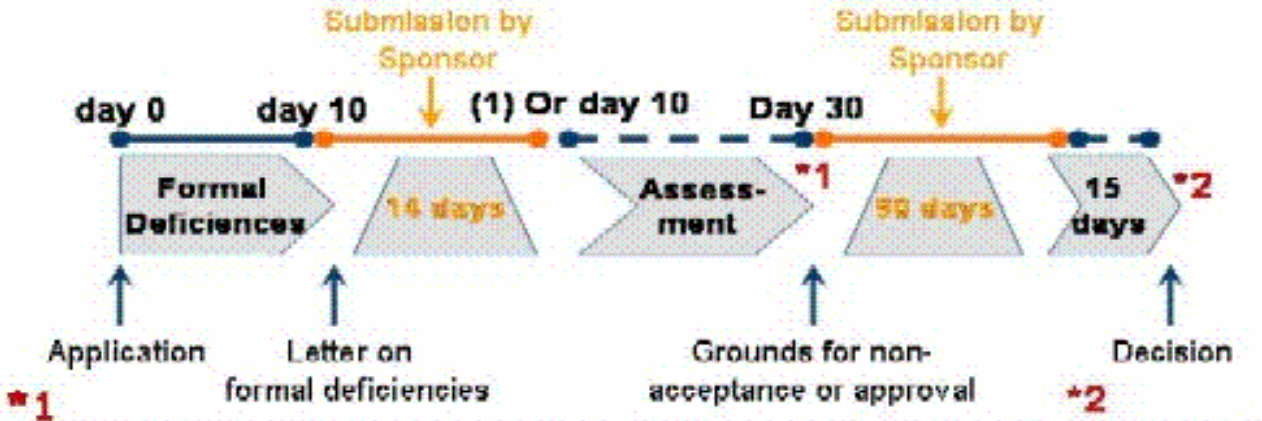
Timelines for Review & Approval of Clinical Trial Applications

- Variability among National Competent Authorities
  - 60 days (limit specified by CTD) for ethics committee approval, same for Health Authorities,
    - Some are faster
  - Some countries (Poland) have sequential applications (ethics first, then Competent Authority)
- Cellular therapy, gene therapy have a review period of 90 days specified in the CTD

Total Time for Procedure is greater than Review and Approval

PEI Time lines for CTA | http://www.pei....uesFenster.html

Graphic display of the periods and process of clinical trial authorisations



*1

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

*2

Products under *1 30 days

Graphic display of the periods and process of clinical trial authorisations
Source: Paul-Ehrlich-Institut

Clinical Trial Directive Works in Practice, but Can be Improved

- CTD is still young (Target date: 1 May 2004)
- Minutes of Meeting at EMEA on 3 October 2007 Highlight Issues
- Differing views by National Competent Authorities of
  - Definition of an IMP (eg., standard of care, but off-label, use in oncology)
  - Single Sponsor – heavy administrative burden for academic institutions participating in multi-national trials
  - Acceptance of QP Declaration of GMP Compliance by 3rd Country Manufacturer
  - Safety reporting is among most diverse implementation at national level
    - Non-commercial sponsors - Unnecessarily complex and burdensome for contribution to improving safety

Other considerations in EU clinical program conduct

- Example: Protocol with repeat radiographs in subjects with metastatic cancer
  - Radiation Exposure regulated under Euratom legislation
  - Some Countries have specific radiation boards outside of Competent Authorities
    - Czech Republic, Slovakia, Germany, UK
  - Required supplemental submission to Radiation Board

Pediatric Investigational Plan is needed earlier in EU than in the US

- Since 2007, sponsors are expected to submit a Pediatric Investigational Plan (PIP) after completion of Phase 1 studies.
- An approved PIP is required for validation of a Marketing Authorisation

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Differences in Interpretation Create Heterogeneity in Response

- Quality Dossier (Manufacturing) for biologics
  - Example Czech Republic and Germany (PEI) – may ask for data during development phases more typical of an MAA
  - Specific Requirements “Hot Buttons”
    - Viral Safety Dossier in France reviewed by a separate committee independently of CTA
    - Viral Clearance – PEI requires “state of the art”

Creation of a submission process of FIH studies for novel agents* - UK

- CHMP Guideline – Identify and Mitigate Risks for FIH Trials
  - http://www.emea.europa.eu/pdfs/human/swp/2836707enfin.pdf
- MHRA
  - http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Currentissues/index.htm
- * Acting via the immune system via a mechanism of action not well characterised.
  - novel compounds where animal data are unlikely to be predictive of activity in humans
- Formation of Expert Advisory Groups (EAG) announced
  - 16 committees (aligned by therapeutic area) charged with expert review of relevant CTAs

MHRA – Overview of FIH Process

- Sponsors **decide**, based on criteria, whether their application comes within this category.
  - pre-submission advice possible on categorization of ‘higher risk’.
  - Sponsors must propose plan to mitigate a risk if identified
- Submit full CTA (**minus the EudraCT application form**)
- MHRA perform initial assessment
- Submit EudraCT application form in the week of the EAG meeting
- MHRA informs sponsor of issues/approval - 7-14 days of CHM meeting
- Responses may be addressed at the next CHM meeting or by MHRA

Overall Timings

If no EAG / CHM issues – decision in 6/7 weeks

With 1 round of CHM questions and responses – decision in 10-11 weeks, but…

Can take (much) longer

Advanced Therapies Legislation

- New Regulation - Hasn't been implemented yet
- Covers Gene Therapy, somatic cell therapy, tissue engineered products
- Committee for Advanced Therapy is created
- Guidelines for GMP specific to such products will be created

There are many choices on where to conduct early studies

- Regulatory Guidance from EU Agencies is an option, but need to choose wisely
  - National Agencies have different levels of expertise and experience at giving clinical trial advice
    - (e.g., MPA, MHRA)
  - EMEA (centralized procedure) is time consuming, expensive. May not be well adapted to specific clinical trial concerns

- With innovative products – look to see if similar types of studies are in clinical trials in that country
  - Experience of Agency in reviewing and approving
  - e.g, AFSSAPS (France) web site has guidance on FIH and lists all studies

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