EU Perspective on Regulatory Issues for Biologics

Oncology Biologics Development Primer
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Robert Charnas
Disclosure

• Employee and shareholder of Amgen, Inc. Thousand Oaks, CA
• Worked in Basel, Switzerland for 19 Years and dealt with European Agencies

• 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
EU Perspective on Regulatory Issues for Biologics
European Union is young and dynamic: it works well with its complexity

– 18 April 1951: European Coal & Steel community
– 7 February 1992: Treaty of Maastricht

• 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

- 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
- Applying for a Clinical Trial Application
- Maintaining a Clinical Trial Application
- Making clinical Trial Applications
- Additional Information
- Fees for Clinical Trials
- Forms for Clinical Trials
- Safety Reporting – Annual Safety Reports and SUSARs
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

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
- MHRA
  - [http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicine/Clinicaltrials/Currentissues/index.htm](http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicine/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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