Biopharmaceuticals – A Regulatory Perspective

Maeve Lally
Senior Pharmaceutical Assessor (Biologics)

CASSS CMC Forum

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Cead Mile Fáilte

A hundred thousand welcomes
Disclaimer

All views are my own and not to be interpreted as those of the HPRA, the EMA or any of its working parties or Committees.
Outline of presentation

• Overview of Biopharmaceutical industry and its regulation
• How the Biopharmaceutical industry is changing
• A look at future developments in medicine, manufacturing and regulatory science
• Developing the HPRA knowledge base and the biological strategy
• How HPRA supports innovation
• Regulatory Science Ireland (RSI)
• Trends in questions raised in quality/CMC section of the dossier
The pharmaceutical industry in Ireland

Technological Diversity
- Manufacturing excellence in drug substance and drug product
- Small molecule and biologics
- €10 billion invested in new biological production in Ireland in the last decade

Dynamic Growth
Biotech manufacturing sites in Ireland:
2003 vs 2015

€39bn
Biopharmaceutical exports

7th largest exporter of medicinal and pharmaceutical products in the world in 2014

Source: IDA Ireland
The Biopharmaceutical Industry in Ireland

15 years ago:
- 3 manufacturers

Today:
- 11 manufacturers
- 6 batch certification sites
**Biopharmaceutical Industry in Ireland**

<table>
<thead>
<tr>
<th>Type of Manufacture</th>
<th>No. of Sites</th>
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<tr>
<td>Biological Active Substance</td>
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<td>Fill / Finish of Biological Active Substance</td>
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<td>Batch Certification (without other manufacture)</td>
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<td>ATMP manufacture</td>
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*Includes 2 sites where both manufacture of biological active and fill / finish operations take place

In addition there are

- other sites in development phase
- companies in early discussions with the HPRA
Biopharmaceutical Industry in Ireland

Types of products manufactured include:

- Monoclonal Antibodies
- Therapeutic Proteins (e.g. enzymes)
- Human Vaccines
- Stem Cell Treatments
Biopharmaceutical Industry in Ireland

Majority of the manufacturing facilities are 21st century:

- High level of automation
e.g. manufacturing control systems
- Electronic historians for recording processes, alarms etc.
- Electronic batch records
Looking to the next 5-10 years: new innovative medicines, manufacturing processes and regulatory science
Research and Technology Centres in Ireland
Multiple research centres funded by SFI / HRB

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<tr>
<th>Key to Primary Sector</th>
<th>ICT</th>
<th>Health &amp; Medical Technologies</th>
<th>Sustainable Food</th>
<th>Energy</th>
<th>Manufacturing &amp; Material</th>
<th>Innovation in Services &amp; Business Processes</th>
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<td>The Irish Centre for Fetal and Neonatal Translational Research</td>
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<td>Wellcome Trust – HRB Clinical Research Facility at St James’s Hospital</td>
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Ultra-rare disease
Gene therapy
Gene editing
Microbiome therapies
Veterinary biologicals
Drug/device combinations
Personalised medicine
Regenerative medicine
Immunotherapy and cancer vaccines
Ultra-rare disease
Single-use systems

Modular facilities

Continuous manufacturing

Disruptive technology

Bedside reconstitution of ATMPs

3D Printing

Increasingly complex supply chains
Changes in Biopharmaceutical Industry

- Single Product ➔ Multiproduct

- Disposable technology
  - Commonplace for cell expansion
  - Application from buffer / media storage

- Quick connect aseptic connectors

- Future changes and areas for development of guidance:
  - Continuous manufacture
  - Application of Process Analytical Technology in Biotech
  - Personalised medicines
  - High yield processes
Biopharmaceutical Industry in Ireland

- Increased use of isolators with VHP surface decontamination for fill / finish operations.

- On line e-beam technology for the aseptic introduction of syringes in fill finish operations
Developing the HPRA knowledge base in biopharma

- Established a cross organisational Working Group to identify how the HPRA could develop the organisation in the Biological/ATMP space
- Involvement in BWP & CAT
- VHP participation at CTFG
- Close collaboration with other EU agencies, multinational assessment teams
- Links to Irish organisations such as NIBRT
- Established a specific focus group to develop a biological strategy
Biological strategy in the HPRA

- Internal initiative to focus on key areas of national importance
- Horizon scanning and liaising with other government organisations to predict the current trends in biopharma and upskilled to meet those needs
- Multidisciplinary approach – quality, clinical, preclinical, compliance, medical devices, veterinary
- The strategy sees the HPRA taking on progressively more complex applications and scientific advices focusing initially on recombinant proteins and mAbs
- Subsequent focussed ATMP strategy to increase involvement in gene therapy and cell therapy and regenerative tissue, cell and scaffold therapies.
- From having a relatively small presence in the regulation of biopharmaceuticals, HPRA now involved as (co-)Rapp for many bio products and very active in scientific advice
Areas of strategic focus for biologicals

- mAbs
- Antibody Drug Conjugates
- Biosimilars
- Heparins
- Veterinary biologicals
- ATMPs
Cross organisational expertise and veterinary biologicals

Typically, development in the veterinary field is an off-shoot of development in the human field.

Examples:

- Recombinant proteins/cytokines (insulin, filgrastim, BMP-2)
- Stem cell based products
- Monoclonal antibodies
- Tumour vaccines

- HPRA hold chair of CVMP
- Provide scientific advice at EU level and regulatory/informal scientific advice at a national level (mAbs)
- Rapp for first centralised MAb
- Cross departmental collaboration to leverage from available expertise in HPAR – greater depth of knowledge/expertise/resource than in vet only agencies
Supporting innovation in partnership with EMA

• Supporting innovation through the EU Medicines Agencies Network Strategy to 2020
• Innovative Medicines Initiative
• Involvement in other EMA initiatives e.g. PAT team, PDCO, CTFG
• Participation in multinational assessment teams, worksharing, VHP
• Irish Vice Chair of PRAC
• Irish CVMP (chair) is an active member in the Group on Novel Veterinary Therapies (ADVENT) and lead in the monoclonal area
National scientific advice

- Meeting at HPRA offices
- 20 days after the meeting, written advice is issued
- Provide advice on biopharma products

- Respiratory medicine
- Rheumatology
- Obstetrics and gynaecology dermatology
- Radiopharmaceuticals
- Indications for Botulinum neurotoxins,
- Common endocrinological
- Common gastrointestinal conditions
- Generic medicines and biosimilars areas
Supporting Innovation – a key strategic objective

- Ireland ranked 14th on a global basis in terms of its R&D and innovation sectors
HPRA Mechanisms to Support Innovation

- QSAC Department
- Scientific Advice
- Involvement in Regulatory Science Ireland
- Innovation Office
- Outreach Programme
- Horizon Scanning
HPRA Innovation Office

• Launched Nov 2016
• Provides an initial point of contact for stakeholders typically involved in the early development of innovative products, devices or technologies
• Submit queries related to innovative research and development
• Emphasis on how regulators can more effectively support product development to assist in providing a timely trajectory from product concept to market access
• HPRA Innovation Day – 25th May 2017, UCD

Promote early engagement

• Novel medicinal products
• Medical devices/ diagnostics
• Emerging veterinary therapies
• Innovative products, ATMPs
• Targeted drug-delivery systems
• New technologies
• New approaches for manufacture/testing
• Drug/device combinations
Horizon Scanning
Horizon Scanning Group formed to identify innovations that may need:

• Changes to the regulatory framework or discussions at EU fora
• Development of knowledge or expertise within the HPRA or identification and recruitment of external experts
• Increased co-operation / sharing of resources between sections and/or departments to ensure effective regulation, e.g. joint assessment / inspection review
• Review or development of strategic goals and objectives

Will consider information obtained by various means including internal and external sources
Examples of information sources

- Meetings/Conferences
- Scientific Literature
- Media Reports
- Expert Groups
- Draft legislation / guidelines
- Innovation Queries
- HPRA Outreach activities
- Site visits / inspections

Horizon Scanning
Regulatory Science Ireland: Biosimilar research project
Biosimilars pipeline

Source: IMS Health, IMS Institute for Healthcare Informatics, Jan 2016
RSI: Biosimilar Project

- Network of interested parties from Academia, HPRA, pharmaceutical and medical devices industry and Government Agencies
- Research activities: HPRA and UCC
- **Objectives**
  - Peer reviewed scientific publications (practical considerations for healthcare professionals)
  - Survey perspectives and understanding of biosimilars
  - Comparative studies of international models for providing safe and effective use of biosimilars
  - Develop training materials and online resources
  - Outreach activities

**Publications to date**
- Biosimilar Medicines: Opportunities and Challenges in the clinical use and supply of Biosimilars (IPN and HPN)
- Biosimilar Medicines: Recent Developments (HPN)
- Regulatory Science Ireland: Bridging the Information Gap on Biosimilar Medicines (GaBI)
Trends in questions raised in the quality/ CMC section of the dossier
Quality questions raised at day 120 (BWP)

- No of dossiers increasing (35 in 2016 versus 30 in 2015, 13 biosimilars in 2016)
- Major objections – % of dossiers with at least 1 MO has increased
- Other concerns remain constant
Recurring issues - MOs

- GMP certs for DS/ DP manufacturing sites (7 MOs, 20.5% of all dossiers)
- Control strategy – clear definition of critical steps and operating ranges in manufacturing process required, level of criticality requires justification
- Process validation – design space not supported, PV plan not sufficient
- Characterisation – of cell substrate, functional activity assay
- DS/DP release specifications – methods not appropriate for use, missing specs (charge variants, impurities), limits not clinically qualified
- Only 1 MO on biosimilarity from 12 biosimilar s
Recurring issues - OCs

- Method transfer – protocols not provided for DP release tests
- Media components not defined – supplier agreement?
- Leachables/ extractables for single-use equipment
- Hold times and suitability to support cumulative hold times – (GL on process validation)
- Time from sterile filtration to filling?
- Risk assessment for elemental impurities (ICH Q3D) – summary?
Conclusions

• Biopharmaceutical industry continues to expand, many challenges ahead

• Regulatory authorities must ensure needs of stakeholders (industry, patients, HCPs) continue to be met, and timely access to medicines facilitated

• Multi-disciplinary approach, sharing expertise inter- and intra-agency

• Lessons to be learned from common deficiencies
Questions