Biopharmaceuticals – Regulatory Challenges for Biopharmaceuticals

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AT Europe

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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 in IE
• How HPRA supports innovation
• A look at future challenges in medicine, manufacturing and regulation
• Questions
National - HPRA

• Role – protect and enhance public and animal health
• Regulate – medicines, medical devices, other health products, cosmetics
• Remit includes clinical trials, controlled drugs, medical devices, blood and blood components, tissues and cells, organs for transplantation, cosmetics
• Inspection of manufacturers, wholesalers
• www.hpra.ie
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:

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<th>Year</th>
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<tr>
<td>Sites</td>
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7th largest exporter of medicinal and pharmaceutical products in the world in 2014

Source: IDA Ireland
The Biopharmaceutical Industry in Ireland

10 OF THE TOP 10 world's pharmaceutical companies

7TH LARGEST EXPORTER of medicinal and pharmaceutical products in the world in 2014

€39BN IN ANNUAL EXPORTS of pharma, bio and chemistry produce

75 PHARMACEUTICAL COMPANIES operate in Ireland
Biopharmaceutical Industry in Ireland

Types of products manufactured include:

- Monoclonal Antibodies
- Therapeutic Proteins (e.g. enzymes, heparin)
- Human Vaccines
- Stem Cell Treatments
# Research and Technology Centres in Ireland

Multiple research centres funded by SFI / HRB

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<th>Key to Primary Sector</th>
<th>ICT</th>
<th>Health &amp; Medical Technologies</th>
<th>Sustainable Food</th>
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<th>Manufacturing &amp; Material</th>
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<td>Welcome Trust – HRB Clinical Research Facility at St James's Hospital</td>
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Looking to the next 5-10 years: new innovative medicines, manufacturing processes and regulatory challenges
Gene therapy

Drug/device combinations

Veterinary biologicals

Gene editing

Regenerative medicine

Personalised medicine

Immunotherapy and cancer vaccines

Microbiome therapies

Ultra-rare disease

Gene editing wave hits clinic

TIME Want to Know My Future?
Single-use systems

Modular facilities

Continuous manufacturing

Disruptive technology

3D Printing

Increasingly complex supply chains

Bedside reconstitution of ATMPs
Developing the HPRA knowledge base in biopharma

- Cross-organisational Working Group to identify how the HPRA continues to develop in the Biological/ATMP space
- Includes assessors (authorisation and vigilance), inspectors (GMP and T&C), devices, veterinary
- EMA Involvement in BWP, CAT, SAWP, ITF, IWG
- VHP participation at CTFG for clinical trials
- Close collaboration with other EU agencies, multinational assessment teams
- Links to Irish organisations such as NIBRT
- Established a specific biological strategy
Areas of strategic focus for biologicals

- mAbs
- Antibody Drug Conjugates
- Biosimilars
- ATMPs
- Heparins
- Botulinum toxins
- Veterinary biologicals

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority
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
- Horizon Scanning
- Outreach Programme

Supporting Innovation
HPRA Innovation Office

• 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

• Participates in EU innovations network at EMA

• 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

Promote early engagement
Regulatory challenges

1. Biosimilars
2. Next generation biologics
3. Brexit
4. Early access to medicines (PRIME)
5. Regulatory changes – Medical devices, clinical trials
How “similar” is similar?
What is a biosimilar?

- A biological medicinal product that contains a highly similar version of the active substance of an already authorised original biological medicinal product (reference medicinal product).

- Not generic due to natural variability and complex manufacturing – cannot exactly replicate molecular micro-heterogeneity.

- There are no clinically meaningful differences in terms of quality, safety, and efficacy based on a comprehensive comparability exercise.

- First biosimilar approved by EU in 2006.
Reduced Cost

Period of market exclusivity for the top ten selling biologics (US)

Lower EPO Cost

Pharmaceuticals 2012, 5(12), 1393-1408
Stepwise approach

- Entire biosimilar process is built on a solid foundation of extensive analytical characterisation which is robustly assessed.

- Principles of biosimilar comparability exercise are based on the evaluation of the impact of changes in the manufacturing process (ICH Q5E).

- Clinical trials can not be used to justify substantial differences in quality attributes. Trials should be used to confirm the biosimilarity already shown at the quality level.
Analysis of biosimilars

Attributes e.g.:
- Primary structure
  - Mass
- Disulfide bridging
- Free cysteines
- Higher order structure
- N- and C-terminal heterogeneity
- Glycosylation
  - Glycation
- Fragmentation
  - Oxidation
  - Deamidation
- Aggregation
  - Particles
- Target-binding
  - Fc effector functions

Methods e.g.:
- MS
- Peptide mapping
  - Ellman’s
  - CGE
- SDS-PAGE
- CD, FT-IR
- H-D exchange
- NMR, X-ray
  - HPLC
  - HPAEC
  - IEF
- 2AB NP-HPLC
  - SE-HPLC
  - FFF
  - AUC
  - DLS
- MALLS
- Bioassays
  - SPR

Combination of attributes
MVDA, mathematical algorithms
Biosimilars pipeline
<table>
<thead>
<tr>
<th>Active</th>
<th>Trade names</th>
<th>Reference product</th>
<th>Date of first approval</th>
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<tr>
<td>Somatropin</td>
<td>Omnitrope</td>
<td>Genotropin</td>
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<td>Epoetin alfa</td>
<td>Abseamed, Binocrit, Epoetin Alfa Hexal, Retacrit, Silapo</td>
<td>Eprex</td>
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<td>Filgrastim</td>
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<td>Neupogen</td>
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<td>GONAL-f</td>
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<td>Inflectra, remsima</td>
<td>Remicade</td>
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<td>Insulin glargine</td>
<td>Abasaglar, Lusduna, Semglee</td>
<td>Lantus</td>
<td>2014</td>
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<td>Enoxaparin sodium</td>
<td>Inhixa, thorinane</td>
<td>Clexane</td>
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<td>Etanercept</td>
<td>Benpali, Erelzi</td>
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<td>Humalog</td>
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<td>Amgevita, Cyltezo, Imraldi, Hyrimoz</td>
<td>Humira</td>
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<td>Rituximab</td>
<td>Rixathon, Truxima, Ritemvia</td>
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<td>Teriparatide</td>
<td>Movymia, Terrosa</td>
<td>Forsteo</td>
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<td>Trastuzumab</td>
<td>Ontruzant, Ogivri</td>
<td>Herceptin</td>
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13/03/2019
Next generation biologics
Next generation biologics - ADCs

- Antibody-drug conjugates (ADCs) – highly effective cytotoxic/radioimmunotherapy/enzyme linked to a mAb
  - Adcetris (Brentuximab vedotin) for cHL
  - Kadcyla (trastuzumab emtansine) for advanced HER-2+ breast cancer
  - Besponsa (inotuzumab ozogamicin) for ALL

- Linker technology – more stable, less toxic, higher efficacy. Site-specific conjugation will permit optimisation of formulation (higher concentrations)

- All for IV infusion – new admin routes?
- All oncology indications – in US currently 60 novel ADC formulations in CTs, >50% in phase I
- Non-cancer indications – immune mediated, Neurological, ophthalmic, infectious diseases
Analytical challenges for ADCs

- Aggregates and fragments - **SEC**
- Charge variants - **IEC**
- Free drug/linker – **UHPLC-MS**
- Average drug to antibody ratio (DAR) - **HIC**
- Drug load biodistribution including unconjugated MAb (**LC-MS**) or (**UPLC-MS**)
- Potency - assesses overall structure, antigen binding, drug loading and drug delivery - **CBA**
- Residual solvents – **GC/MS**

LCGC Chromatography Online Vol 36, 6, pp 362 - 374
Next Generation biologics - ATMPs

• In EU since 2009, 13 cell and gene therapies have been authorised (Kymriah, Yescarta)
• Mid-2018 – 950 CTs worldwide
• Recent FDA publication – estimate 200+ CTs/ year by 2020
Analytical challenges for ATMPs

- New analytical techniques required to monitor CQAs
- Complex testing requirements - specific characterisation, purity, potency and identity assays for each product
- Rapid methods to account for short shelf-life (endotoxins, mycoplasma, sterility)
- Potency assay – to correlate with clinical efficacy, mode of action
- Characterisation NB especially for comparability studies to support process changes during development. Next-gen techniques include proteomics, transcriptomics.
- Limited batch sizes– method adaptation to deal with small sample volumes
- Validation of non-compendial methods? Reference standards?
Brexit
• From London

• To Amsterdam
Brexit related guidance for companies

• Protection of availability of medicines and market integrity are priorities of HPRA

• Issues include:
  - Location of MAH, QPPV
  - Location of manufacturing and batch release sites
  - EMA/ HPRA websites have guidance on many topics
Early access to medicines
Priority medicines (PRIME)

PRIME: in brief

Medicines eligible for PRIME must address an unmet medical need.

Preliminary data must be available showing the potential to address this need and bring a major therapeutic advantage to patients.

EMA will provide early and enhanced support to optimise the development of eligible medicines, speed up their evaluation and contribute to timely patients’ access.

Benefits of PRIME

FOR PATIENTS

- PRIME is driven by patients’ needs.
- It focuses on medicines that address an unmet medical need, i.e. offer a major therapeutic advantage over existing treatments, or benefit patients with no current treatment options for their disease.
- It helps to translate research into the development of medicines while meeting regulatory requirements.
- It aims to bring promising treatments to patients earlier, without compromising high evaluation standards and patient safety.

FOR MEDICINE DEVELOPERS

- PRIME helps developers of promising new medicines to optimise development plans.
- It fosters early dialogue with EMA to facilitate robust data collection and high quality marketing authorisation applications.
- It speeds up evaluation so that medicines can reach patients earlier.
- It encourages developers to focus resources on medicines likely to make a real difference to patients’ lives.
PRIME – two year review 2018

36 products eligible to PRIME since launch

30 in new diseases | 16 for pediatric patients | 15 Advanced Therapy Medicinal products

3 marketing authorisation submitted and under evaluation

EMA PRIME; a two year overview, 2018
Regulation changes
Medical device regulations 2017/745 & 2017/746
Devices incorporating a medicinal substance

• Medicinal substance is an integral part the device but has an ancillary action it is assessed authorised under MDR.
  – the quality, safety and usefulness of the substance is verified under Annex I, Directive 2001/83/EC.

• Medicinal substance has the principal action the device governed by Directive 2001/83/EC or Regulation 726/2004
  – the device element complying with Annex I of the MDR.

Full application of MDR – 26 May 2020
Full application of IVDR – 26 May 2022
Article 117- Amendment to Directive 2001/83/EC

For integral device components,
- Declaration of conformity
- Or CE certificate
- Or Notified Body Opinion confirming conformity with relevant GSPRs
Clinical trial regulation EU No. 536/2014

- Consistent rules for conducting trials throughout EU – harmonised electronic submission and assessment
- Increased transparency - Publically available information on authorisation, conduct and results of each trial
- Aims to foster innovation and research while avoiding unnecessary duplication
- Simplifies safety reporting
- Authorisation and oversight remains MS responsibility, EMA manages database and publication of content
- Implementation dependent on EU portal (single point of submission) and database – 2020?
Guidelines on the horizon

• ICHQ12 - Guideline on Product Lifecycle management. – PACMP, established conditions
  - Chapter 8.1 – encourages implementation of newer methods

• ICHQ14 – analytical procedure development and to revise ICHQ2(R1) Guideline on Validation of Analytical Procedures (merged doc?), cover newer methods e.g. NIR, Raman

• Pharma 4.0 – envisages highly efficient automated processes with integrated manufacturing control strategy, guidance required
Conclusions

• Biopharmaceutical industry continues to expand, many regulatory challenges ahead

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

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

• Newer guidance to provide additional clarity on analytical methods
Questions