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Biopharmaceuticals – Regulatory Challenges for Biopharmaceuticals

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AT Europe

Croke Park March 2019

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

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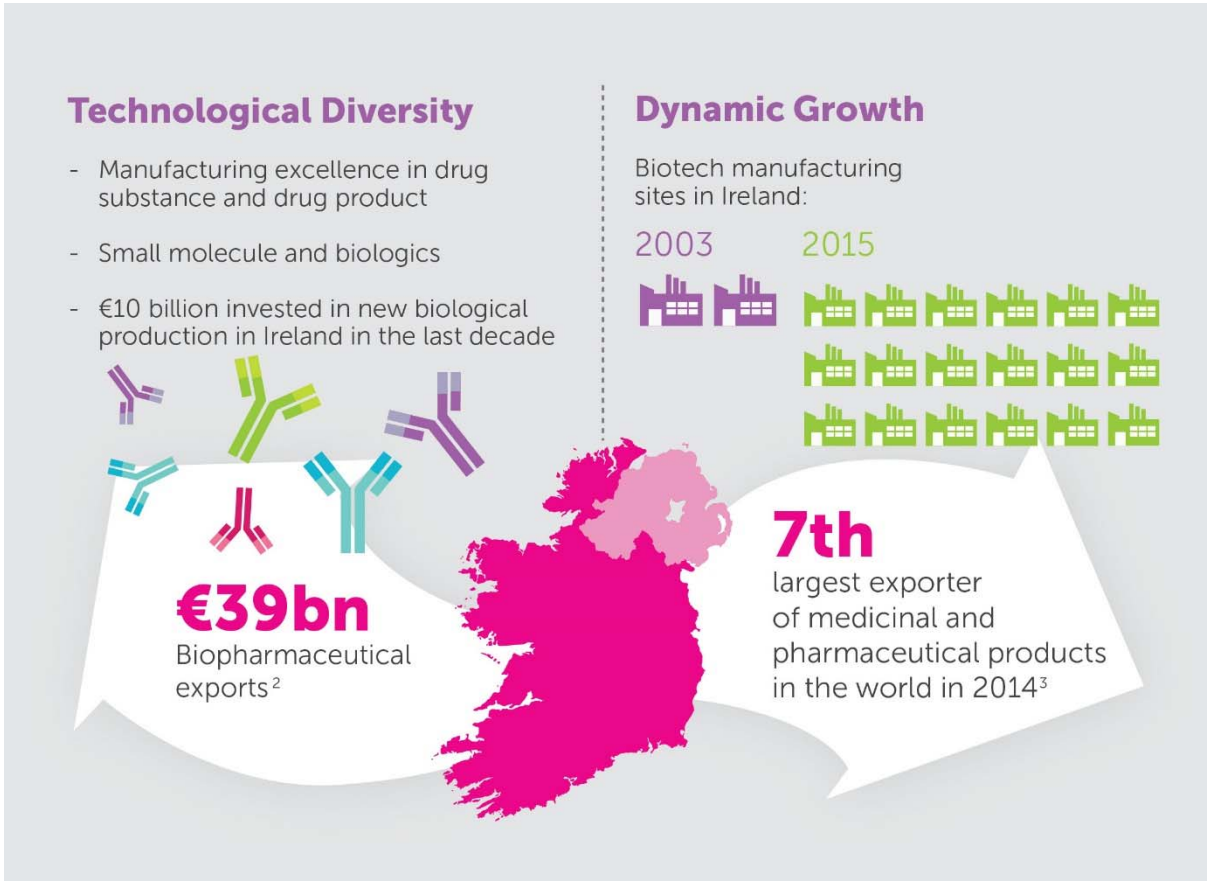
National - HPRA

- 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



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

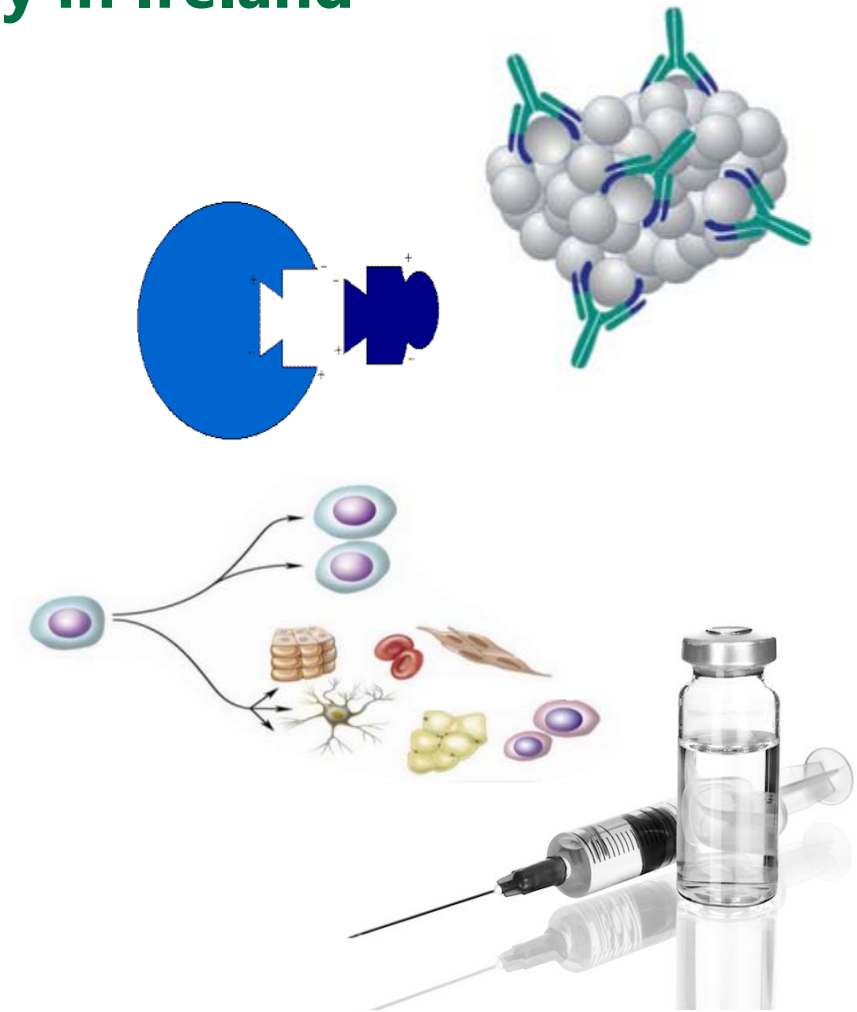
75 PHARMACEUTICAL COMPANIES

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



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Research and Technology Centres in Ireland

Multiple research centres funded by SFI / HRB

KEY TO PRIMARY SECTOR

ICT | Health & Medical Technologies | Sustainable Food | Energy | Manufacturing & Material | Innovation in Services & Business Processes

ADAPT	Centre for Digital Content Platform Research	www.adaptcentre.ie
AMBER	Advanced Material and Bioengineering Research	www.ambercentre.ie
APC	Microbiome Institute	www.apc.ucc.ie
ARCH	Applied Research for Connected Health	www.arch.ie
BDI	Biomedical Diagnostics Institute	www.bdi.ie
CeADAR	Centre for Applied Data Analytics Research	www.ceadar.ie
CONNECT	The Centre for Future Networks and Communications	www.connectcentre.ie
CÚRAM	The Centre for Research in Medical Devices	www.devices.ie
DPTC	The Dairy Processing Technology Centre	
FHI	Food for Health Ireland	www.fhi.ie
FMC2	Financial Mathematics and Computation Cluster	www.fmc-cluster.org
GRCTC	Financial Services Governance, Risk and Compliance Technology Centre	www.grctc.com
IC4	The Irish Centre for Cloud Computing and Commerce	www.ic4.ie
IMR	Irish Manufacturing Research	www.imr.ie
ICOMP	Irish Centre for Composites Research	www.icomp.ie
ICRAG	Irish Centre for Research in Applied Geosciences	www.icrag-centre.org
IERC	International Energy Research Centre	www.ierc.ie
INFANT	The Irish Centre for Fetal and Neonatal Translational Research	www.infantcentre.ie
INSIGHT	Centre for Data Analytics	www.insight-centre.org
IPIC	Irish Photonics Integration Centre	www.ipic.ie
IVI	Innovation Value Institute	www.ivi.nuim.ie
Learnovate	Learning Technologies	www.learnovatecentre.org
LERO	The Irish Software Research Centre	www.lero.ie
MaREI	Marine Renewable Energy Centre	www.marei.ie
MCCI	Microelectronic Circuits Centre Ireland	www.mcci.ie
PMTC	Pharmaceutical Manufacturing Technology Centre	www.pmtc.ie
SEES	Sustainable Electrical Energy Systems	http://erc.ucd.ie/
SSPC	Synthesis and Solid State Pharmaceutical Centre	www.sspc.ie
HRB-CRCI	Health Research Board – Clinical Research Coordination Ireland	www.rcsicrc.ie
HRB Clinical Research Facility, Galway		www.nuigalway.ie/hrb_crfg/
HRB Clinical Research Facility, Cork		www.ucc.ie/en/crfc/
HRB-Clinical Research Coordination Ireland		www.hrb-crci.ie/
ICHEC	Irish Centre for High-End Computing	www.ichec.ie
Marine Institute		www.marine.ie
NIBRT	National Institute for Bioprocessing Research and Training	www.nibrt.ie
TEAGASC	Food Research Centre (Moorpark and Ashtown)	www.teagasc.ie
Tyndall National Institute		www.tyndall.ie
Wellcome Trust – HRB Clinical Research Facility at St James's Hospital		www.sjhcrf.ie/
RCSI CRC at Beaumont Hospital		
UCD-Clinical Research Centre		

Looking to the next 5-10 years: new innovative medicines, manufacturing processes and regulatory challenges

Gene therapy

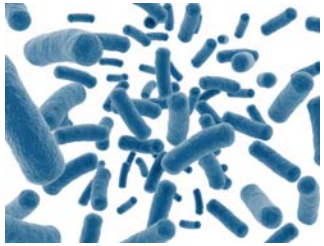
Drug/device combinations

Veterinary biologicals

Gene editing

Personalised medicine

Microbiome therapies



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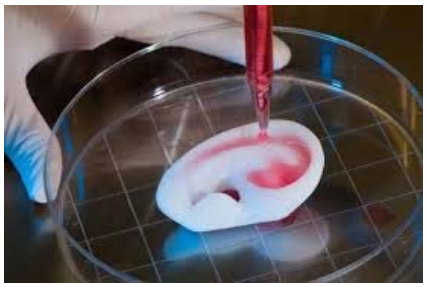
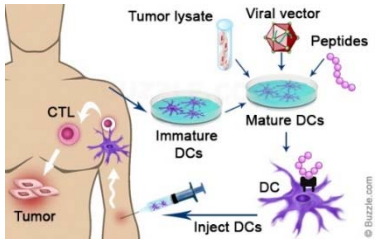
Regenerative medicine



Immunotherapy and cancer vaccines



Ultra-rare disease

Single-use systems

Modular facilities

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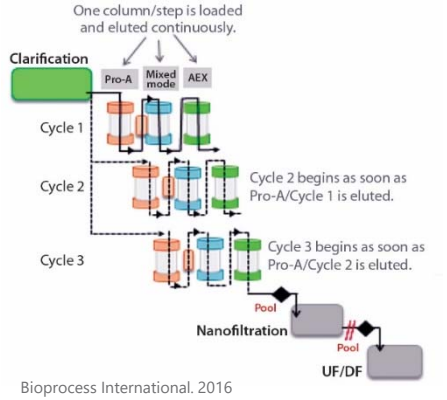
Continuous manufacturing

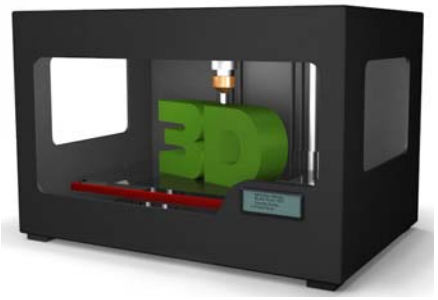


Bioprocess International. 2016

Disruptive technology

ICH Q12
harmonisation for better health

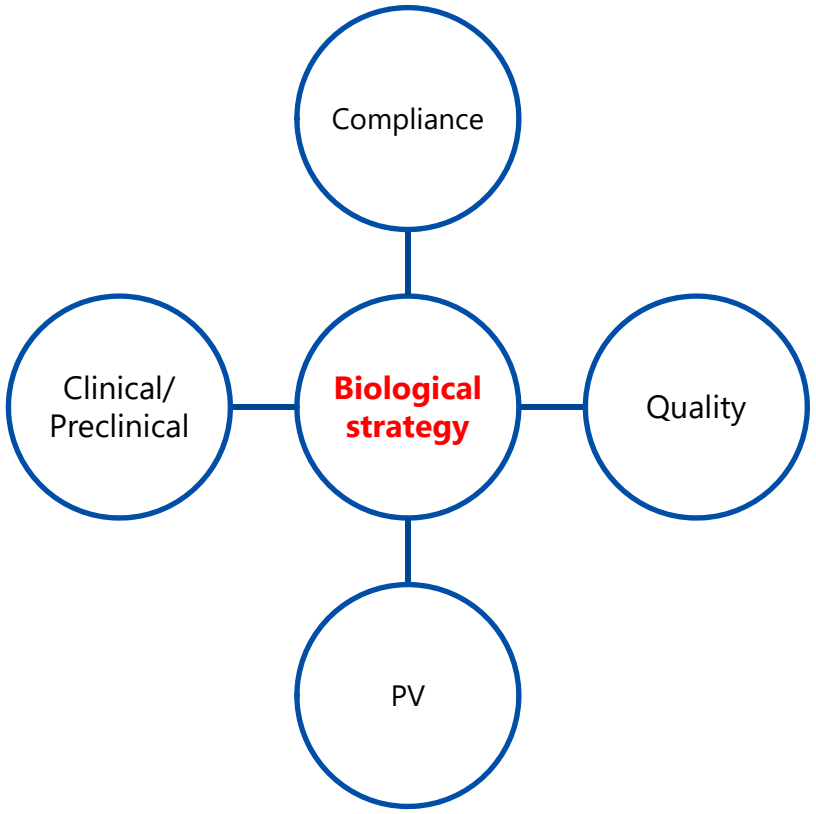
3D Printing



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

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mAbs

Biosimilars

Antibody Drug Conjugates

Heparins

Botulinum toxins

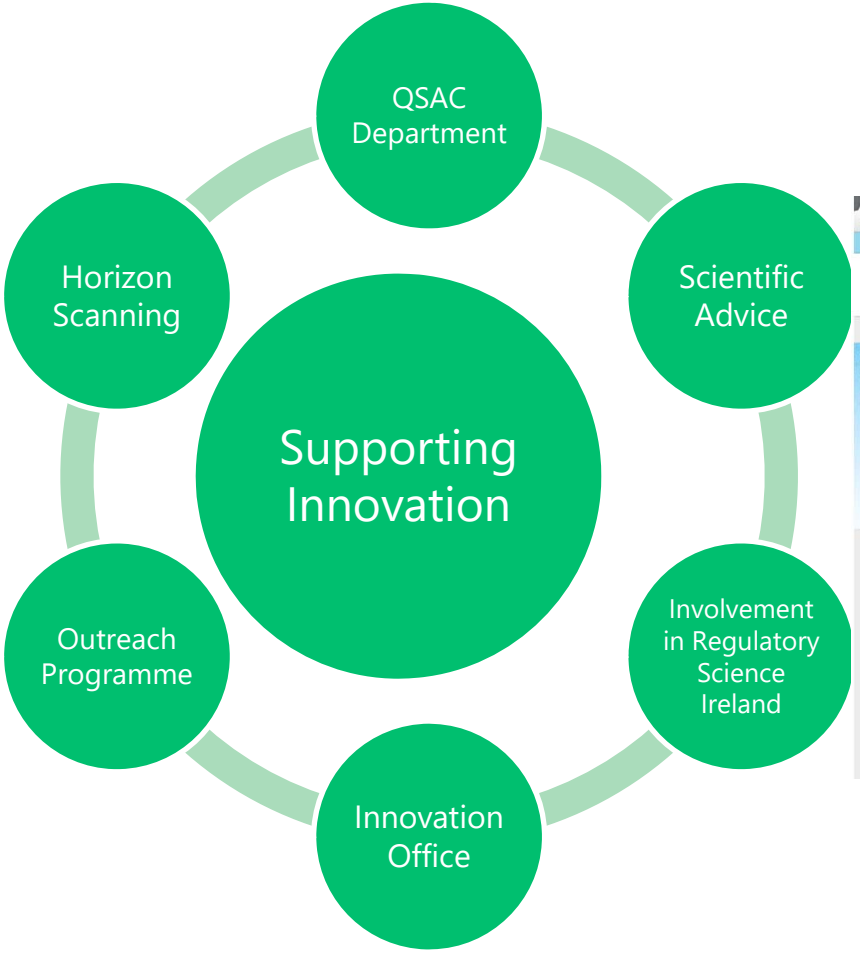
Veterinary biologicals

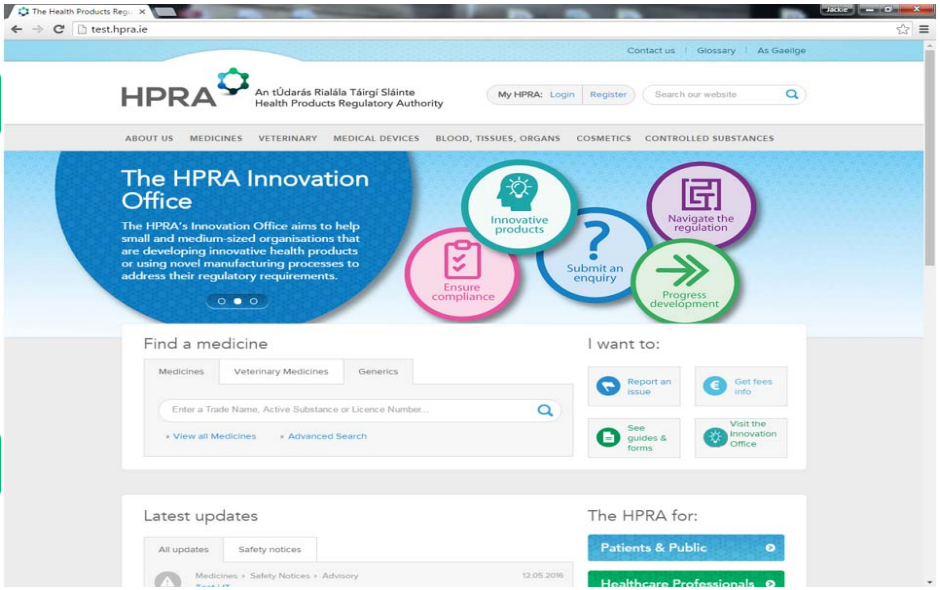
ATMPs

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





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

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Regulatory challenges

1. Biosimilars
2. Next generation biologics
3. Brexit
4. Early access to medicines (PRIME)
5. Regulatory changes – Medical devices, clinical trials

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Biosimilars

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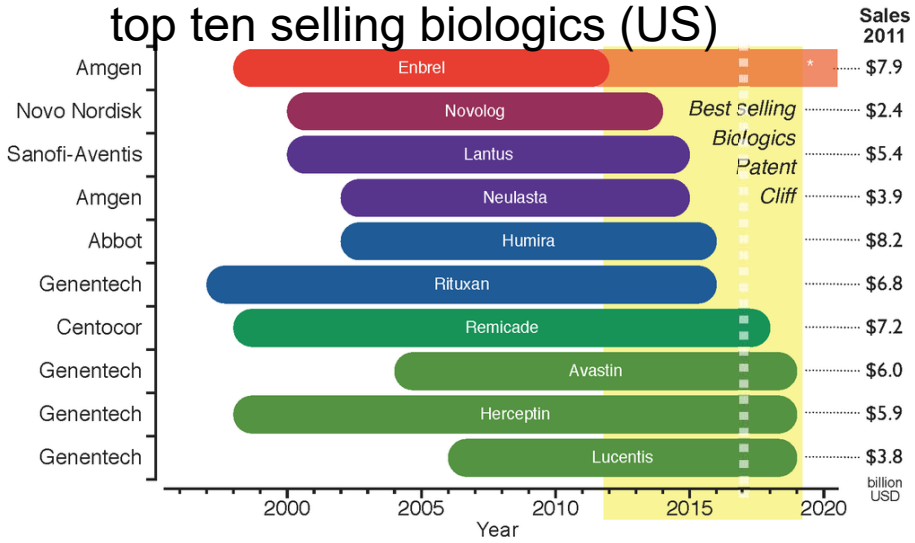
How “similar” is similar?

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

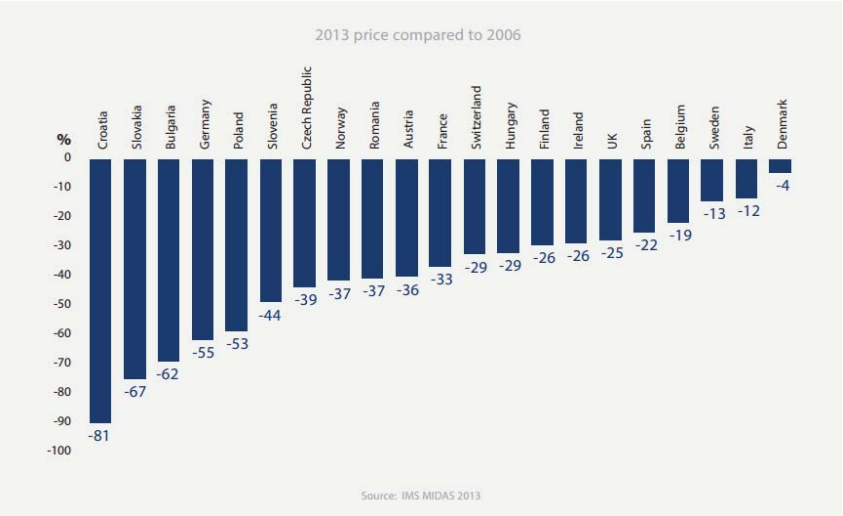
Reduced Cost

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

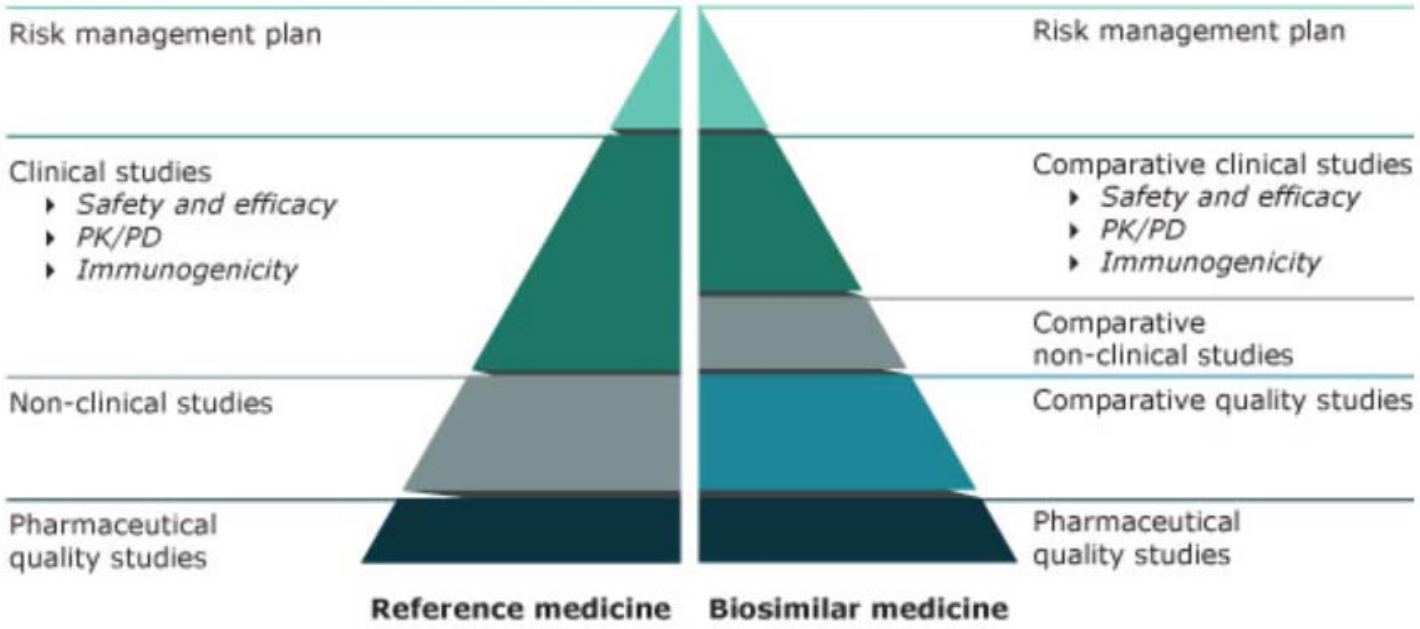


Pharmaceuticals 2012, 5(12), 1393-1408

Lower EPO Cost



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

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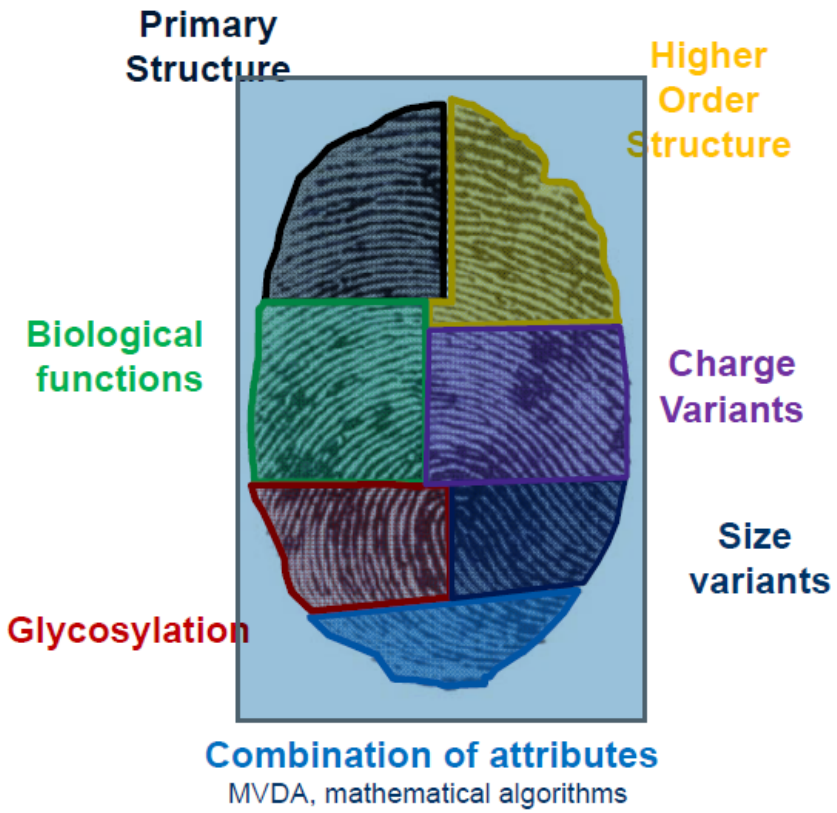
Attributes e.g.:

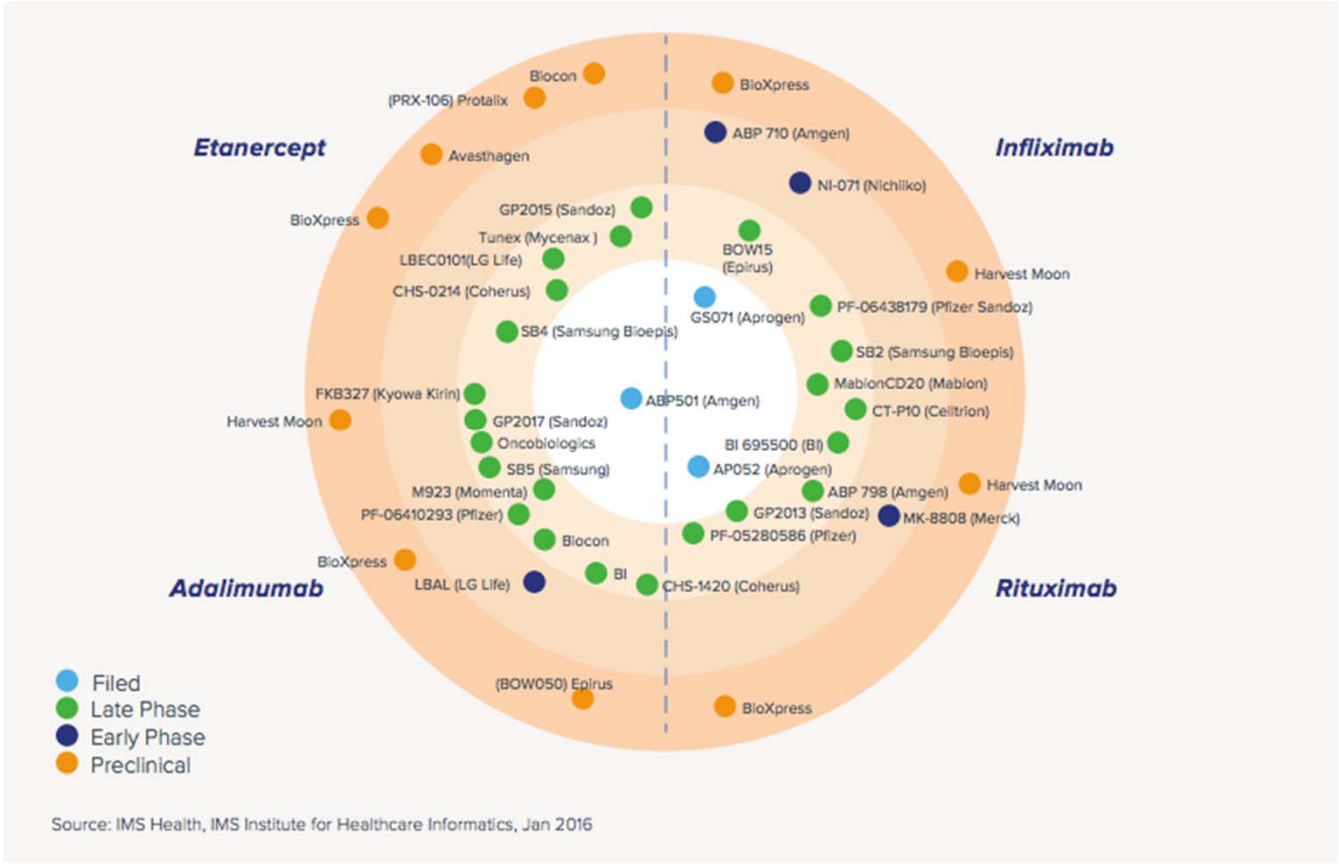
- Primary structure
  - Mass
- Disulfide bridging
  - Free cysteines
  - Higher order structure
- N- and C-terminal heterogeneity
  - Glycosylation
  - Glycation
- Fragmentation
  - Oxidation
  - Deamidation
  - Aggregation
  - Particles
- Target-binding
  - Fc effector functions



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

Biosimilars pipeline



Active	Trade names	Reference product	Date of first approval
Somatropin	Omnitrope	Genotropin	2006
Epoetin alfa	Abseamed, Binocrit, Epoetin Alfa Hexal, Retacrit, Silapo	Eprex	2007
Filgrastim	Accofil, filgrastim Hexal, Grastofil, Nivestim, Ratiograstim, Tevagrastim	Neupogen	2008
Follitropin alfa	Bemfola, Ovaleap	GONAL-f	2013
Infliximab	Inflectra, remsima	Remicade	2013
Insulin glargine	Abasaglar, Lusduna, Semglee	Lantus	2014
Enoxaparin sodium	Inhixa, thorinane	Clexane	2016
Etanercept	Benpali, Erelzi	Enbrel	2016
Insulin lispro	Insulin lispro Sanofi	Humalog	2017
Adalimumab	Amgevita, Cyltezo, Imraldi, Hyrimoz	Humira	2017
Rituximab	Rixathon, Truxima, Ritemvia	Remicade	2017
Teriparatide	Movymia, Terrosa	Forsteo	2017
Trastuzumab	Ontruzant, Ogivri	Herceptin	2017

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Next generation biologics

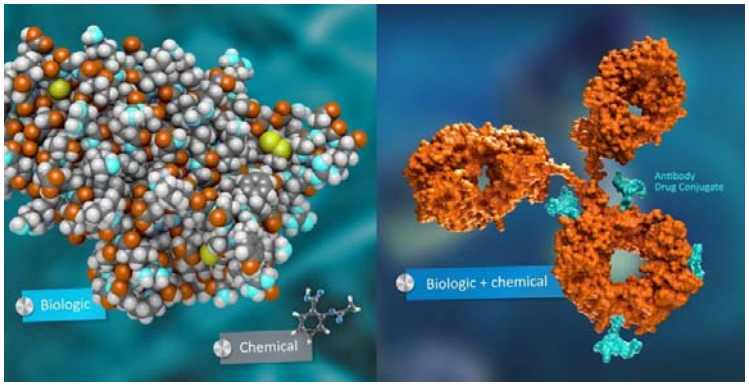
Next generation biologics - ADCs

- 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,

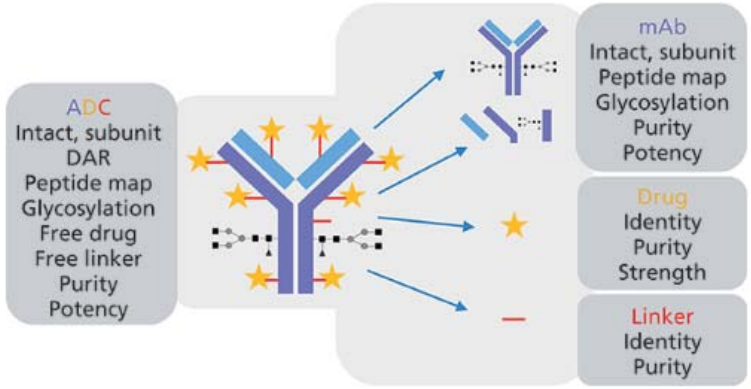
Neurological, opthalmic, infectious diseases



https://www.statnews.com/sponsor/2017/05/11/biotechs-hidden-innovation-engine-next-generation-manufacturing/

Analytical challenges for ADCs

- Aggregates and fragments - *SEC*
- Charge variants - *IEC*
- Free drug/linker – *UHPLC-MS*
- Average drug to antibody ratio (DAR) - *HIC*

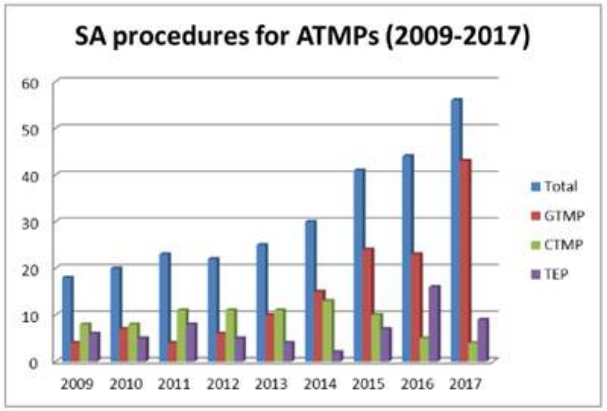


- Drug load biodistribution including unconjugated MAb (*LC-MS*)
- Potency - assesses overall structure, antigen binding, drug loading and drug delivery - *CBA*
- Residual solvents – *GC/MS*

LCGC Chromatogrpahy 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



CAT statistics 2009-2017

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?

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Brexit

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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- 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
- Batch Testing of products upon import into EU27 – exemption possible in specific circumstances https://ec.europa.eu/health/sites/health/files/files/documents/brexit_batchtesting_medicinalproducts_en.pdf
- EMA/ HPRA websites have guidance on many topics

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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

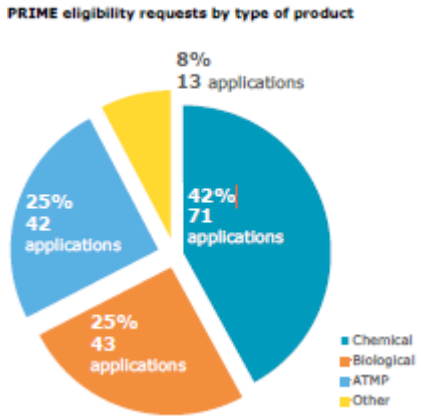
- PRIME is driven by patients' needs.
- It focuses on medicines that **address an unmet medical need**, i.e. offer a major therapeutic advantage over existing treatments, or benefit patients with no current treatment options for their disease.
- It helps to translate research into the development of 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.

EMA – Prime, Paving the way for promising medicines for patients

PRIME – two year review 2018



36 products eligible to PRIME since launch

30 in rare diseases | **16** for paediatric patients | **15** advanced therapy medicinal products

3 marketing authorisation submitted and under evaluation

Cancer
- Acute lymphoblastic leukaemia
- Diffuse large B-cell lymphoma
- Glioma
- Sarcoma
- Multiple myeloma
- NTRK fusion-positive solid tumours

Haematology/Haemostaseology
- Beta-thalassaemia
- Haemophilia
- Post-Transplant Lymphoproliferative Disorder
- Primary haemophagocytic lymphohistiocytosis
- Sickle Cell Disease

Neurology
- Alzheimer's disease
- Major depressive disorder
- Post-partum depression
- Spinal muscular atrophy Type 1

Infections
- Hepatitis D
- Septic shock
- Ebola Virus Disease

Immunology/Rheumatology/Transplantation
- ANCA-associated vasculitis
- Prevention of graft rejection

Metabolism
- Acid sphingomyelinase deficiency
- Hepatic porphyria

Uro-nephrology
- Primary Hyperoxaluria Type 1

Hepatology/Gastroenterology
- Primary Biliary Cholangitis
- Progressive Familial Intrahepatic

Dermatology
- X-linked hypohidrotic ectodermal dysplasia

Ophtalmology
- Achromatopsia associated with defects in CNG

Other
- Osteogenesis imperfecta types I, III and IV

EMA PRIME; a two year overview, 2018

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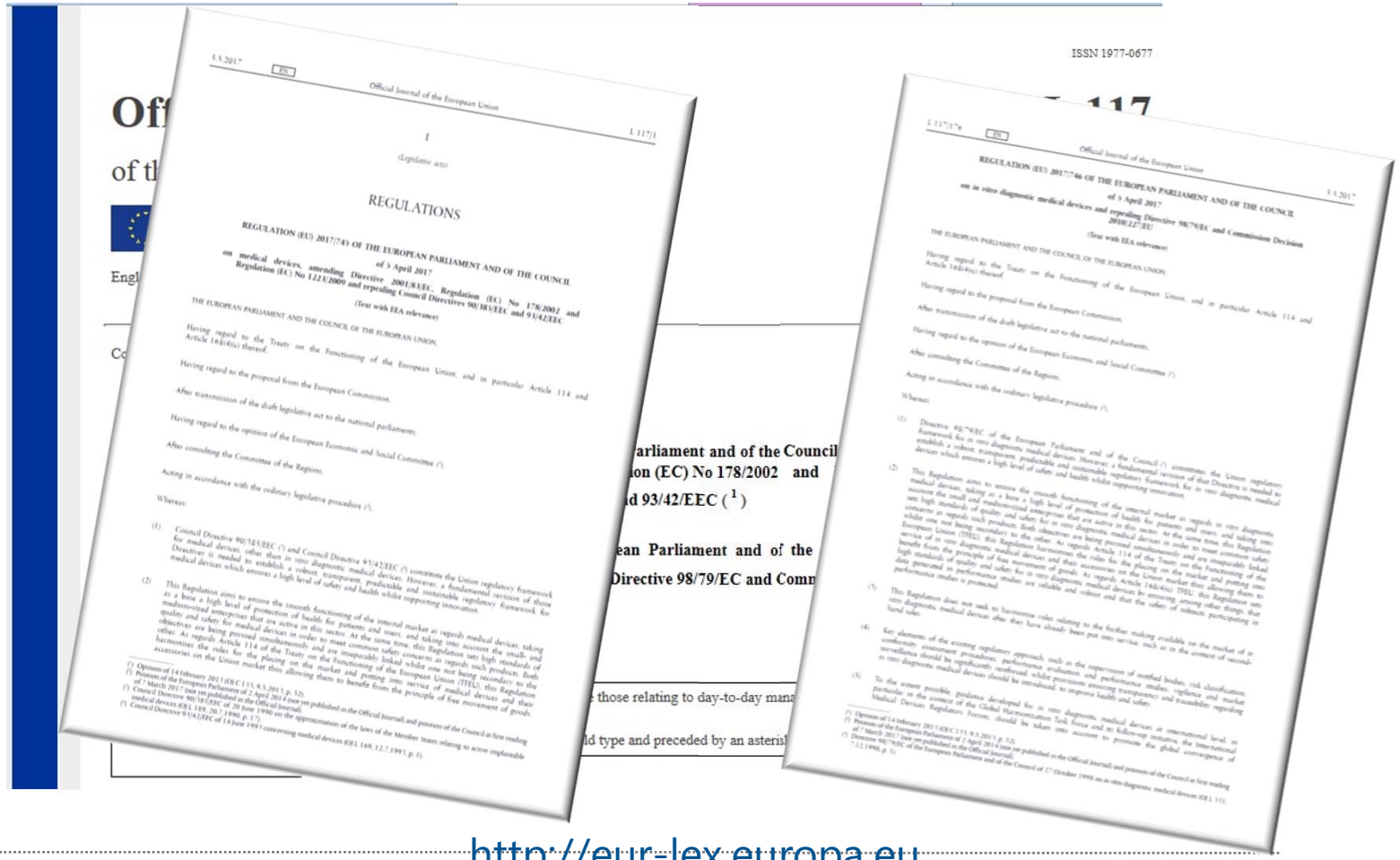
Regulation changes

Medical device regulations 2017/745 & 2017/746



http://eur-lex.europa.eu

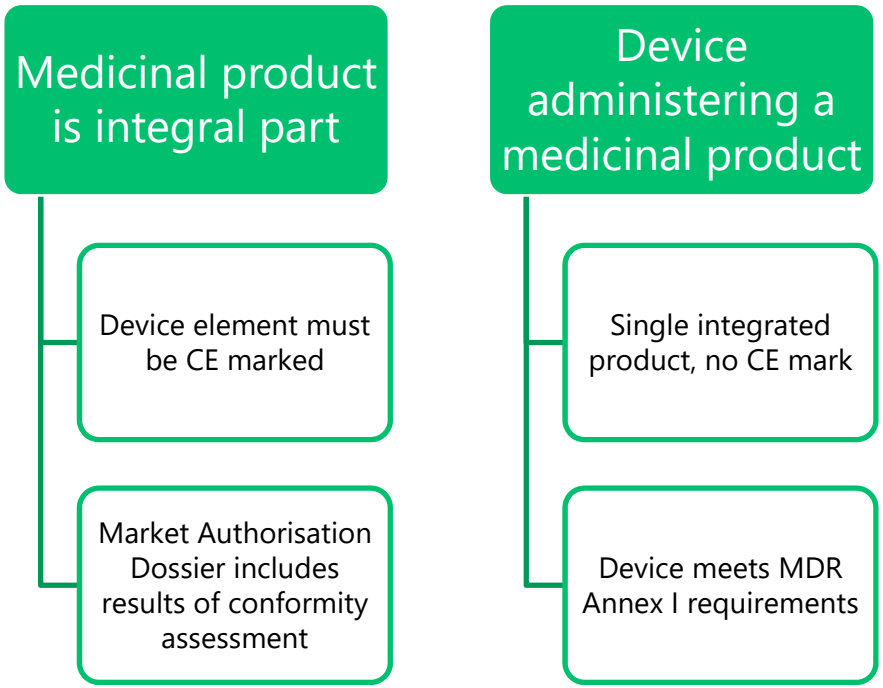
Devices incorporating a medicinal substance

- 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

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