The European Experience With Follow-on Biologics Legislation

Federal Trade Commission Roundtable on Follow-on Biologic Drugs: Framework for Competition and Continued Innovation

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The topics I have been asked to address:

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- European experience with the legislation
- European approach to exclusivity
- Exclusivity for new indications
- Exclusivity for product improvements and second-generation products
- How interchangeability is handled

The views presented are mine, not those of Hogan & Hartson LLP or any of our clients.

Introduction: EU / U.S.

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Biosimilars: "similar biological medicinal products"

- One set of laws for all "medicinal products" without a separate biologics law
- Since 2004/05, a regulatory pathway for biosimilars
- General exclusivity period of 8+2+1 years

Follow-on biologics (or follow-on proteins)

- Two laws for pharmaceutical approvals
- Public Health Service Act: No biosimilar pathway
- Federal Food, Drug and Cosmetic Act, 505(b)(2): FDA believes it has authority to approve follow-on versions of those therapeutic proteins handled as new drugs under the FDCA, e.g., Omnitrope somatropin (recombinant human growth hormone); Hatch-Waxman periods apply

Similarities and Differences: EU / U.S.

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Relevant similarities

- All biotech products, including biosimilars, go through centralized EMEA process (national Member State agencies might approve non-biotech biosimilars if the reference product was not one assessed by the EMEA)
- Rigorous review; much harmonization (ICH) and cooperation
- 20 years patent life; belief in strong IP system and in regulatory exclusivity

Relevant differences and a few cautionary notes

- Each of the 27 EU Member States has its own healthcare system and makes its own decisions about reimbursement, pricing etc., and medicine substitutability
- In the EU, national differences persist in the patent system.
- No linkage, no Orange Book, no Paragraph IV, no 180-day generic exclusivity in the EU: EU pharma regulators ignore patents and patent litigation
- Origin of EU 10-year exclusivity was 1987 “EU Hatch Waxman” law; biosimilar approval pathway came separately and much later (2004). In the U.S. we have the benefit of studies that might more accurately predict timelines/cost for biologics

EU Biosimilar Experience

A quick overview

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Biosimilar medicinal products: EU

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EU REGULATORY PATHWAY:

- Article 10(4), Community Code on Medicinal Products (Directive 2001/83/EC):
  - *"Where a biological medicinal product which is similar to a reference biological product* ***does not meet the conditions in the definition of generic medicinal products****, owing to, in particular,* ***differences*** *relating to raw* ***materials*** *or differences in* ***manufacturing processes*** *of the biological medicinal product and the reference biological medicinal product,* ***the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.*** *The type and quantity of supplementary data to be provided* ***must comply*** *with the relevant criteria stated in the* ***Annex and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided."***
- The Annex referred to is the EU version of the International Conference on Harmonization's Common Technical Document (CTD). It specifies data requirements for biologicals & "similar biological medical products."
- Under EU law there could, in theory, be a "biogeneric" if the sameness and bioequivalence requirements in Article 10.1 were met. This is not viewed as possible today, unless the innovator/marketing authorization holder seeks approval under the generic pathway of a product completely identical to its own, directly or through a licensee.

Overview of Regulatory System

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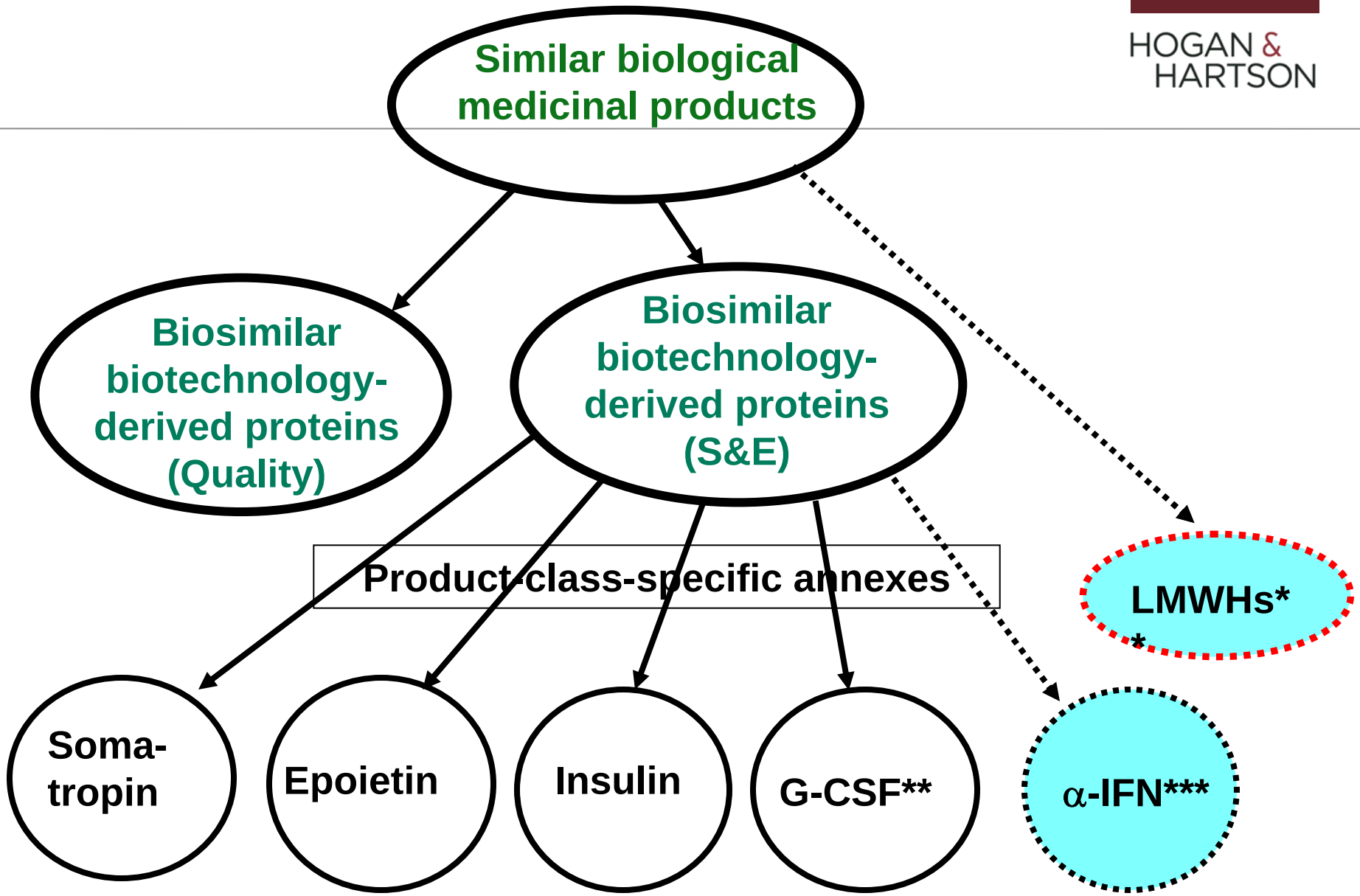
Biosimilars are authorized:

- by the European Commission
- through the centralized authorization procedure; EMEA's Committee on Medicinal Products for Human Use (CHMP) assesses the application
- the Reference Product must have been authorized in the EU

- Comparability studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product.
- Whether a medicinal product would be approvable using the "similar biological medicinal product" approach depends on the state of development of analytical procedures, the manufacturing processes employed, and clinical and regulatory experiences.
- The EMEA has issued a series of guidelines, including annexes applicable to product classes, to guide sponsors, rapporteurs, and the CHMP as a whole. The EMEA emphasizes a "case by case" approach.



Courtesy of Dr. P. Kurki

* Low-molecular weight heparins
** Filgrastim
*** Alfa interferon

Overview of 5 EU Biosimilar Products: 2 HGHs (from 2 mfrs), 5 EPOs (from 2 mfrs), 4 filgrastims (from 1 mfr)

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Authorized biosimilars:

- Omnitrope® (somatropin) (Sandoz): Recombinant human growth hormone - Reference product Pfizer's Genotropin®.
- Valtropin® (somatropin) (BioPartners): Recombinant human growth hormone - Reference product Lilly's Humatrope
- Binocrit® (epoetin alfa) (Sandoz)-Reference product J&J's Eprex for all authorizations
- Epoetin alfa Hexal® (epoetin alfa) (Hexal Biotech Forschungs)
- Abseamed® (epoetin alfa) (Medice Arzneimittel Pütter)
- Silapo® (epoetin zeta) (Stada Arzneimittel AG)
- Retacrit® (epoetin zeta) (Hospira Enterprises B.V.)
- **Ratiograstim (filgrastim) (ratiopharm GmbH)-Reference product Amgen's Neupogen for all**
- **Biograstim (filgrastim) (CT Arzneimittel GmbH)**
- **Tevagrastim (filgrastim) (Teva Generics GmbH)**
- **Filgrastim ratiopharm (filgrastim) (ratiopharm GmbH)**

Rejected as biosimilar; negative opinion: Alpheon ® (BioPartners): Recombinant interferon alpha – Reference product Roche's Roferon-A ®

Withdrawn by applicant: 3 biosimilar versions of insulin from Marvel LifeSciences (of MJ Group, Mumbai) when EMEA committee would not extend time for answering questions after previous extension: intended reference product—reference product Lilly's Humulin

European Approach to Exclusivity

What does the “8 + 2 + 1” mean and where did it come from?

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“8+2+1”

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- 8 years data exclusivity dating from the European Commission authorization decision: before that, no generic applications are fileable
- +2 years marketing protection: no generic applications approvable
- + 1 year: new indication(s) if it constitutes a significant clinical benefit
- For all products, regardless of centralized or Member State agency approval procedure
- Not retroactive; does not affect exclusivity periods for products for which applications were submitted before effective date (late 2005)

Exclusivity: types

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- With **data exclusivity**, there can be neither disclosure of regulatory data to a competitor nor regulatory reliance upon the data.
- However, unless a patent blocks the way, a competitor can reach the market by generating his own data on his version of the drug ("testing his way to market").
- With **marketing exclusivity**, agency cannot allow a competing product to enter the market during a time period in which an innovator has a right of exclusivity
- Competitor cannot generate own data to get around the exclusivity

Purpose of exclusivity

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- Whether in the form of data protection or market protection, the purpose of exclusivity is to provide an incentive for companies to undertake the expensive and lengthy process to develop a new product and bring it to market.
- Exclusivity is independent of patents and runs concurrently.
- For medicinal products in the EU under patents, the 20-year patent period with a 5-year Supplementary Protection Certificate may run longer than 10 years, post-approval.
- However, not all medicinal product innovations are covered by patents and regulatory exclusivities are intended to provide a measure of certainty that investments in product development can be recouped. Also patent law alone is viewed as not providing adequate certainty in this regard.

For centrally authorized products assessed by EMEA

- Art. 14.11 of the EMEA Regulation:
- Without prejudice to intellectual property law, medicines authorized under the EMEA Regulation shall benefit from an 8 year period of data protection and a 10 year period of marketing protection.
- The latter period shall be extended to a maximum of 11 years if, during the first 8 of the 10 years, the marketing authorization holder obtains an authorization of one or more new therapeutic indications which are held to bring a significant clinical benefit in comparison with existing therapies.
- All biotech biosimilars are assessed by EMEA.

This provision applies to all applications submitted to the EMEA after November 20, 2005.

For generic products (not biosimilars) authorized by Member State agencies

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- Art. 10(1),Community Code on Medicinal Products: Without prejudice to intellectual property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the product is a generic of a reference medicinal product which is or has been authorized for not less than 8 years in a Member State or in the Community.
- A generic authorized under this provision shall not be placed on the market until 10 years have elapsed from the initial authorization of the reference product.
- As with centrally authorized products assessed by the EMEA, an 11th year is available, governed by the same criteria.
- Note: this provision governs approvals by national Member State agencies and by its terms relates to generics, not to biosimilars. It might apply in rare cases where a national agency approves a non-biotech biologic whose reference product was not one assessed by the EMEA.
- This provision should apply to all applications submitted to Member State agencies after October 30, 2008 [European Commission guidance says after Member State implementation of Directive.]

Where the 8:2+1 came from: Legal Landmarks: EU Exclusivity Law

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1965 1987

- 1965: First European Community medicines law, Directive 65/65, established framework requirements for authorization of medicinal products
- 1987 amendments, Directive 87/21: generic pathway and DATA PROTECTION:

- "The applicant shall not be required to provide the results of pharmacological and toxicological tests or the results of clinical trials if he can demonstrate…either that the medicinal product is **'substantially similar'** …or that the medicinal product is essentially similar to a product which has been authorized within the Community…**for not less than six years and is marketed in the Member State for which the application is made; this period shall be extended to 10 years in the case of high-technology medicinal products** …furthermore, **a Member State may also extend this period to 10 years by a single decision** covering all the products marketed on its territory where it considers this necessary in the interests of public health." Art. 4.8.a.iii

- Case law: *Generics* (1998) and *Novartis* (2004) cases in European Court of Justice

Legal Landmarks: EU Exclusivity Law

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- 1993 Regulation establishing the European Agency for the Evaluation of Medicinal Products (EMEA) provided:
  - 10 years of DATA PROTECTION for centrally authorized products
  - This continued the 10-year period for high-tech products approved through an earlier expert committee ("ex-concertation")
  - All biotech products are required to go through the "centralized authorization procedure", assessed by EMEA and then authorized by a European Commission Decision

- Orphan Medicinal Products Regulation141/2000: MARKET PROTECTION
  - The first product to obtain an approval in the EU blocks for 10 years any existing marketing authorization for the "same therapeutic indication" in respect of a "similar medicinal product."

WTO EU v. Canada “Bolar” case

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2000

- In 2000, the WTO issued a panel report in EU vs. Canada regarding “Bolar plus” law allowing not only regulatory testing in Canada but also stockpiling.
- The WTO Panel concluded that Canada's law is a "limited exception" within the meaning of TRIPS Article 30 only “[a]s long as the exception is confined to conduct needed to comply with the requirements of the regulatory approval process.”
- However, the Canadian law went too far in allowing stockpiling.
- During the patent life of the pioneer drug, the generic competitor is allowed to make the drug *only* for regulatory review purposes.
- Stockpiling is not allowed. Selling drugs made and stockpiled during patent term also is not allowed.
- Afterward: Canada eliminated stockpiling provision AND European Commission decided to propose its own Bolar testing provision in 2001draft legislation.

For Reference

Legal Landmarks: EU Exclusivity Law

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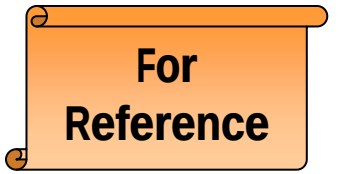
2001

- November 2001 recodification: Community Code on Medicinal Products 2001/83 codified a huge number of post-1965 EU pharma laws (including 1987 law)
- Earlier that year, in July 2001, Pharmaceutical Review Legislation was proposed by the European Commission:
  - Proposed Bolar provision
  - Proposed harmonization of exclusivity periods in all EU authorizations to 10 + 1—the +1 for a new indication



Landmarks: Biosimilars

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2003

- 2003/63:New Annex 1 to Directive 2001/83 (ICH Common Technical Document; different requirements for biologics, scaled down for similar products)
- 2003: EMEA Guidance documents on comparability: EMEA encompasses “inter-company-comparability” in addition to the “intra-company-comparability” encompassed by FDA guidance and ICH Q5A
- 2003: Favorable opinion by EMEA Committee on Proprietary Medicinal Products on Sandoz Omnitrope; Commission did not grant authorization due to lack of legal basis

For Reference

Legal Landmarks: EU Exclusivity Law

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2004

- March 31, 2004 Action completed on Pharmaceutical Review including:
- 2004 Amendment Community Code on Medicinal Products Directive 2001/83 with
  - harmonized exclusivity period of 8+2+1 for national authorizations
  - Bolar testing provision
  - definition of “similar biological medicinal products”
- 2004 EMEA Regulation replacing 1993 regulation: exclusivity in Article 14.11 is 8+2+1 post2005
- Notes: 10 new Member States were scheduled to join the EU on May 1, 2004. Old EU Member States and major stakeholders wanted the legislation concluded prior to accession
- All 10 of the new States favored 6 years over 10 years; some requested derogations (denied).
- Achieving a harmonized exclusivity period--eliminating the choice of 6 years versus 10 years—was a major priority for industry, although the 10+1 period would have been preferred.
- During legislative process, Commission resisted having a disparity in the length of protection in centralized approvals as compared to national approvals.
- Commission also refused to insert in the EMEA Regulation a cross reference to the Community Code provision on 8+2+1--so EMEA Article 14.11 is a self-contained, standalone provision.

Other Exclusivity or Related Provisions

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- **New combinations of old medicinal products** are treated as new products eligible for 8+2+1 years exclusivity (Art. 10b Community Code; Notice to Applicants Volume 2A Procedures for Marketing Authorization, Section 5.5)
- 1 year data exclusivity for a **new indication for a well-established substance**
- 1 year data exclusivity for **change of the classificatio**n from Rx to OTC or vice versa
- **Orphan** drugs 10 years market exclusivity remains unchanged. Product may have 10 years market exclusivity for orphan indications and 8+2+1 for others.
- New **pediatric** regulation: marketing authorization holder can extend supplementary protection certificate from 5 years to 5.5 years
  - OR use the +1 extension of exclusivity (not both)
  - OR add +2 years to orphan drug market exclusivity for total of 12 years
- Also new **Pediatric Use Marketing Authorization (PUMA)** for off-patent products offers 8+2 exclusivity period
- Since 1992, there has been the possibility of a 5-year **Supplementary Protection Certificate** for a patent in force, covering an authorized pharmaceutical (somewhat analogous to U.S. patent term restoration). This potential 20+5 patent/SPC period runs separately from regulatory exclusivity.

EU exclusivity periods are in transition

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- From 1987 until October 30, 2005, EU Member States had a choice whether to implement 6 years of data protection or 10 years.
  - 10 years: Belgium, France, Germany, Italy, Luxembourg, The Netherlands, Sweden and the UK
  - 6 years: Austria, Denmark, Finland, Greece, Ireland, Portugal, Spain and all the new Member States who joined EU in 2004 (Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, and Slovenia); also Iceland and Norway (linked to the EU by European Economic Area treaty)
- The old "10/6" system continues to govern all applications submitted to Member State agencies prior to October 30, 2005.
- The old 10 year system continues to govern all applications to the EMEA submitted prior to November 20, 2005, under the centralized system.
- **Therefore, the old exclusivity system will continue to be significant for a long time, until late 2011 in the Member States with 6 years, until late 2015 for other Member States and for EMEA-assessed authorizations.**

Exclusivity:

New Indications
Next Generation Products

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Legal provisions on improvements

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- All biotech biologicals, including biosimilars, go through the centralized EMEA route. Therefore the exclusivity provision for centralized products is relevant.
- Art. 14.11 of the EMEA Regulation:
- Without prejudice to intellectual property law, **medicinal products authorized under the EMEA Regulation "shall benefit from an eight-year period of data protection and a ten- year period of marketing protection,** in which connection the latter period shall be extended to a **maximum of 11 years** if, during the first 8 of the 10 years, the marketing authorization holder obtains an authorization of one or more new therapeutic indications which are held to bring a significant clinical benefit in comparison with existing therapies.
- It would appear that every medicinal product that enters the EU market via the EMEA centralized procedure should receive a full 8+2+1 period. On the face of this provision, any medicinal product authorized under the EMEA Regulation "shall" be eligible for 8+2+1.

Applicants wishing to market their own versions of biotech biologics already on the market could, by submitting full applications, enjoy the benefits of Article 14.11.

This does not appear to be possible for applicants that use the biosimilar route.

For generic products (and non-biotech biosimilars) authorized by Member State agencies

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- Art. 10(1),Community Code on Medicinal Products: Without prejudice to IP, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the product is a generic of a reference medicinal product which is or has been authorized for not less than 8 years in a Member State or in the Community.
- A generic authorized under this provision shall not be placed on the market until 10 years have elapsed from the initial authorization of the reference product.
- As with centrally authorized products assessed by the EMEA, an 11th year is available.

“Global marketing authorization”

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- There is debate as to whether a legal construct—”global marketing authorization”--in the 2004 amendment to the Community Code on Medicinal Products (new Article 6(1)) will apply to biosimilars authorized through the centralized EMEA process.
- “When **a medicinal product** has been granted an initial marketing authorization…, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorization …or be included in the initial marketing authorization. All these marketing authorizations shall be considered as belonging to the same global marketing authorization, in particular for the purpose of the application of Article 10(1).
- Note: European Commission guidance states that applications from different marketing authorization holders are not treated as being under the same global marketing authorization.

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* Article 10(1) is the generics provision that includes the 8+2+1 provision. Article 6.1 was intended to codify case law that arose from generic applications under the previous EU pharma laws (Generics case).

“Global marketing authorization”

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- The term “a medicinal product” in the provision on “global marketing authorization” is a key term.
- Changes that are treated as “line extensions” of the origination authorization (other than the indication +1) do not entitle the marketing authorization holder to get a new exclusivity period.
- However, where a 2nd generation product is a different product—e.g., a pegylated version of an older biotech product—the EMEA has treated these products as distinctive products and thus not the same “medicinal product.” Therefore, the concept of “global marketing authorization” should not stand in the way of a new exclusivity period for the 2nd product.
- However, it should be noted that there is uncertainty on this point due to case law interpreting the 1987 Directive (Novartis case).

Case Law: Generics Case

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- The “global marketing authorization” concept was meant to codify case law.
- GENERICS European Court of Justice (ECJ) Case C-368/96 (1998):
- Do additional data, which allow the registration of an improved product that is <u>essentially similar</u> to the reference product, benefit from Data Exclusivity?
- No.

a) 10/6 years after the first marketing authorization of the original product, generic products that are essentially similar can benefit from any improvement (new indications, doses etc.), registered by the innovator. Data related to the improvement do not benefit from a protection on their own.

b) Set forth the criteria for essential similarity: same active “principle;” same pharmaceutical form ; bioequivalence.

- Note: case was under 1987 Directive; concerned a Member State authorization; did not involve a biosimilar.

Case law: Novartis case

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- Do additional data, which allow the registration of an improved product that is not essentially similar to the reference product, benefit from data exclusivity?

  NOVARTIS / SANGSTAT ECJ Case C-106/01 (2004): No protection

- Is a full dossier required for the registration of a second-entry product that is not essentially similar to the reference product? Or are bridging data sufficient?
- Products that are not bioequivalent are not essentially similar.
- After the expiry of the Data Exclusivity term, a second-entry product that is not bioequivalent to the reference product, due to the fact that it is administered by different route or in different doses, could be approved on the basis of bridging data.
- Broad definition of the concept of pharmaceutical form.
- Note: case was under 1987 Directive; concerned a Member State authorization; did not concern a biosimilar.

EU exclusivity:

New Indications

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Guidance on 11th year in 8+2+1

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- It is too soon for experience with this provision.
- However, the European Commission has issued guidance, Nov. 2007, applies to both centrally authorized products and products authorized by Member States
- Guidance takes a broad view of significant benefit:
- New target disease, different stages or severity of disease, extended population for same disease
- Change from 1st line to 2nd line treatment or vice versa or from combination therapy to monotherapy
- Change from treatment to prevention or vice versa
- Change from short-term to maintenance treatment
- Improved safety, efficacy, contribution to patient care
- Applicant must justify 11th year, address existing therapy

Interchangeability

How this is handled in the EU

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EMEA CHMP Guideline

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- "*It should be recognised that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established.*"

EMEA CHMP Guideline on Similar Biological Medicinal Products, CHMP/437/04, 30 Oct. 2005, p. 4

Interchangeability - EMEA View

- *"It is not possible we would guarantee a biosimilar is interchangeable (with its originator). Substitution is a national competency and needs to be discussed at the national level"*

EMEA Executive Director Thomas Lönngren, 21 July 2006

- EMEA/74562/2006, 19 April 2007

  "Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional."

Views of former chair of working party, Dr. P. Kurki

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- Substitution is a national decision in EU
- Generic substitution is not harmonised
- Evidence-based guidance may not be possible
- Decision to substitute can be seen from an individual and public health point of view
- Substitution is a result of a mixture of ethical, political, economical, and scientific considerations

Thus:

EU-wide *or* local guidance?
Regulatory agencies *or* learned societies/hospitals?

New EU pharmacovigilance guideline advises inclusion of brand-specific information in adverse event reports

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September 2008, Volume 9A Rules for Medicinal Products on Pharmacovigilance, at 57, 114.:

- "For adverse reactions relating to biological products, the definite identification of the product with regard to its manufacturing is of particular importance. Therefore, Competent Authorities [1] should give advice to reporters[2] to provide the name[3] of the medicinal product and the batch number and should follow-up the reports when this information is missing."
- This advice contemplates that the doctor has prescribed by brand name and there is no possible substitution by pharmacist OR, if substitution is allowed, someone is prepared to go back and check dispensing records in the pharmacy or hospital and find an accurate record of what was actually dispensed to the patient.
- This is just one part of substantial post-marketing pharmacovigilance responsibilities.

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[1] i.e., national drug regulatory agencies.

[2] those who report adverse reactions, generally the market authorization holder or health care professionals.

[3] "The name, which may be either an invented name ["brand name"] not liable to confusion with the common name [INN or "generic name"], or a common or scientific name accompanied by a trade mark or the name of the marketing authorization holder." Art 1(20), Community Code

EU countries forbidding substitution-1

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- **Austria:** Physicians are obliged to prescribe by brand name
- **Czech Republic:** Physicians are obliged to prescribe by brand name
- **Denmark:** Official guidelines against substitution.
- **Finland:** By law, no injectable drug may be automatically substituted.
- **France:** law prohibits the automatic substitution of one biological medicine for another, without the consent of the treating physician (reason given: innovator biotech products and follow-on medicines are not identical).
- **Germany:** Since biosimilars are not generics, they are not automatically substitutable.
- **Greece:** Physicians are obliged to prescribe by brand name.
- **Hungary:** Since biosimilars are not generics they are not automatically substitutable.
- **Italy:** The Italian Medicines Agency (AIFA) recommends, for clinical reasons, that no substitution of these products take place

EU countries forbidding substitution

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- **The Netherlands:** The Royal Society of Pharmacists has issued guidance against automatic substitution of biologics.
- **Norway:** The Medicines Agency has stated that “biosimilars” are complex products and should not be substituted.
- **Slovakia:** An official list sets forth products which cannot be substituted;list includes many biotech medicines (e.g. epoetins, Factor VII, GCSF, HGH, insulin).
- **Slovenia:** A law has been adopted that prohibits substitution of biologics.
- **Spain:** A recent amendment to the law includes all biotech medicines on a list of products that cannot be automatically substituted.
- **Sweden:** Regulatory authorities have informed the pharmaceutical industry in writing that biologics are not to be substituted automatically.
- **UK:** The UK Medicines and Healthcare products Regulatory Agency (MHRA) has stated that biologics should be prescribed by brand name to ensure that automatic substitution of a biosimilar does not occur when the medicine is dispensed by the pharmacist.

Reminder: U.S. exclusivities

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- Hatch-Waxman
  - New molecular entity - 5 year data exclusivity
  - New use - 3 year
    - applications
    - supplements
  - 1st filed Abbreviated New Drug Application - 180 day marketing
- Orphan Drug Exclusivity - 7 years market exclusivity
- Pediatric Exclusivity

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