

Generic Medicines: Understanding the Legal Framework in the EU, US and Canada

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Products for Local Action

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Overview

- I. Brief Historical Context on Pathways to Generic Approvals
- II. Understanding European Regulatory Definitions
- III. European Approval Processes
- IV. Other Important Considerations
- V. Conclusions

Disclaimer: this presentation is not meant to represent legal advice

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2

I. Brief Historical Context on Pathways to Generic Approvals

- European Union
- Canada
- United States

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European Union

- > Prior to 1995, drug companies had been encumbered by different licensing and authorization process in each member state.
 - Fractured process became increasingly untenable as European integration progressed.
- > European Medicines Agency (EMA) – Created in 1995 as a supranational licensing and authorization body.
 - EMA processes still allow for some member state control over drug authorization.
 - Name
 - First was named in 1993 by EC Regulation No. 2309/93 as the European Agency for the Evaluation of Medicinal Products (abbreviated to European Medicines Evaluation Agency, or EMEA)
 - Renamed in 2004 by EC Regulation No. 726/2004 as the European Medicines Agency, but retained the acronym EMEA
 - At the end of 2009, changed the acronym to EMA

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4

Canada

- > Canada
 - By 1966, Canada had established a universal healthcare program for hospital and physician care.
 - Universal program is decentralized and relies on provincial governments, which must meet certain conditions to qualify for federal funding.
 - Health Canada – Federal department in charge of regulating the pharmaceutical industry, including drug licensing and authorization.

United States

- > 21 U.S.C. § 355 – Statute dealing with new drug applications.
- > *Roche Prods. v. Bolar Pharm.*, 733 F.2d 858 (Fed. Cir. 1984) – Held that a generic manufacturer’s use of a patented product to perform tests necessary to obtain generic approval once the patent had expired qualified as patent infringement.
- > Hatch-Waxman Act (21 U.S.C. § 355(j)) – Overturned *Bolar*, and allowed generic manufacturers to use competitors’ patents for ANDA (Abbreviated New Drug Application) testing purposes, even if original manufacturer was still in exclusive period.
 - “Experimental use” exception

II. Understanding European Regulatory Definitions Relating to Generic Medicines

- Overview of Relevant Definitions
- Comparison with Similar US and Canadian Definitions

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European Regulatory Definitions Relating to Generic Medicines

> Definitions:

- **Generic Medicinal Product:** “[A] medicinal product which has (1) the same qualitative and quantitative composition in active substances and (2) the same pharmaceutical form as the reference medicinal product, and (3) whose **bioequivalence** with the reference medicinal product has been demonstrated by appropriate bioavailability studies.” -- *Article 10(2)(b) of Directive 2001/83/EC*
 - “Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.”

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8

EU Definitions (continued)

> Bioequivalence:

- “Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure **comparable *in vivo* performance, i.e. similarity in terms of safety and efficacy.**”

Committee for Proprietary Medicinal Products, *GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE*, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** (2010)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

EU Definitions (cont'd)

- > Demonstration of bioequivalence may be required for:
 - Generic applications [Dir. 2001/83/EC as amended*, Art. 10 (1)]
 - Full applications [*id.*, Art. 8(3)]
 - Fixed combinations [*id.*, Art. 10b]
 - Hybrid applications [*id.*, Art. 10(3)]
 - Extension and variation applications [Commission Regulations (EC) No 1084/2003** and 1085/2003***]

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 ***http://eur-lex.europa.eu/pri/en/oj/dat/2003/l_159/l_15920030627en0240045.pdf

US Federal Food, Drug and Cosmetics Act

SEC. 505. [21 USC §355]

- > 505(b) New Drugs
- > 505(b)(2) – “Paper” NDAs (relying on some studies not conducted by applicant)
- > 505(j)(2) – Abbreviated New Drug Applications:
 - Same active ingredient(s)*
 - Same route of administration*, dosage form*, and strength*
 - Bioequivalent to the RLD
 - Same labeling*

*Petitions for deviations are possible

US Definitions

- > **Bioequivalence:** “[T]he absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents* or pharmaceutical alternatives becomes **available at the site of drug action** when administered at the same molar dose under similar conditions in an appropriately designed study.”-- 21 C.F.R. § 320.1(e) (2009)
- > “Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents* or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, and are considered medically insignificant for the particular drug product studied.” -- 21 C.F.R. § 320.23(b) (2009)

* have the same active ingredient(s), dosage form, route of administration and strength

US Approach for OIPs

- > Expected Elements of Bioequivalence for Orally Inhaled Drugs:
 - *Formulations* of the drug are qualitatively and quantitatively the same (within 5% of RLD)
 - Equivalent systemic exposure when given at a relevant dose that gives measurable systemic levels
 - Comparative in vitro performance based on a variety of tests
 - Local delivery bioequivalence based on pharmacodynamic measurements, preferably using clinically relevant endpoints

Canadian Definitions

- > **Subsequent entry drugs ("generic drugs")**
 - Require Abbreviated New Drug Submission (ANDS) pursuant to section C.08.002.1 of the Food and Drug Regulations. Must be bioequivalent to a [Canadian Reference Product](#) (pursuant to Section C.08.004 (4)), which will be stated on the Notice of Compliance.
 - (a) the new drug is the pharmaceutical equivalent of the Canadian reference product;
 - (b) the new drug is bioequivalent with the Canadian reference product, based on the pharmaceutical and, where the Minister considers it necessary, bioavailability characteristics;
 - (c) the route of administration of the new drug is the same as that of the Canadian reference product; and
 - (d) the conditions of use for the new drug fall within the conditions of use for the Canadian reference product.
 - **Pharmaceutical Equivalent:** "[A] new drug that, in comparison with another drug, contains identical amounts of the identical medicinal ingredients, in comparable dosage forms, but that does not necessarily contain the same non-medicinal ingredients." -- Section C.08.001.1 of the Food and Drug Regulations

Comparison of Definitions Relating to Generic Medicines

- > EU, US and Canada all require bioequivalence
 - Common goal: Determine the effectiveness of the proposed generic's active ingredient[s] at the primary site of action.
- > Requirements for chemical "sameness" of the active and non-active ingredients vary among regions
- > Dosage form/pharmaceutical form and conditions/route of administration need to be the same
- > Requirements for device in a generic OIP are not legislated
 - Requirements may be clarified through guidelines
 - Same labeling required in the US
- > Disparate EU member state interpretations of generic drugs and bioequivalence can cause inconsistent national approvals.
 - Arbitration processes are available under the Mutual Recognition and Decentralized Procedures.

III. European Generic Medicines Approval Processes

- Overview of European Approval Processes
 - Data Exclusivity
 - Comparison with US and Canada

EU Authorization

- > Directive 2001/83/EC as amended by Directive 2004/27/EC.
 - “[A]pplicant shall not be required to provide the results of pre-clinical tests and clinical trials if he can demonstrate that the medicinal product is a generic medicinal product of a reference medicinal product which is or has been authorized under Art. 6.” – Art. 10(1)
- > Methods:
 - Centralized Authorization
 - Mutual Recognition
 - Decentralized Authorization

Centralized Authorization

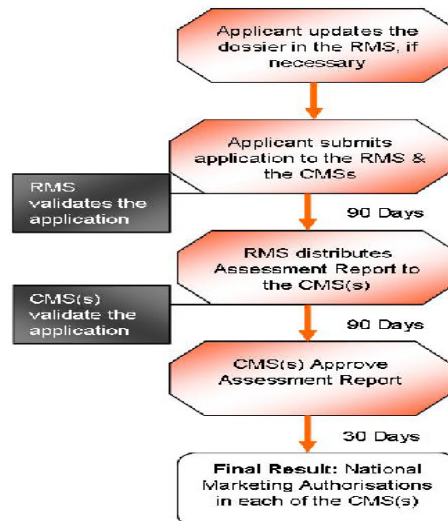
- > Results in a single authorization valid in EU, Norway, Iceland and Liechtenstein.
- > Application evaluated by an assigned Rapporteur.
- > EMA opinion issued within 210 days, and submitted to European Commission for final approval.
- > Centralized process is compulsory for:
 - Medicines derived from biotechnology processes, such as genetic engineering
 - Medicines intended for the treatment of HIV/Aids, cancer, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions
 - Medicines officially designated 'orphan medicines' (medicines used for rare diseases)

Mutual Recognition Procedure

- > Used when marketing authorization has been granted in one EU member country (Reference Member State), but not others (Concerned Member States).
- > Applicant submits identical dossier to all EU member states in which it wants authorization, including information in Articles 8, 10, 10a, 10b, 10c and 11 of Directive 2001/83/EC.
- > RMS issues a report to other states on its own findings.
- > Other states have 90 days in which to accept and grant authorization.

Figure 1: Mutual Recognition Procedure

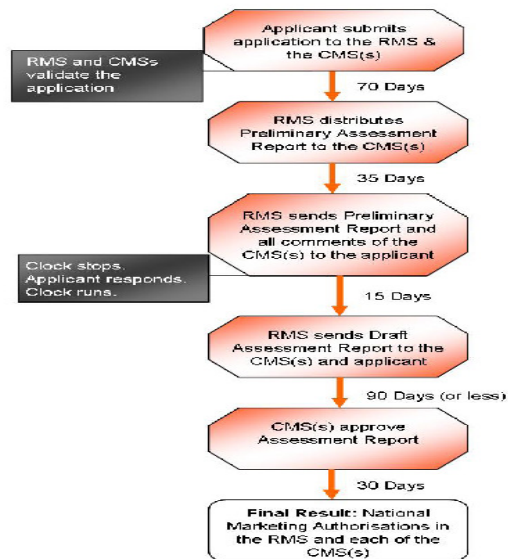
Marketing approval already granted by an EU Member State, now referred to as the Reference Member State (RMS)



Decentralized Procedure

- > Used when no EU member state has yet granted authorization for the drug.
- > Applicant submits application to state in which it wants original authorization (Reference Member State), and all other states.
- > RMS conducts initial assessment and sends assessment to other states for their comments. Comments from RMS and other states are returned to applicant.
- > Applicant responds to comments as necessary.
- > RMS then grants authorization and sends Assessment Report to other states.
- > Other states then grant authorization.

Figure 2: Decentralized Procedure



EU Community Referral

- > **Art. 29 of Directive 2001/83/EC – Community Referral**
 - If a dispute arises over the validity of a country's medical authorization in the Mutual Recognition or Decentralized Procedure, the problem is sent to the Coordination Group for Mutual Recognition and Decentralized Procedure for Human Medical Products (CMDh) of EMA to conduct negotiation on the issue.
 - If negotiation fails, EMA will arbitrate.
 - EMA committee will issue an opinion with 60 days (longer for certain applications). – Art. 32(1)
 - Committee can solicit experts, testimony, and explanations from the applicant and Concerned Member State. – Art. 32(2) & (3)
 - If authorization is denied to the applicant, it may request reexamination of opinion.
 - Final EMA opinion is forwarded to European Commission for final binding order either granting or revoking authorization in all member states.

European Generic Eligibility

- > EMEA Procedural Advice for Users of the Centralised Procedure for Generic/Hybrid Applications, EMEA/CHMP/225411/2006 (2008)
- > Centralized Procedure:
 - Automatic eligibility for the potential generics of medicinal products already approved under the Centralized Procedure. -- Art. 3(3) of Regulation (EC) No 726/2004
 - Eligibility for the potential generics of medicinal products approved under Mutual Recognition or Decentralized Procedure if applicant shows:
 - Significant therapeutic, scientific or technical innovation; or
 - Community authorization is in the interest of EU patients
 - Art. 3(2) of Regulation (EC) No 726/2004
- > Mutual Recognition or Decentralized Procedure: Eligibility based on particular national rules and regulations.

European Data Exclusivity

- > Since November 2005: 8+2+1 years
 - 8 years – Applications for generic drugs cannot be submitted.
 - 10 years (8 + 2) – Generic may not be sold in EU until 10 years have elapsed from the granting of the initial marketing authorization.
 - Further one year extension if original authorization holder obtains additional authorization for a new therapeutic use of the product resulting in clinical benefits.
- > Prior to Nov. 2005 (Directive 2001/83/EC): either 6 or 10 years
 - 6 years – in Austria, Denmark, Finland, Greece, Ireland, Portugal, Spain, Norway and Iceland
 - 10 years – in Belgium, Germany, France, Italy, Luxembourg, the Netherlands, Sweden, the UK and for originator products approved through the Centralised Procedure.

US Generic Medicines Authorization Process

- > Hatch-Waxman Act § 505(j) (21 U.S.C. § 355 (2006))
- > ANDA – Approval can be granted to generic drugs if there is sufficient bioequivalence data to an existing Reference Listed Drug
- > Generally, generic need not be identical to RLD; some differences are allowed, so long as the rate and extent by which the active ingredient reaches the patient's primary site of action.
- > If original drug manufacturer claims a patent infringement by the generic manufacturer, ANDA approval can be delayed up to 30 months.

US Data Exclusivity

- > 5 year pioneer drug exclusivity
 - 35 U.S.C. § 271(e)(1) – Experimental Use Exception – Allows companies to test patented drugs for bioequivalence within the 5 year exclusive window without infringing on the patent. Thus, generic applications can be prepared early and submitted on the day the window expires.
- > ANDA generics receive only 180 day exclusivity against other generics of the same original drug.

Canadian Authorization Process

- > Section C.08.002.1 of *Food and Drug Regulations*
 - A manufacturer of a new drug may file an abbreviated new drug submission for the new drug where, in comparison with a Canadian reference product:
 - The new drug is the pharmaceutical equivalent of the Canadian reference product;
 - The new drug is bioequivalent with the Canadian reference product, based on the pharmaceutical and, where the Minister considers it necessary, bioavailability characteristics;
 - The route of administration of the new drug is the same as that of the Canadian reference product; and
 - The conditions of use for the new drug fall within the conditions of use for the Canadian reference product.

Canadian Authorization (cont'd)

- Section C.08.002.1 of *Food and Drug Regulations*
 - An abbreviated new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following:
 - Basic description of ingredients used and tests performed in accordance with paragraphs C.08.002(2)(a) to (f) and (j) to (l);
 - Information identifying the Canadian reference product used in any comparative studies conducted in connection with the submission;
 - Evidence from the comparative studies conducted in connection with the submission that the new drug is
 - » The pharmaceutical equivalent of the Canadian reference product, and
 - » Where the Minister considers it necessary on the basis of the pharmaceutical and, where applicable, bioavailability characteristics of the new drug, bioequivalent with the Canadian reference product as demonstrated using bioavailability studies, pharmacodynamic studies or clinical studies;

Canadian Data Exclusivity

- Products first authorized prior to June 17, 2006:
 - 5 year exclusivity
- Products first authorized after June 17, 2006:
 - 6 years – Applications for generics cannot be submitted.
 - 8 years (6 + 2) – No-marketing period during which a notice of compliance will not be granted to manufacturer.
 - Further 6 months of data exclusivity can be added for for active ingredients that have been the subject of pediatric studies designed and conducted with the purpose of increasing knowledge about the use of the drug.

Comparison Overview

- > EU tripartite model less consistent than centralized US and Canadian systems.
- > Vastly different timeframes for data exclusivity in drug authorizations.
 - US – 5 years
 - Canada – 8+ years
 - EU – 10+ years

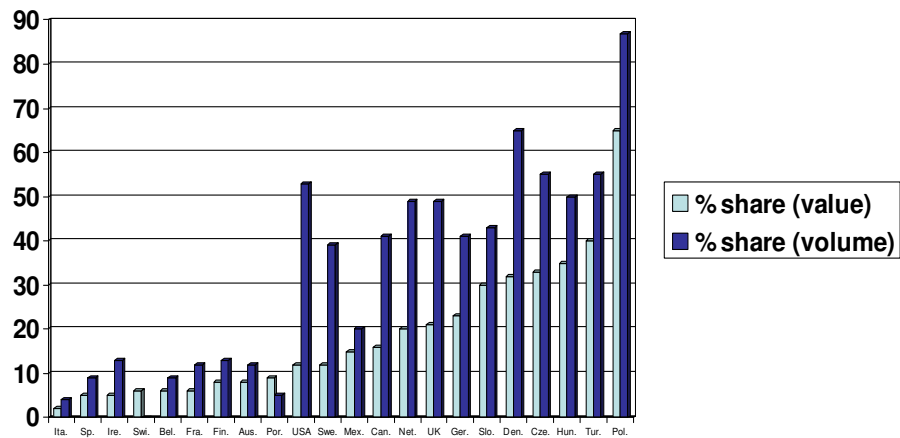
IV. Other Important Considerations

- Market Share
- The Impact of Price Controls

Market Share

- > Generic drug market shares vary by country according to a number of factors
 - Legal regimes, particularly patent protections
 - Regulatory rules
 - Ease of generic drug authorization
 - Ease of generic manufacturers' barriers to entry

Market Share – 2004



OECD Health Policy Studies, *Pharmaceutical Pricing Policies in a Global Market* (2008)

Price Controls

- > EU – Individual states control via single-payer health systems.
 - EMA has no centralized pricing control mechanism.
- > US – None
 - Generic versions tend to be priced 30-50% lower than branded drugs.
- > Canada – Price controls on original drugs; none on generics.
 - Patented Medicine Prices Review Board (PMPRB) – Charged with regulating prices charged by manufacturers to ensure they do not become “excessive.”
 - No central control of generic pricing, but generic drugs are often “structurally” set by provincial governments’ via their single-payer buying power.

Price Controls (cont'd)

- > Generally, branded drugs enjoy a first-mover advantage in the market; they benefit from brand loyalty and a marketing-induced image of being “superior” to generic drugs.
- > Generic manufacturers rarely advertise because of a desire to keep costs low, and due to free-rider problems with other generic manufacturers.
- > Effects on price (OECD Health Policy Studies, *Pharmaceutical Pricing Policies in a Global Market* (2008)):
 - US
 - Generics: 35% above OECD average
 - Originals: 25% above OECD average
 - Canada
 - Generics: 65% above OECD average
 - Originals: 20% above OECD average

Thank You!

For Further Information

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