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Biosimilar Medicinal Products A Reality in Europe

The Bolar Provision : a Safe Harbour in Europe?

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Purpose of Bolar

Issue

- No regulation for the use of a reference product for regulatory purposes, such as bioequivalence testing (generics) or comparability studies (biosimilars)
- Patent infringement
- No clear and consistent legal application of the national research exemption, leading to diverging and inconsistent judgements
- Preparation of abridged applications in Central/Eastern Europe, Iceland or third countries

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(Research) Exemption in the US

Merck v. Integra Lifesciences

Merck v. Integra Lifesciences

Overview of US experimental use exemptions

- Common law
  - *Whittemore v. Cutter* [1813]:

    "*It could never have been the intention of the legislature to punish a man who [dealt with the patented invention] for philosophical experiments, or for the purpose of ascertaining the sufficiency of the [invention] to produce its described effect*"
  - *Roche Products v Bolar Pharmaceutical* [1984] (narrow interpretation):

    Studies on a patented pharmaceutical a few months prior to patent expiry for the purposes obtaining regulatory approval was not experimental use under the *Whittemore v. Cutter* exemption. Bolar's activities were regarded as solely for business reasons and not for "*amusement, to satisfy idle curiosity or for strictly philosophical inquiry*"

Merck v. Integra Lifesciences

Overview of US experimental use exemptions

- Statutory exemption
  - Hatch-Waxman Act 1984
  - *Bolar exemption :* 35 U.S.C. § 271(e)(1) : limited industry specific experimental use exemption for testing drugs and medical devices for purposes reasonably related to regulatory data gathering . Exempted acts:

    "*make, use, offer, or sell within the US or import into the US a patented invention solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs, (…)*
  - Ambiguous language, resulting in disputes such as Merck v. Integra Lifesciences

Merck v. Integra Lifesciences

Procedural Background

- Integra owns 5 patents related to "RGD peptides."
- Merck tested patented RGD peptides, *in vitro* and *in vivo,* through its efforts to develop "integrin antagonists as angiogenesis inhibitors." Merck conducted experiments to develop a new drug and not for gathering information!
- Integra alleged that Merck's use of the patented RGD peptides in preclinical testing constituted patent infringement.
- Merck contended that its use of the RGD peptides was protected under the safe harbor provision of 35 U.S.C. §271(e)(1).

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Merck v. Integra Lifesciences

Issue

- Whether uses of patented inventions in preclinical research, the results of which are not ultimately included in a submission to the Food and Drug Administration (FDA), are exempted from infringement by 35 U. S. C. §271(e)(1).
- Could the Bolar exemption apply to the upstream development and identification of new drugs that will in turn be subject to FDA approval? (Experiments → approval v Experiments → drug → approval)

Section 271(e)(1)

There is no patent infringement for use of a patented invention "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs."

Merck v. Integra Lifesciences

Federal Circuit (2003): Confirmation of the first instance decision : the safe harbor of § 271(e)(1) does not protect Merck's use of the patented RGD Peptides.

- The Merck "*experiments did not supply information for submission to the [FDA], but instead identified the best drug candidate to be subject to future clinical testing under the FDA processes*."
- "[*T]he exemption does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process*."
- Extending the exemption to new drug development would be contrary to the purpose and language of the Hatch-Waxman Act

Merck v. Integra Lifesciences

Supreme Court : Reversed (13 June 2005)

- The "*use of patented compounds in preclinical studies is protected under §271(e)(1) as long as there is a reasonable basis for believing that the experiments will produce the types of information that are relevant to a [new drug application*]."
- §271(e)(1) is broad enough to encompass " *all uses of patented inventions that are reasonably related to the development and submission of any information under the FDCA*"
- This includes:

  * preclinical data pertaining to drug safety

  * preclinical studies related to a drug's efficacy, mechanism of action, pharmacokinetics and pharmacology

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Merck v. Integra Lifesciences

Supreme Court Decision

- **Phase of Research Irrelevant:** "[*T*]*here is simply no room in the statute for excluding certain information from the exemption on the basis of the phase of research in which it is developed or the particular submission in which it could be included*."
- **Identified Pharmaceutical Candidate Not Required:** The exemption is not limited to situations in which a pharmaceutical candidate has already been identified and is being tested in order to obtain FDA approval. It also applies to developing such candidate.
- **Application Need Not Be Filed:** Because "*scientific testing is a process of trial and error*", the exemption extends to research for which a new drug application is not ultimately filed.
- **No Exemption Where Reasonable Belief Lacking:** Basic scientific research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce, is surely not reasonably related to the development and submission of information to the FDA.

Merck v. Integra Lifesciences

Conclusion:

- Landmark U.S. Supreme Court decision
- Broad interpretation of the research exemption
- Pharmaceutical companies now have more freedom to research and experiment with patented compounds
- Preclinical studies of patented compounds may be exempted from patent infringement under 35 U.S.C. § 271(e)(1)
  - Exemption requires a reasonable basis to believe that the studies will produce information relevant to an application to be filed with the Food and Drug Administration ("FDA").
  - It does not cover other research or research outside the industry sector

Merck v. Integra Lifesciences

Conclusion:

- The Supreme Court refused to address the question whether the use of patented "research tools" in preclinical experiments are exempted
  - Patents relating to technology aimed at discovering new drugs or new drug candidates (e.g. screening methods).
  - Valuable in basic research and research in drug development
  - Open discussion and cause for concern for biotech companies
  - General US view : the use of a research tool is different from the study of the tool itself. Hence, such a tool does not fall under the research exemption

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(Research) Exemptions in Europe: the Bolar Provision

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Research Exemptions in Europe

- Traditional exemptions in (national) patent law
  - e.g. research exemption for experimental purposes relating to the subject matter of the invention
  - Inspired by the Community Patent Convention
  - No clear and consistent legal application of 'experimental use' provisions regarding clinical trials:

    * UK : *Monsanto v Stauffer*

    * Germany : *Clinical Trials I* and *II*

    * France : *Wellcome v Parexel*; *Parienti v Peugeot ; AJC Pharma Expanpharm v Servier*

    * Italy : statutory provision ; *Squibb & Sons v Testaguzza*

    * The Netherlands : *ICI v Medicopharma* ; *ARS v Organon*

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Research Exemptions in Europe

- Belgium:

  * Clinical trials : *Fabricom v ABB* , legal doctrine

  * Filing of samples

  ***"Attendu qu'il n'apparaît pas prima facie que l'introduction d'une demande d'enregistrement pour un produit générique, sans jonction au dossier d'échantillions du produit, et les autres actes préparatoires à la commercialisation du médicament générique doivent être assimilés à une utilisation ou une mise dans le commerce du médicament objet du brevet: que pour qu'il y ait mise dans le commerce, il faut que l'objet de l'invention soit mis à la disposition d'un tiers. Que (...) il ne s'agit pas d'actes de contrefaçon mais d'actes préparatoires à un usage licite d'un produit concurrent après l'expiration du brevet* (Brussel 10 November 2000 - *fluoxetine*);**

  * Filing of a request for a MA

  "*il n'est dès lors pas permis, dans le cadre d'une saisie description, d'ordonner la saisie d'une AMM*" (Rb. Brussel 1 april 2003 - *paroxetine*);

  "*De aanvraag van de marktvergunning kan begrepen worden als een eerste handeling van het aanbieden in de zin van artikel 27* (Rb. Brussel 13 mei 2005 - *clarithromycine*);

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Research Exemptions in Europe

– Transposition of the Biotech Directive:

* Article 28 Belgian Patent act : *The exclusive rights deriving from a patent do not extend to acts **on and/or with** the patented invention for scientific purposes (handelingen die op en/of met het voorwerp van de geoctrooieerde uitvinding worden verricht voor wetenschappelijke doeleinden)*

* broader exemption than most other European countries which might be disadvantageous for the research tool industry

* Further than US Supreme court!

* But limited application “for scientific purposes”

* General exemption

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Research Exemptions in Europe

- Patent infringement exemptions in pharmaceutical law: Article 10(6) Directive 2001/83
  - "*Conducting the **necessary studies and trials** with a view to the application of **paragraphs 1, 2, 3 and 4** and the **consequential practical requirements** shall not be regarded as contrary to patent rights as or supplementary protection certificates for medicinal producst*"
  - European "Bolar"-provision
  - General and ambiguous wording – Scope of Bolar-provision

    * *Necessary*? Who will judge this?

    * S*tudies and trials*? Type of studies and trials have been discussed but no list has been agreed upon at EU level

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Research Exemptions in Europe

* *with a view to the application of* ***paragraphs 1, 2, 3 and 4***

  - Generic abridged applications (10.1/10.2), hybrid applications (10.3) and biosimilar applications (10.4). Not for bibliographical applications or applications for new combinations.

  - Limitation to applications in the European Union

  - no exemption for all activities: e.g. use of trial information or production in Europe in support of applications outside the EU ; acts done for export (rejected by the European Commission*)* ; production for trials in support of applications outside the EU;

  - Not applicable to experiments with the aim of proving product yield or a new variant of the patented product?

  - What if the application for a MA fails?

* " *and the consequential practical requirements*" (application for a MA, filing, samples, P&R, production of commercial batches, stockpiling, publications and marketing, taking pre-orders, etc.)

* more narrow then US provision (not for developing new drugs)

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Research Exemptions in Europe

- Implementation in national legislation (due 30 October 2005)
  - UK : implemented (17 October 2005)

* Amendment of section 60(5) of the Patents Acts 1977: *An act which, apart from this subsection, would constitute an infringement of a patent for an invention shall not do so if* (…) *it consists of:*

  (i) an act done in conducting a study, test or trial which is necessary for and conducted with a view to the application of paragraphs 1 to 5 of Article 13 of Directive 2001/82/EC or paragraphs 1 to 5 of Article 10 of Directive 2001/83/EC, or

  (ii) any other act which is required for the purpose of the application of those paragraphs"

* Literal transposition (incorporation by reference)

* MHRA consulting document with view on how the exemption should be construed

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Research Exemptions in Europe

- Implementation in national legislation
  - Due on October 30, 2005
  - Belgium :

* Implemented (May 1, 2006) ; transposition in Medicines Act

* Artikel 6*bis*, §1, laatste lid Geneesmiddelenwet**:**

> *Het uitvoeren van de noodzakelijke studies, testen en proeven met het oog op het voldoen aan de voorwaarden en de modaliteiten bedoeld in de leden 1 tot en met 7 van deze paragraaf en alle daaruit voortvloeiende praktische vereisten worden niet beschouwd als een inbreuk op octrooien of aanvullende beschermingscertificaten* (...)"

- "Studies, testen en proeven" v. "studies and trials"
- Alomosr literal transposition

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Research Exemptions in Europe

- Implementation in national legislation
  - France : no implementation yet

* Proposal to amend Article L.613.5 CPI (IP Code) by introducing a new paragraph d): "*The rights afforded by a patent shall not extend to:*

  (b) acts done for experimental purposes relating to the subject matter of the patented invention;

  (d) the studies and trials necessary in order to obtain a marketing authorisation for a medicinal product in any Member State of the European Community or any Member State of the European Economic Area, as well as any acts necessary for their performance"

* Broad implementation : Not limited to generic applications, not limited to EU (also EEA)

* Proposal to amend article L.5121 of Public Health Code (CSP)

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Research Exemptions in Europe

- Implementation in national legislation
  - The Netherlands : no implementation yet

  * Proposal for a literal implementation into the Medicines Act (Geneesmiddelenwet article 42, § 10) : *"Het uitvoeren van de noodzakelijke studies, tests en proeven met het oog op het toepassen van het vijfde lid onder a, zesde en zevende lid, alsmede van de daaruit voortvloeiende praktische vereisten, worden niet beschouwd als een inbreuk op octrooien of aanvullende beschermingscertificaten"*

  * Literal transposition

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Research Exemptions in Europe

- Implementation in national legislation
  - Germany : implemented and in force as from September 6, 2005

* Article 3 of the Drug Act adding a new paragraph 2b to section 11 of the German patent act:

"The effect of a patent shall not extend to (…)

2. Acts done for experimental purposes relating to the subject matter of the patented invention (…)

2b. Studies and trials and the consequential practical requirements necessary for obtaining an authorisation according to the Drug Law for the marketing in the European Union or an authorisation according to the Drug Law for the marketing in the Member States of the European Union or in third countries"

* Broad implementation : not limited to generics and not to the European Union !

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Research Exemptions in Europe

- Implementation in national legislation
  - Ireland : no implementation yet

* Proposal to amend section 42 of the Patent act by inserting the following subsection:

(g) acts done relating to the subject matter of the relevant patented invention which consist of :

(i) acts done in conducting the studies, tests and trials which are necessary for and are conducted with a view to satisfying the application requirements under Community law for a marketing authorization for a generic medicinal product for human or veterinary use or

(ii) any other act which is required as a consequence of the acts in (i) for the purposes stated in (i)

* Does not cover biosimilars nor hybrid applications!

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Research Exemptions in Europe

- Implementation in national legislation
  - Italy : implemented

* Amendment of the new Industrial Property Code (art. 68 (1) a):

  'Whatever the subject of the invention is, the exclusive right granted by the patent does not extend to:

  a) acts performed privately and for non-commercial purposes, or for experimental purposes even if aimed at obtaining, in any country, an authorization to market a finished dosage form and at accomplishing the consequential practical requirements, including the preparation and the use of the active pharmaceutical ingredients which are strictly necessary

* Not limited to generics, nor to the European Union.

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Research Exemptions in Europe

- Implementation in national legislation
  - Spain : no implementation yet

* Draft amendment to Article 52 (b) Patents Act:

Rights conferred by the patent do not cover (…):

b) actions for experimental purposes in relation to the objective of the patented invention; particularly studies and trials carried out for the authorization of generic medicines and the consequential practical requirements, including the preparation, obtaining and use of the active ingredient for these purposes"

* Not limited to the European Union ; some guidance regarding "consequential practical requirements" (limited view)

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Conclusions

- Some degree of certainty by introducing a Bolar-clause : Europe is a safe harbour where testing can be done
- Again too late and too limited in view of US developments (also applicable for development of new drugs)
- Ambiguous wording and different transposition in national law : ECJ-ruling necessary?
- Continued forum shopping (studies and trials in jurisdiction with the broadest exemption)
- Application of both patent and pharmaceutical law
- Lawyers paradise!