Hoffmann-La Roche - Some Broader Implications

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Overview

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- Italian Proceedings
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Factual Background

The Products Concerned

- Roche's subsidiary Genentech developed two medicines from related active ingredients
  - Avastin (bevacizumab), distributed by Roche
    - Approved in January 2005 for certain oncology indications
    - Included in the list of reimbursable products by AIFA in September 2005
  - Lucentis (ranibizumab), out-licensed to Novartis (Novartis holds 33% stake in Roche)
    - Approved for the treatment of certain vascular eye conditions (including macular degeneration and glaucoma) in January 2007
    - Included in the list of non-reimbursable products by AIFA in May 2007
- Doctors started prescribing Avastin to treat vascular eye conditions, before Lucentis obtained its MA
  - Avastin's active ingredient slows down the growth of new blood vessels
  - Genentech developed Lucentis specifically for the treatment of eye conditions
  - Lucentis was more expensive than Avastin, such that prescription of Avastin continued after Lucentis was placed on the market

Unlicensed Use of Avastin

- AIFA permitted unlicensed use after Lucentis received its MA
  - Under Italian law, unlicensed use of a product may be reimbursed in the absence of an authorised valid therapeutic alternative for the indication
  - AIFA included the use of Avastin for eye conditions in the list of reimbursable products in May 2007
- AIFA included Lucentis in the list of reimbursable products for the treatment of eye conditions in December 2008
  - Reimbursement of unlicensed use of Avastin for eye conditions progressively excluded
- In August 2012, summary of Avastin's characteristics amended to refer to certain side effects associated with its use for eye conditions
- In October 2012, AIFA removed Avastin from the list of reimbursable products for eye conditions

Italian Proceedings

Italian Competition Authority's Decision

- In 2014, the Italian Competition Authority (ICA) found that:
  - Avastin and Lucentis are equivalent in all respects for the treatment of vascular eye conditions
  - Roche and Novartis co-ordinated their strategies to limit unlicensed use of (cheaper) Avastin for vascular eye conditions, to the benefit of Lucentis
    - Arrangement intended to artificially differentiate between the products, using safety concerns about unlicensed use of Avastin: alarmist interpretation of the data, potentially influencing HCPs' prescription behaviour
    - Arrangement also related to disclosure of information to the EMA, exaggerating the perception of the risks to (i) obtain the amendment of the summary of Avastin's characteristics and (ii) send formal communications to HCPs, drawing their attention to these risks
  - Resulted in a shift in demand toward Lucentis and a cost increase for the national health service (€45 million in 2012)
  - The ICA imposed fines totaling €92 million and €90,6 million on Novartis and Roche, respectively

Appeal and Preliminary Reference

- In December 2014, the TAR Lazio dismissed the Parties' appeal
  - Concluded that Novartis and Roche were actual competitors since Lucentis and Avastin (unlicensed) were competing
  - Confirmed ICA's findings of market sharing on the market for ophthalmic drugs for serious vascular eyesight conditions
- Appeal to Italian Council of State (ICS) which referred several questions to the ECJ, including in particular:
  - Whether the relevant product market should be defined autonomously vis-à-vis content of marketing authorisation;
  - Whether a market can contain unlicensed products and products authorised for the same therapeutic indication;
  - Whether it should be established that products have been supplied in accordance with regulatory framework

ECJ Judgment

Assessment of the Relevant Market (1)

- In principle, medicinal products used for the same therapeutic indications fall into same market
  - Products manufactured or sold unlawfully cannot be considered substitutable for products manufactured or sold lawfully. But, Avastin has a valid MA for the treatment of certain oncology conditions
- ECJ rejected Roche's arguments re Avastin's repackaging without authorisation and sale to HCPs before submission of individual prescriptions
  - Directive 2001/83 does not prohibit use of products for indications not covered by MA
  - Article 5(1) enables member state (to fulfil special needs) to exclude from Directive 2001/83 medicinal products supplied in response to a *bona fide* unsolicited order, prepared in accordance with specifications of an authorised HCP for use by an individual patient under direct personal responsibility – exception only applies when HCP considers a patient's health requires medicinal product for which there is no authorised equivalent available
  - Repackaging to allow intravitreal injection requires authorisation unless carried out solely for retail supply by pharmacists in dispensing pharmacies or persons legally authorised in the member states

→ *"EU rules on pharmaceutical products prohibit neither off-label prescription of a medicinal product nor repackaging for such use but do require that they comply with conditions*"

Assessment of the Relevant Market (2)

- It is for the relevant national authorities or national courts – not the competition authority – to determine whether products are lawfully prescribed and repackaged
  - When such an assessment has been carried out, the national competition authority must take it into account when determining whether the products are substitutable
- At time of ICA's decision, no evidence a competent authority had established the unlawfulness of the conditions under which Avastin was repackaged and prescribed (for unlicensed use)
  - Although it is a matter for the national court, the ECJ noted that, at the time the ICA's decision was adopted, the EMA and EC did not grant Roche's request to include in the "adverse reactions" in the summary of Avastin's characteristics certain side effects resulting from intravitreal use, taking the view that the effects only warranted mention in "special warnings and precautions for use"
  - In those circumstances, uncertainty over the lawfulness of repackaging and prescription of Avastin for eye diseases did not prevent the ICA from finding that the two products belonged to the same market

Assessment of the Relevant Market (3)

- ECJ noted that "[g]*iven the specific features of competition in the pharmaceutical sector, the relevant market* [...] *is, in principle, capable of comprising medicinal products that may be used for the same therapeutic indications, since the prescribing doctors are primarily guided by considerations of therapeutic appropriateness and the efficacy of medicines*"

- Avastin was frequently prescribed for the treatment of eye diseases, despite fact its MA did not cover those indications; this revealed existence of specific relationship of substitutability between Avastin and products authorised for those eye diseases (including Lucentis)
- Possible to assess accurately demand for Avastin for treatment of eye diseases not covered by its MA – Avastin was subject to prescription
- Conformity of product with provisions governing manufacture/marketing (as determined by relevant authorities/courts) relevant in assessing effects on structure of supply and demand

Licensing Agreement and Ancillary Restraints

- ECJ does not directly address whether licences may infringe competition law when they are between non-competitors – focuses on interaction between licence and apparent agreement to jointly disseminate information
- "Arrangement" to disseminate information not designed to restrict commercial autonomy of parties to agreement; designed to influence conduct of third parties (*e.g.*, regulatory authorities and HCPs) to limit use of Avastin in favour of Lucentis (aiming to reduce competitive pressure), can fall within the scope of Article 101(1) TFEU
- Arrangement not ancillary to the licensing agreement
  - Not designed to restrict the commercial autonomy of the parties regarding Lucentis
- Arrangement not objectively necessary for the implementation of the licence
  - Conduct was agreed upon several years after conclusion of the agreement
  - Designed to reduce use of Avastin for eye diseases and increase the use of Lucentis (to increase profitability for Novartis)

Misleading Nature of the Information

- ECJ considered whether an agreement under which the parties disseminated allegedly misleading negative information (concerning adverse reactions) about a medicinal product on the basis of safety concerns (that were not scientifically proved) is a restriction "by object"
- ECJ noted that the Parties' objectives for the dissemination of information were unrelated to pharmacovigilance
  - Pointed to the fact that it is the MA holder who is responsible for engaging with the EMA re amendment of summary of characteristics of a product and for providing information to HCPs about the risks of this product
- ECJ provided a framework to the national Court to determine if the information was misleading, stating that it would be if the purpose of the information was to:
  - Confuse the EMA/EC and have adverse reactions added to the summary of the product's characteristics, in order to enable the MA holder to launch campaign aimed at HCP/patients/*etc.* to artificially exaggerate perception; and
  - Emphasise, in context of scientific uncertainty, public perception of the risks associated with unlicensed use of Avastin (given that EMA and Commission did not amend the summary of characteristics re its "adverse reactions", merely issued "special warnings and precautions for use"

Restriction by Object

- ECJ found that it was likely that the dissemination of the information would encourage HCPs to refrain from prescribing Avastin for eye conditions, resulting in the expected reduction in demand for Avastin

- ECJ found that arrangements constitute restrictions of competition "by object"
  - Concept of restriction of competition "by object" must be interpreted strictly (*Cartes Bancaires*)
  - The objectives of the arrangement between Roche and Novartis were sufficiently harmful to competition, such that there is no need to assess its effects

Broader Implications

Market Definition and Competitors

- Authorised medicinal products used for the same therapeutic indications fall into same market
  - Conditions for repackaging and prescription must be met, but this is not question for competition authority – competition authority take decision of relevant authority into account in supply- (and demand-) side analysis
  - → Next step beyond developing practice for oncology and respiratory indications
  - → Timing of regulatory and competition reviews significant
- Illegally manufactured or sold products "in principle" not substitutable
  - Legal, economic, technical risks (and reputational damage) on supply-side
  - Risk to public health among HCPs and patients on demand-side
  - → How does this sit with pay-for-delay cases – infringing products (that are unlawfully supplied) are in the market in those cases?
  - → Does "illegal" mean "not yet authorised"?
- Licensee only in market as result of licence is competitor of licensor (if molecule used in same indication or licence for particular field)

Licensing Agreements and Ancillary Restraints

- Court does not address whether underlying licence is anticompetitive – expressly says there is no information on the file casting doubt on favourable or at least neutral nature of licence
- In addressing whether dissemination of allegedly misleading information was ancillary, describes that agreement as having been reached with a view to eliminating substitutability between use of Avastin and Lucentis

→ Distinguishable on basis agreement not part of licence and relates to third party conduct, but take care with restrictions in licences re

- Supply for indications not in relevant MA
- Supply for indications reserved to licensor (e.g., in a field of use licence)
- Restrictions on obtaining repackaging authorisation (or working with dispensing pharmacies or taking similar steps)
- Cooperation or information exchange relating to matters relevant to pharmacoviligance or other regulatory obligations where regulatory obligation rests of entity disclosing information rather than the recipient
- Cooperation in relation to public communication of technical or scientific matters not included in the product's summary of characteristics" by relevant regulators

"By Object" Infringement

- Object of agreement is its "economic function" (its objective rationale)
- If agreement is plausible means to achieve a pro-competitive objective, not "by object" anticompetitive
- AG applied to alleged concerted practice
  - Concluded issue turned on which information about efficacy and safety is misleading (if not misleading, conduct would fall outside Article 101(1) altogether, since exchange of such information would improve competitive conditions)
  - Reflects very "effects-based" nature of ECJ's approach to identifying "object"
- ECJ noted
  - Agreement regarding dissemination of allegedly misleading information might evidence an objective unrelated to pharmacovigilance
  - Agreement to exaggerate risk perceived by doctors, such that they refrain from prescribing (where information does not meet regulatory requirements of completeness and accuracy), is sufficiently harmful to competition that examination of effects superfluous