Generic Medicines: Data Exclusivity

There are a number of generic drugs on the market and generic companies have to abide by certain laws in order to bring any new generic products onto the market in the European Union ("EU"). In this article, Dr Rosanna Cooper explores the legal issues surrounding **generic medicines** and **data exclusivity**. In this article the term generic medicines and generic drugs are interchangeable.

Meaning of generic medicine?

A generic medicine is a replica of a pharmaceutical medicine that has already obtained a marketing authorisation from an authorising agency ("**reference medicine**"), for instance, the Medicines and Healthcare Products Regulatory Agency ("MHRA") in the United Kingdom.

In terms of its composition, a generic medicine must contain the **same active ingredients** as its reference medicine. The **same dosage** has to be used as the reference medicine to **treat the same disease(s)**. There could however be variation in the appearance of the generic drug, in relation to colour, shape and packaging.

Composition of a Generic Medicine

In terms of the composition of a generic medicine, the **quantity of the active ingredients has to be exactly the same** as its reference medicine. The expedients (inactive ingredients) in a generic medicine could differ from its reference medicine.

Although the quantity of the active ingredients of a generic medicine has to be the same to have the exact therapeutic effect of the reference medicine, the **form of an active ingredient of a generic medicine may be different**. By way of example, the generic company may use a 'hydrochloride' salt to give a more stable product, provided the efficacy of the generic medicine is not affected.

Generic companies may choose to:

- Develop generic medicines with different strengths or different routes of administration to the reference medicines.
- Develop '**hybrid**' medicines i.e. with limited indication to enable them to be sold without prescription. The data for supporting the application for the marketing authorisations for the generic medicines would be partly clinical tests trials on the reference medicines and partly on new data.

Development of a Generic Medicine

In the EU, a generic company is obliged under the law to develop a generic medicine for marketing only **after** the period of **'exclusivity'** on the reference medicine has expired.

The pharmaceutical company, when applying for regulatory approval from a regulatory body such as the MHRA in the UK for a new medicinal product, must submit a

dossier relating to the product comprising data on the **efficacy**, **toxicity** and **safety** of the medicinal product, including pre-clinical and clinical trials results.

Under **regulatory law**, a generic company may seek approval for the same active ingredient(s) of the reference medicine by relying on the data submitted in the dossier by the pharmaceutical company to the regulatory agency.
In seeking approval of the generic medicine, the generic company must prove that the generic medicine has the **same qualitative and quantitative composition as the reference medicine** and that it is bioequivalent.

What is Data Exclusivity?

There are regulatory laws in place in the EU to protect pharmaceutical companies with marketing authorisations for their pharmaceutical medicines on the market in the EU. This period is termed '**data exclusivity**' whereby generic companies are not allowed to reference pre-clinical and clinical trials data in their applications for authorisation of their generic drugs. The pharmaceutical companies are therefore given a lead time as **development of generic drugs cannot take place until after the exclusivity period has expired** for the same active ingredient(s).

There is also '**market exclusivity**' during which time a generic company may not market an equivalent generic version of the reference drug. There is no prohibition on the generic company making and processing an application for authorisation during this period to enable the generic company to market the generic drug at the end of the exclusive period.

The rationale is to compensate the pharmaceutical companies for the extremely high costs for the development of their pharmaceutical drugs and for the generation of the huge amount of data required to obtain marketing authorisations for their drugs:

- **Data exclusivity** lasts for 8 years from the date of first authorisation in the EU.
- **Market exclusivity** lasts for 2 years.
- **Total Exclusivity** lasts 10 years from the date of the first marketing authorisation for the reference medicine.

A company can only develop a generic medicine for marketing once the period of **exclusivity** on the reference medicine has expired. This is usually **10 years** from the date of first authorisation.

In addition, the medicinal drug may have **patent protection**. In which case, if there is a '**use patent**' granted for the reference medicine, the generic company cannot market the generic medicine for the life of the patent even if the period of exclusivity on the reference medicine has expired. Therefore, until the use patent has expired, the generic company can only market the generic medicine for indications where there is no patent protection.

How are generic medicines manufactured?

Generic medicines must be manufactured by generic companies using the **same quality standards as pharmaceutical medicines** i.e. in accordance with good

manufacturing practice.

How are generic medicines authorised?

As with the regulation of all pharmaceutical medicines, before generic medicines can be placed on the market in the EU, they must have marketing authorisations.

The generic company has to **submit a dossier** to the regulatory authority to obtain a marketing authorisation. The regulatory authority, such as the MHRA in the UK, will then conduct a scientific evaluation of the drug's efficacy, safety and quality.

How are generic medicines evaluated?

The generic company would have the data on the **efficacy** and **safety** of the active ingredient(s) of the reference medicine available to it. There are specific tests that the generic company has to carry out to obtain marketing authorisation for its generic medicine. These tests are laid down in the pharmaceutical legislation. What is required for the generic company to prove that the generic medicine is comparable to the reference medicine.

The following information must be provided to the regulatory authority:

- Data on the **quality** of the medicine.
- Data from a **bioequivalence study** to prove that the same levels of the active ingredient in the body (whether human or animal) are produced by the generic medicine as the reference medicine.
- Bioequivalence studies where relevant:
    - For instance, bioequivalence studies are only required for medicines that are absorbed by the body before release into the bloodstream, such as medicines that are taken orally.
    - Otherwise, generic medicines that are administered directly into the bloodstream do not require testing for bioequivalence against the reference medicine.
- The regulatory authority will decide whether additional tests are required for the generic medicine to be granted a marketing authorisation, if the generic medicine comprises a **different salt of the active ingredient** to that of the reference medicine.
- Additional tests may be required if the generic medicine is a **hybrid**, including results of clinical trials that prove the efficacy of the generic medicine.

Upon authorisation of the generic medicine, the said information will have to be inserted in the 'product information' of the generic medicine, as set out in the product information for the reference medicine:

- A summary of the **characteristics** of the drug.
- The **labelling** and the **packaging leaflet**.

There might be differences:

- In terms of **excipients**.
- Any **patented indications**.
- Any **precautions** due to excipient (must be described both on the label and in the packaging leaflet of the generic medicine).

If the reference medicine is claiming certain benefits from patent protection for some indications, they will be excluded from the product information of the generic medicine.

How is the safety of generic medicines monitored?

The safety of generic medicines will be monitored by the regulatory authority after authorisation. The generic company is obliged to **set up systems to monitor the safety of any generic medicine** that it sells and markets in the EU.

There are instances where the regulatory authority may perform an inspection of the monitoring systems for example, if specific safety precautions have to be considered by patients when taking the reference medicine, the same precautions will generally apply to the generic medicine.

The MHRA is responsible for **assessing applications** from companies to market generic medicines in the UK. The MHRA assesses applications if:

- The reference medicine was authorised centrally via the European Medicines Agency; or
- The generic medicine has been shown to provide a **significant innovation or advantage for patients** or animals.

How does Directive 2004/27/EC and the Bolar Defence relate to Research & Development ('R & D') in respect of generic medicines?

The Bolar type defence originated from the US case of *Roche v Bolar* (733 F.2d 858.221 USPQ 937) in which it was decided that a generic pharmaceutical company was not permitted to conduct R&D tests on a patented compound prior to patent expiry, even if such tests were conducted in order to fulfil regulatory requirements for obtaining a marketing authorisation for a generic drug. Following this decision, US patent law was amended to include an **exemption** to permit such experiments.

Directive 2004/27/EC requires the introduction into Article 10 of the Directive 2001/83/EC (the "Medicines Directive") of a new Article 10(6) which states that:

"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 or to supplementary patent certificates for medicinal products".

To simplify and relate these two instruments, paragraphs 1, 2, 3, and 4 of Article 10 set out the abridged procedures whereby manufacturers of medicinal generic products/medicinal products can obtain marketing authorisation without submitting a full dossier of pre-clinical tests and clinical trials (in the case of Article 10(3) a full dossier will have to be submitted for a medicinal product)).

The intended effect of the Bolar provision is to permit applicants, for the purpose of obtaining marketing authorisations of generic medicinal products, to conduct the necessary trials and studies on reference products before the expiry of the patents covering those reference products, without infringing the rights of the patent holder.

In order to implement the Bolar provision in the UK, the MHRA proposed the amendment of the UK Patents Act 1977 (the "Act") such that the Bolar provision would be added to the list of exemptions of actions which would otherwise constitute patent infringement. In this regard, section 60(5)(i) of the Act, which came into force on 30 October 2005, accurately reflects the wording of Article 10(6) of the Medicines Directive.

'…s.60 (5) An act which, apart from this subsection, would constitute an infringement of a patent for an invention shall not do so if:

…

(i) It consists of:

(i) An act done in conducting a study, test or trial which is necessary for and is conducted with a view to the application of paragraphs 1 to 5 of article 13 of Directive 2001/82/EC or paragraphs 1 to 4 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..'

The practical effect of this legislation on a generic company is that the exemption would apply if the study, test or trial is to be carried out for the purpose of submitting an application under Article 10 (1) to (4). In looking specifically at Article 10(3), the Directive seems to allow a situation where the medicinal product does not fall within the definition of a generic medicinal product, in which case a dossier containing pre-clinical/clinical trial results would have to be submitted to the relevant authority.

Who is liable, if the generic company can show there is no infringement?

Counterfeit goods

- Goods, including packaging bearing without authorisation a trade mark which is identical, or cannot be distinguished in its essential aspects from, validly registered UK or EU trade marks for the same type of goods.

- Any symbol (including any logo, label, sticker, brochure, instruction manual or guarantee document bearing a symbol) whether presented separately or not, carrying a trade mark without authorisation.

- Packaging materials, presented separately, bearing the trade marks of counterfeit goods.

According to HM Revenue & Customs Reference: **Notice 34** (November 2012), a party who wishes to be made aware of any potentially patent infringing goods passing through customs, and for those goods to be detained, has to submit such an application under Council Regulation (EC) No 1383/2003. Council Regulation (EC) No 1383/2003 allows a right-holder to lodge an application with HMRC for the detention by Customs, generally for a period of ten working days, of any goods suspected of infringing an intellectual property right that are detected at the EU external border. This period may be extended by a maximum of a further ten working days upon request.

When this application is made, the patent holder gives an undertaking to pay all **costs and liabilities** in the event that the goods are wrongly detained i.e. are not infringing the patent holders patent(s). The following are examples given by Customs of what may be recoverable:

- Storage charges when they have correctly detained suspected goods which are subsequently found not to be infringing goods;
- Storage charges where the detention or seizure of infringing goods results in a notice of claim and the outcome of proceedings is awaited;
- Storage charges for correctly detained and seized goods which, due to the nature and quantity of goods, have been stored in commercial warehouse facilities;
- Legal costs and compensation for any loss suffered if you or the courts confirm that the goods are not infringing; or
- Costs incurred in the destruction of the goods.

The Customs enforcement action described in this Notice is possible only where intellectual property right protection has been granted by an appropriate organisation or, in the case of any copyright, related right or unregistered design where it arises by operation of law. Where appropriate, the official government body within the UK for approving and registering an intellectual property right is the Intellectual Property Office. The IPO website describes their work and provides advice.

IP rights covering the EU can be registered via the Office for Harmonisation in the Internal Market (OHIM); the OHIM website describes their work and provides advice.

If an application has not been accepted, Article 4 of the Council Regulation also enables us to contact the right-holder if we come across suspected infringing goods during the course of our other checks. In this case the goods may be detained and the right-holder will be invited to lodge an application within three working days, this deadline cannot be extended. Please note that under Article 6 of the 2004 Commission Regulation this facility cannot be applied to perishable goods, these may only be detained if there is a valid application already in place.

What procedures should companies implement if importing materials from outside the EU for research?

It is suggested that if the generic company is to import generic drugs from outside the EU, it should adopt a policy/procedure to insert a notice on its purchase order and on packaging that:

"The contents contained within are to be used for pharmaceutical research and development in accordance with s.60(5)(i) of the Patents Act 1977 and Article 10 (6) of Directive 2001/83/EC."

The packaging should make the ultimate destination clear, and should not be of an excessive quantity inconsistent with the purpose of research and development.

Conclusion

Generic companies must consider data exclusivity in the development of generic drugs.

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