

Prodrugs and metabolites – in the twilight zone of patentability?

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Prodrugs and metabolites – in the twilight zone of patentability?

Metabolites and prodrugs are the chicken and egg of the biosciences. Inextricably connected – the one transforming to the other within the body – they remain structurally distinct, leading to the conundrum of how best to protect them

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It is estimated that between 5% and 20% of drugs approved worldwide can be classified as 'prodrugs'. These are defined as bioreversible, inactive derivatives of drug molecules which must undergo an enzymatic and/or chemical transformation in the patient's body (ie, *in vivo*) to release the active metabolite. In these cases, the active metabolite that is ultimately responsible for the drug's *in vivo* pharmacological effect differs structurally from the compound present in the pharmaceutical composition that was administered to the patient – that is, the prodrug.

From a patent practitioner's perspective, several intriguing and partially unresolved questions arise from the interplay between prodrugs and their respective metabolites. For example:

- Can a patent covering the active metabolite be obtained if prodrug versions of this metabolite were disclosed in a previous patent filing?
- Can prodrugs that were developed as improvements or line extensions of already approved and known drugs be patented?
- Can a patent covering the active metabolite of an approved drug

be enforced against a competitor marketing a prodrug version of the patented metabolite?

This article aims to shed some light on these issues, taking into account the current practice of the European Patent Office (EPO) and the legal situation in Germany, which – with more than 1,000 infringement actions filed every year – is by far the most important patent litigation venue in Europe.

Scientific background

Striving to improve the physicochemical, biopharmaceutical or pharmacokinetic properties of a given drug candidate, prodrug design has become an invaluable tool in modern drug development.

There is abundant precedent for the usefulness of prodrugs in overcoming various hurdles in drug formulation and delivery, such as poor absorption, too rapid metabolism or excretion, inadequate solubility, poor lipophilicity, chemical instability, unfavourable organoleptic properties, systemic toxicity or negligible blood-brain-barrier (BBB) penetration.

Prodrugs are thought to offer a key to safer, more sophisticated and better targeted drugs.

Most prodrug approaches require a 'synthetic handle' on the drug molecule (ie, a functional group that is amenable to chemical derivatisation). In practice, such functional groups are commonly heteroatomic moieties, such as hydroxyl, carboxylic, carbonyl, amine or phosphate/phosphonate groups. In most prodrugs these groups have been derivatised into the corresponding esters, carbonates, carbamates, amides, phosphates or oximes. By far the most common prodrug strategy is the formation of esters, which account for approximately 49% of all marketed prodrugs.

Recent advances in cell biology and immunology have paved the way for drug targeting and drug-delivery approaches in which the prodrug either actively targets the drug to its place of action and/or selectively releases the active metabolite site. For example, the common anti-viral drug acyclovir suffers from low aqueous solubility and poor bioavailability. Hence, intravenous administration is necessary to achieve high plasma concentrations. The development of valacyclovir, a prodrug version of acyclovir derivatised with the amino acid valine, was a breakthrough in this respect. Valacyclovir transforms the otherwise poorly resorbed drug acyclovir into a welcome cargo for a specific nutrient transporter present on the surface of the intestinal epithelium. Following its transporter-mediated delivery into the bloodstream, valacyclovir is again converted to acyclovir by esterase enzymes of the hepatic first-pass metabolism. This prodrug mechanism boosts the bioavailability of the parent drug substantially, thereby allowing for lower and/or more patient compliant dosing regimens.

Similarly, L-Dopa, the most commonly prescribed medication for treating Parkinson's disease, is a prodrug version of the neurotransmitter dopamine. In contrast to dopamine, L-Dopa can overcome the BBB by channelling through a selective transporter in the BBB. Having entered the brain, L-Dopa is rapidly converted into dopamine.

Further advances in prodrug design are expected to occur in the field of oncology. Many avenues of current research are trying to achieve the selective delivery of anti-cancer agents to tumour tissue, thereby avoiding the cytotoxic effects on unaffected, healthy tissue and organs. One approach is to exploit tumour-specific metabolic pathways for prodrug degradation and site-specific release of the active metabolite. An example of this approach is Roche's anti-cancer drug Xeloda®, which is a prodrug of the anti-proliferative agent 5-fluorouracil (5-FU). Antibody-drug conjugates are another way to approach tumour-specific targeting and release.

Hence, prodrugs can not only improve a drug's efficacy, but also serve to decrease any unwanted systemic toxicity.

Devising patent claims covering prodrugs

The European Patent Convention (EPC) defines the basic criteria of patentability as novelty (Article 54), inventive step (Article 56) and industrial applicability (Article 57). Moreover, in order to be patentable, an invention must be sufficiently disclosed in

the specification (Article 83) and claimed in a clear manner (Article 84).

Prodrugs offer a valuable opportunity to extend the lifecycle of a given drug. When devising patent claims to cover prodrugs, three scenarios can be distinguished.

The first, the so-called 'usual prodrug case', is where the active metabolite is already in the public domain and a first patent application has been filed and published covering the same. In these cases, the prodrug is developed intentionally (ie, with knowledge of the active metabolite and in an effort to improve the physicochemical, biopharmaceutical or pharmacokinetic properties of the parent compound).

If the chemical structure of the prodrug has not been disclosed previously, it can be considered a new chemical entity and hence will fulfil the novelty requirement of Article 54 of the EPC. However, for an inventive step to be acknowledged, the applicant will have to demonstrate that the prodrug's design was not obvious to the skilled person. Optimally, the prodrug should show a surprising technical effect when compared to the known parent drug. Difficulties in overcoming an obviousness objection may arise where the structural difference between the prodrug and the previously disclosed metabolite is small. Such cases will be particularly difficult to prosecute if:

- The prodrug approach employed is a common one (eg, forming an ester).
- Statements in the previous parent drug patent filing teach or suggest possible prodrug derivatisations.
- The prodrug is encompassed by broad Markush formulae in the genus claims of the parent drug patent filing.

The second scenario concerns cases where the actual prodrug has not yet been developed. However, the parent patent filing claims not only the compounds of the invention, but also – in generic form – possible (future) prodrugs thereof. Such a claim could, for example, read "compound of [formula X] or a prodrug thereof".

Claims including generic prodrug language are rarely allowed by the EPO. A claim to a prodrug without defining it structurally is considered to be unclear in the sense of Article 84 of the EPC. In addition, the mere recitation of the term 'prodrug' in a claim is not considered to be a technical teaching disclosed in sufficient detail for it to be carried out by the skilled person. This is especially the case if a broad Markush formula is claimed, which already encompasses a vast array of different compounds. However, based on our own



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“The mere recitation of the term ‘prodrug’ in a claim is not considered to be a technical teaching disclosed in sufficient detail for it to be carried out by the skilled person”

experience, there are cases in which the EPO can be convinced to grant patents with prodrug language in the claims. This may be possible if the metabolite to which the prodrug relates is a specific compound or a limited set of structurally related compounds, and/or if the term ‘prodrug’ in connection with the claimed class of compounds has a specific, well-defined meaning. To increase the chances of success, it is advisable to include in the specification a definition of ‘prodrugs’ a description of viable prodrug approaches and a test method to evaluate whether a given compound constitutes a prodrug within the scope of the claim.

In a third scenario both the metabolite and one or more prodrugs are discovered at the same time and included in a single patent filing. Here the question may arise as to which claim – to the prodrug or to the metabolite – is more valuable and should proceed to grant preferentially.

Arguably – at least in some jurisdictions – a claim to the metabolite may offer the broader scope of protection, as it potentially could be construed also to cover any (future) prodrugs that are converted into the patented metabolite *in vivo*. However, it is still advisable to pursue additional claims for the prodrug as such. First, in some jurisdictions, prodrugs may not be considered to infringe a metabolite claim and if so, perhaps only by way of proving indirect (ie, contributory) infringement, which can be a complicated undertaking when compared to direct infringement. Second, if the patent proprietor will itself obtain marketing authorisation for only the prodrug (eg, because the metabolite shows adverse effects in clinical studies), it may not be possible to obtain patent-term extension by way of a supplementary protection certificate (SPC) based on this marketing authorisation, if only the metabolite is specified in the claims’

wording and not the prodrug compound that has been authorised.

Devising patent claims that cover metabolites

Although rarer, there are also cases in which, serendipitously, the first-generation drug to be discovered is a prodrug and the actual active metabolite is only discovered later. In such unusual cases, the question arises as to whether the later discovered metabolite is still susceptible to patent protection with regard to the prior art disclosure and use of the prodrug. The argument against novelty of the metabolite would be that the previous disclosure of the prodrug inherently disclosed and thereby anticipated the metabolite, because administration of the prodrug would inevitably lead to the *in vivo* formation of the metabolite, which therefore could not be considered ‘novel’.

This line of argumentation does not accord with the EPO’s current practice. Given that the chemical structure of the metabolite has not been disclosed previously, there are good chances of obtaining a European patent directed to the metabolite even if a related prodrug was known. According to established EPO case law, for a prior art disclosure to be novelty destroying, it must contain an enabling disclosure of the subject matter. The mere fact that biochemical degradation of a compound after its ingestion affords a certain metabolite, without any teaching as to its structure or how to isolate or prepare the metabolite, will normally not prejudice the novelty of a later claim directed to the metabolite as such.

This is an important difference from the situation in the United States. In the seminal case *Schering Corp v Geneva Pharmaceuticals* (67 USPQ 1664, Fed Cir 2003), the Federal Circuit held that patent

claims for a compound necessarily produced as metabolite in the human body upon ingestion of a prodrug were inherently anticipated by the previous disclosure and sale of said prodrug. The House of Lords took a similar view in the United Kingdom in *Merrell Dow Pharmaceuticals Inc v HN Norton & Co Ltd* (1996 RPC 76).

The different novelty assessments performed by the EPO, the US Patent and Trademark Office, the UK IP Office and possibly in other countries should be kept in mind when filing an international patent application. For example, it is advisable to include fallback positions directed to the metabolite in its pure and synthetic form (eg, as part of a pharmaceutical composition, with a pharmaceutically acceptable carrier, as amorphous or crystalline form; or as a claim to a method of administering the metabolite to a patient and its use in medicine). There is a chance that if the wording of the claims is carefully chosen, even jurisdictions following the US 'inherent anticipation' doctrine will consider claims allowable that distinguish the – thus far undisclosed – synthetically prepared and solid metabolite (ie, in amorphous or crystalline form) from the anticipated compound which is formed *in vivo* upon ingestion of the prodrug.

The scope of metabolite patents

There is a reason why some jurisdictions consider the grant of a patent on a metabolite problematic in view of the disclosure of a prior patent covering the prodrug. A sequence of patent filings involving a first filing covering the prodrug and a later filing covering the metabolite could be used for the purpose of effectively extending the prodrug's term of protection. Some infringement courts may hold that sale of the prodrug, which – in the body of the patient – is converted to the patented metabolite, would constitute an infringement of the later metabolite patent.

A landmark case in this regard relates to Marion Merrell Dow, the proprietor of a patent covering the antihistamine Terfenadine. It later turned out that Terfenadine was in fact metabolised *in vivo* and that its pharmacological effects were exerted by its acid metabolite Fexofenadine. Marion Merrell Dow secured a second patent on Fexofenadine in the 1980s, several years after the first filing on the prodrug Terfenadine. After expiry of the original Terfenadine patent, several companies entered the market with generic versions of Terfenadine. This prompted Marion Merrell Dow to sue one of these companies, Norton, in various

jurisdictions – including the United States, Germany and the United Kingdom – for infringing the later Fexofenadine patent, which had not yet expired.

In all three jurisdictions – albeit with different reasonings – the courts were somehow bound and determined to find the Fexofenadine patent either invalid (United Kingdom) or not infringed (United States and Germany), since ruling otherwise would have effectively extended the claimant's monopoly beyond the term of the original, expired patent on Terfenadine.

Terfenadine is somewhat special because an older and expired prodrug patent existed, which in addition was owned by the same proprietor as the later metabolite patent.

Unfortunately, there is little case law on so-called 'usual prodrug cases', with a first patent on the active metabolite and the prodrug only being developed later. In an old UK case, *Beecham v Bristol Laboratories* (1978 RPC 153), the sale of Hetacillin, a prodrug of the antibiotic Ampicillin, was found to infringe Beecham's patent covering ampicillin under the doctrine of equivalents. Most commentators predict that if a Beecham-type situation were to be tried before a UK court again today under the 1977 UK Patents Act, sale of the prodrug would be considered a contributory (indirect) infringement of the ampicillin patent. By contrast, the majority of German commentators and scholars predict that a Beecham-type situation might even be considered a direct infringement if it were tried before one of the highly specialised German infringement courts.

In summary, the protective scope afforded by product claims in European patents can generally be considered to be strong and adequate, and likely to cover prodrug derivatives. With the few precedents available, it will be intriguing to follow how courts rule in prodrug cases in the future. In view of the prospective unified European Patent Court, hopes are high that a uniform case law can be established throughout Europe. In the meantime, applicants are advised to pursue a balanced and sophisticated patent prosecution and lifecycle strategy to ensure adequate protection of prodrug and metabolite forms. ■



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