Life Cycle Management: Impact of Patent Expiry

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When will the patents expire?

- Patent life (generally) is 20 years from date of filing
- Some older (pre ’95) US patents can have longer lives
- Certain patents can be extended by Supplementary Protection Certificates (SPCs) (in EU) or by patent extensions (in US)
- Extension dependent on date of first marketing authorization:
  - EU: 15 years from first MA in Community
  - US: 14 years from first MA in US
- Maximum of 5 years extension of term
- Generally one patent can be extended
When will the patents expire?

- The innovator’s product(s) will be protected by several patents
- Which of these, if any, will determine when generic competition occurs?
  - Substance patent?
  - Use patent(s)?
  - Formulation patent(s)?
  - SPC(s)?
- What other factors are to be taken into consideration?
  - Regulatory issues?
  - Production issues
What is a Generic Drug?

Drug identical to a marketed drug, in terms of:

• active principle

Functionally equivalent to the marketed drug, in terms of:

• therapeutic profile
• safety profile
• pharmaceutical form
Barriers to Generic Competition

Three controlling factors:

• ability of genericist to make a functionally equivalent product

• availability of abridged regulatory procedure to gain approval for that product

• exclusive rights preventing sale of that product
Timing of Generic Entry

- Wait until originator has established safety and efficacy of original product - expiry of “data exclusivity period”
- Make ‘abridged application’
- Get approval for a *functionally* equivalent product that avoids later expiring patents
- Wait until expiry of patent(s) relating to active principle before launch
Data Exclusivity Periods

In Europe:
- Apply for abridged MA 8 years after originator MA
- Get MA after 10/11 years
- Additional year exclusivity if new indication
- No additional protection for formulations

In US
- Apply after 5 years, 4 if patent challenged
- 30 month delay before marketing
- Additional 3 years for formulation
Patents v Data Exclusivity

- Regulatory barrier is most significant barrier to generic entry
- Generic company will rarely want to repeat safety and efficacy studies
- Even without patent protection, very effective barrier to generic competition for NCEs
- Data exclusivity much less valuable for line extensions: new uses, new formulations, etc
- Patents to active principles usually very strong
- Secondary patents (salts, formulations, etc) can be evaded and more susceptible to attack
UK: Interim injunctions

• Generic entry may be blocked by innovator getting interim injunction before full trial
• Tend to be granted in UK pharma cases
• UK courts now keen to maintain status quo: generic product kept off the market until validity and infringement of patent can be considered at full trial
• Generic expected to “clear undergrowth” of doubtful patents well before generic entry
• Court will require undertaking from patentee to compensate genericist in event that decision to prevent entry into market was wrong:
  – Genericist would be compensated for lost profit
  – Dept. Health intervened in Abbott for compensation
Speed to trial

All jurisdictions can move fast, eg Abbott/Clarithromycin form II:

- Patent granted: 04 Aug 2004
- Nullity actions filed: 04 Aug 2004
- Hearings, UK, NL, DE: early Nov 2004
- Judgments 18/19 Nov 2004
- UK patent revoked

Timetable determined by expiry date of SPC on earlier, “basic” patent

On the other hand, EPO slow – patent on clarithromycin form II finally revoked October 2007
# Patents to Stop Generics

<table>
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<tr>
<th>Active principle</th>
<th>Formulations</th>
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<td>Salt</td>
<td>Processes</td>
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<td>Polymorph</td>
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<td>Enantiomer</td>
<td>Devices</td>
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Active principle patent invariably first to expire, eg:
- Amlodipine, Salmeterol, sibutramine

• Most likely to be subject of SPC/extension
  - Protection AP patent is broadest

• Patent will describe:
  - Active principle
  - Variety of salts, derivatives, etc
  - Simple formulations
  - Laboratory preparation
  - Range of uses

• Less likely to describe:
  - Different polymorphs or solvates
  - Enantiomers, if AP chiral
  - Possible combinations (except for cardiovascular)
Salts

• Sometimes a specific salt is found to have surprising advantages over those described in basic patent, eg
  – Amlodipine besylate has formulation advantages over amlodipine maleate disclosed in basic patent

• Difference in filing dates of basic patent and salt patent may given extra life to franchise
  – But only if earlier disclosed salt is not commercially viable

• From regulatory point of view, different salts of active principle will be seen as equivalent – safety data on one can be used to register the other, eg
  – Paroxetine mesylate/hydrochloride
Solvates

- Changing processing conditions can lead to discovery of stable solvates with advantageous properties
- Generally will be hydrates
- Value will depend on importance of solvate and genericists ability to use materials described in basic, active principle patent, eg
  - Mometasone hydrate (API for nasal formulation)
  - Sibutramine hydrochloride monohydrate (only form authorized)
Polymorphs

• Polymorphs of active ingredient frequently found during drug development process
• Patentable if they offer surprising advantages over crystal form(s) disclosed in earlier patents
• Often problems with novelty:
  – Polymorph may have been produced by earlier processes (eg perindopril)
• Care needs to be taken in characterising polymorph
• Polymorph patent cannot stop generic product based on original crystal form or different salt form
Enantiomers

• Nowadays, chiral compounds are generally resolved or chirally synthesised in time for basic patent filing
• However, up to late 80s, initial patent filing often described only racemic mixture, eg:
  – Omeprazole
  – Lanzoprazole
  – Citalopram
  – Clopidogrel
• Whether earlier disclosure of racemic mixture destroys novelty or inventive step in relation to later enantiomer patent depends on the facts
• May be able to get SPC on enantiomer
• Enantiomer generally considered to be new substance
Fixed Combinations

• Hugely important area
• Well established in cardiovascular:
  – ACE inhibitors + diuretic
  – All antagonists + diuretic
• Huge respiratory market:
  – Salmeterol + fluticasone (Serevent®, Advair®)
  – Formoterol + budesonide (Symbicort®)
• Growing market in diabetes
  – Rosiglitazone + metformin (Avandamet®)
  – Pioglitazone + metformin (Competact®)
• Sometimes disclosed in basic patent
• Often difficult to patent later (“a priori obvious”)
• Can be subject of separate SPC
Processes and intermediates

• Bulk of process done outside of EU/US
• Inevitably there will be later, improved and patented processes
• Is process (or final step) disclosed in basic patent commercially viable?
  – If so, genericist will use it
  – If not, can genericist come up with an alternative?
• Later process patents often relatively easy to avoid
• Patents to intermediates which appear as impurities in final product may be of value – infringement issue at the 0.2% level!
New uses

- Opportunity for later expiring patents
- Additional use or sole use authorised?
  - If sole use authorised, will be of value (must be on SmPC)
  - If additional use, much less valuable (no need to include on SmPC)
- Difficult to enforce – validity issues, eg sildenafil
- Infringement?
Formulations, New Dosage Forms

- Inevitable that new formulations will be developed over those disclosed in basic patent
- Tendency for initial formulations to be routine – difficult to patent
- Best formulation patents are those developed to solve particular problems
- Unless claims are functional (difficult to get), tendency for genericist to avoid infringement by developing functionally equivalent formulation
- Genuinely useful line extensions can be vital part of life cycle management
Formulations, New Dosage Forms

New formulation/delivery system often vital part of line extension

- Patches (eg Intrinsa® testosterone patch)
- Liposomes (DepoCyte®)
- Microspheres
- Cyclodextrin complexes
- Matrix formulation (eg Gliadel®)

New dosing regimens much more difficult to protect with patents (in UK at least).
Propellant driven MDIs

- CFC propellants banned
- Alternative, eg 134, 227a different physical properties –eg density, vapour pressure
- New suspending agents?
- New bulk density of known active ingredients?
- Solution rather than suspension?
- New methods of production?
- Extended protection for known inhalation drugs
- But dry powder devices are alternatives!
Dry Powder Inhalation Devices

- Originally single dose capsules (1960’s)
- Multidose DPI’s developed later (1980’s)
  - Reservoir
  - Metering means (or predetermined dose)
  - Transport to inhalation zone
- Enabling technology: Turbuhaler/Diskhaler
- 1st device sets standard – eg dose uniformity
- Brand loyalty extremely important
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• Are pharma companies breaching EU competition law by abusing dominant position (cf Art 82)?

• European Commission fined AstraZeneca €60 million for alleged breaches of competition law in relation to life cycle management issues in relation to Losec®.

• In particular, Commission alleged that AstraZeneca abused it dominant position through misuse of supplementary protection certificate (“SPC”) and marketing authorisation procedures as part of a strategy to exclude competition from generic manufacturers.

• EC taking close look at life cycle strategy issues within pharma

• Number of investigations in progress
Conclusions

- Interplay of regulatory and patent barriers
- Regulatory law reasonably harmonised, but patents state by state – some big differences
- Generic industry winning most of battles
  - No real signs of any let up!
- Get the patents right at the start
- Plan a long way ahead
- When planning life cycle management strategies, respect competition law!
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Some Recent Cases

Perindopril
- Polymorphs
- Enabling disclosure of prior art

Escitalopram
- Enantiomer
- Novelty, Obviousness and Sufficiency

Atorvastatin
- Scope of claims
- Novelty, Obviousness and Selection Inventions
Perindopril

EP 1 296 947

- Filed July 2001, priority July 2000
- Concerned α-perindopril erbumine, active ingredient of Coversyl
- Compound patent, + SPC expired June 2003
- Process patent EP 0 308 341, filed Sept 1988 described industrial prep. of erbumine salt
- Turnover of Coversyl in UK £70M

At the EPO:

- Feb 2004: granted
- Nov 2004: 10 oppositions
- July 2006: Oral proceedings
- Sept 2006: Written decision to maintain patent
- Nov 2006: Notices of appeal
- Feb 2007: Statement of grounds
Perindopril

Oct 2006: *Les Laboratoires Servier v KRKA Polska sp Zoo*
Application for interim injunction

- Servier developed COVERSYL, the active ingredient of which was perindopril, and patented both perindopril erbumine in the alpha crystalline form and its method of preparation
- KRKA obtained marketing authorisation for generic perindopril in the UK
- Having previously analysed KRKA's generic perindopril which was sold elsewhere, Servier concluded that it contained an alpha crystalline form of perindopril that infringed its patent and brought infringement proceedings.
- KRKA sought summary judgment, claiming patent invalid for lack of novelty or obviousness, being anticipated by an earlier Servier patent or by the sale of COVERSYL tablets before the priority date of the disputed patent.
- Servier sought interim injunctive relief, arguing that there was a real risk that, if KRKA was allowed to sell its generic product, Servier would suffer severe and unjustified losses due to the downward spiral in the price of the drug.
Perindopril

Oct 2006: *Les Laboratoires Servier v KRKA Polska sp Zoo*
Kitchin J granted interim injunctive relief

- serious issue to be tried on question of patent infringement
- clear conflict of evidence on issues of anticipation and obviousness, which had to be determined at trial
- although KRKA had established that COVERSYL containing an alpha crystalline form of perindopril had indeed been sold by Servier before the priority date of the disputed patent, KRKA had not shown that Servier had no prospect of defending the patent in the face of this challenge - summary judgment application accordingly dismissed
- real risk that, if Servier not granted an injunction, other generic manufacturers would launch their generic perindopril by the time judgment in the action was given
- substantial risk that Servier would suffer severe damage through price erosion, which would continue after trial
- COVERSYL crucial to Servier's business, while KRKA produced many different generic products
- KRKA had not yet launched its product and had not issued revocation proceedings, even though it had been preparing to launch the product for some time
- on the balance of convenience it was therefore right to grant the injunctive relief sought.
α crystalline form of the compound of formula (I):

![Chemical structure](image)

characterised by the following powder X-ray diffraction diagram, measured using a diffractometer (copper anticathode) and expressed in terms of inter-planar distances d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage with respect to the most intense ray):

<table>
<thead>
<tr>
<th>Angle 2 theta (°)</th>
<th>Inter-planar distance d (Å)</th>
<th>Intensity</th>
<th>Relative intensity (%)</th>
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<tr>
<td>7.680</td>
<td>11.50</td>
<td>390</td>
<td>8.8</td>
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Infringement

Dr Cima (Apotex):

all the spectra, both those relating to infringement and those relating to validity, would be recognised by the skilled man as the same

Dr Tarling (Servier)

distinction between the differences in the infringement spectra and some of those relied on for invalidity.

HELD:

Claim infringed

Validity Attacks

1. anticipation by 341:
   • skilled person carrying 341 into effect would inevitably fall within claim. Differences between various PXRD patterns obtained in respect of purported repeats of 341 process are no more different from claimed pattern than is pattern obtained for Apotex’s own perindopril erbumine, and no more different from claimed pattern than is result of recrystallising product of 341 according to teaching of patent in suit as to cooling regimes.

2. Insufficiency
   • If the material resulting from the recrystallisation does not fall within the claims, then the patent is insufficient.

3. Anticipation by sale
   • all of Servier’s production since perindopril erbumine went on market has been in form α, and thus anticipates patent in suit.

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Prior Art: EP 308 341

• Place in a reactor approximately 140 litres of ethyl acetate and 10 kg of [material obtained previously]. Add gradually approximately 2.20 kg of tert-butylamine, heat to reflux until all has dissolved; filter. Cool, filter off and dry. Yield: 95%
• Concentration is 87g/litre

Patent: EP 1 296 947

• heat tert-butylamine salt in ethyl acetate at reflux
• cool gradually until crystallisation is complete
• concentration of tert-butylamine salt in ethyl acetate preferably from 70-90 g/l
• advantageous to carry out cooling in two stages:
  1. from reflux to between 55°C and 65°C at a rate of from 5 to 10°C/hour, preferably from 6 to 8°C/hour
  2. then to ambient temperature.
• advantageous to seed during cooling step.
Pumfrey, J on difference between sufficiency and anticipation by enablement of an inevitable result:

“Of course, the criteria for sufficiency of description on the one hand and the enablement of an inevitable result on the other are not the same. For the purpose of anticipation, the prior documents must enable something which inevitably falls within the claim.

Where the prior art does not describe the end to be achieved, it is illegitimate to employ a refinement of technique or whatever to cause the desired result to be achieved.

Where the sufficiency of a disclosure of a method is under discussion, of course the skilled person is entitled to do such preliminary work and carry out such un inventive refinements, without undue effort, with a view to producing a product falling within the claim.”
Pumfrey J found patent anticipated by 341 and obvious over 341:

- “So far as the claim is concerned, it could scarcely be supposed that any problem of interpretation is raised. But it is, or perhaps the problems are better viewed as a lack of specification.”
- “Matters of particular concern are overlapping peaks, peaks entirely lost underneath others, and peaks that have been smoothed out by averaging routines within the computer program or which have been obscured by noise suppression techniques. So there is a degree of subjective assessment in any XRPD analysis.”
- Process obvious in light of 341 – therefore product of process obvious (but no detailed reasoning on obviousness)
- Did not consider “what is a difficult question” - whether the sale of Servier's own material, which was in the α form, invalidates the claim
• Escitalopram (Lundbeck) launched in 2002 as antidepressant
• 60% of Lundbeck’s turnover
• Single enantiomer version of citalopram, patented in 1972 and launched in 1989
• Revocation actions brought by:
  – GUK
  – Arrow
  – Teva
• Actions consolidated
• Trial May 2007
• Order for costs

Three independent claims:
• Product claim to (+) enantiomer and salts (claim 1)
• Pharmaceutical composition in unit dose form of product of claim 1 (claim 3)
• Method of converting (-) enantiomer intermediate to (+) enantiomer product (claim 6)
Claimants allege:

i) Claims 1 and 3 invalid for lack of novelty over:
   a) US Patent number 4,136,193 ("193");
   b) US Patent number 4,650,884 ("884").

   The lack of novelty attack turns upon a question of construction:
   *Does the claim exclude the (+) enantiomer in the racemic mixture?*

   Lundbeck met allegation with a conditional application to amend, which is opposed.

ii) Claims 1, 3 and 6 invalid for obviousness in light of 193 and 884 patents and common general knowledge.

iii) Claims 1 and 3 invalid for insufficiency: inventive concept disclosed by Patent was not idea of resolving citalopram - scope of invention lay, and lay only, in devising a way to obtain it.

   Claims 1 and 3 therefore extend beyond any possible inventive contribution of Patent in that they monopolise all ways of arriving at (+) citalopram.

Lundbeck argues unobvious because of commercial success
• **skilled addressee** comprises **team of persons**, all with different basic skills, equipped with common general knowledge but, at same time, unimaginative.

• **primarily, medicinal chemists**. Their role is to find new drug candidates and they usually start by identifying a target disease, a biological mechanism for treating the disease, for example, by selective inhibition of an enzyme and finally, identifying molecules which may be effective in that mechanism. Such medicinal chemists would characteristically be PhDs with two or three years experience or with less formal qualifications but 10-15 years of practical experience.

• **analytical chemists** responsible for verification of structures and determination of purities of molecules identified by medicinal chemists. **Clinicians** able to identify areas of unmet need and so guide any line of research undertaken by medicinal chemists.

• suggestion that **process research chemists** and **pharmaceutical chemists** would be part of the team rejected by judge.
Judge found that single enantiomer was an obvious goal, which could not be easily achieved:

- any medicinal chemist in this position in 1988 would have appreciated that enantiomers might well have different activities:
  - an inactive enantiomer was, at best, ballast but might be toxic
  - might have some other negative effect
  - regulators considered that an investigation of enantiomers was desirable and that such an investigation might in due course become mandatory.

- All of these matters provided a clear motive to isolate and test enantiomers - would have been well understood by notional skilled addressee.

- Investigation of the enantiomers of citalopram was an obvious goal for the ordinary skilled medicinal chemist in 1988.

- However, methods for resolving citalopram available at that time would not have given a sufficient likelihood of success to render invention obvious.
Claims 1 and 3 found to be insufficient:

Inventive step taken by inventors of Patent was not deciding to separate enantiomers of citalopram but finding a way it could be done.

“The first person to find a way of achieving an obviously desirable goal is not permitted to monopolise every other way of doing so. Claims 1 and 3 are too broad. They extend beyond any technical contribution made by Lundbeck.”

As such, Kitchen J concluded that Claims 1 and 3 of the Patent are invalid for insufficiency.
Escitalopram

Costs

• Both claimants and defendant sought costs, on the grounds that they had been, partially, successful.
• Generics (UK): £0.886M
• Arrow: £0.554M
• Teva: £0.624M
• Lundbeck: £1.815M

• In the end costs divided between claimants and defendant
CAFC: Forest Labs, Lundbeck v Ivax, Cipla (5 September 2007)

- Argument novelty and obviousness broadly similar
- No enablement of (+) enantiomer in prior art
- Failure of inventors and others to resolve citalopram without undue experimentation fully support conclusion that claimed subject matter would not have been obvious to one of ordinary skill in art
- No suggestion that product or method claims insufficient
- Patent found valid and infringed: Ivax and Cipla enjoined from commercialising (+) citalopram
Ranbaxy and another v Warner-Lambert: HC 2005, confirmed CA 2006
Atorvastatin (LIPITOR®)

- Concerned three patents:
  - EP 0 247 633: disclosed racemic atorvastatin
  - WO 89/07598: concerned salts of atorvastatin
  - EP 0 409 281: disclosed calcium salt of (R)-atorvastatin

- Ranbaxy sought a declaration that the 633 patent would not be infringed by commercialisation of (R)-atorvastatin

- Both claimants argued that 281 patent lacked novelty or inventive step over the 598 application.
Atorvastatin

Refusal to grant declaration of non-infringement

- At the time of filing 633 patent statins, as a class, where known and it was known that just one enantiomer of statins tended to be active
- Issue with 633 patent was did it only cover the racemate or did it also cover the (undisclosed) enantiomer.
- Refusing the declaration, Pumfrey J said:
  “In the '633 patent, it is absolutely clear from context throughout that formula (I) is being used to denote a racemate. In my judgment, every time the skilled person sees formula I or formula X he will see it with eyes that tell him that in that racemate, there is a single enantiomer that is the effective compound, and that he can resolve the racemate using conventional techniques to extract that enantiomer. When one comes to claim 1, which echoes the purpose of the invention with its conventional reference to pharmaceutically acceptable salts, he will, in my judgment, continue to see the formulae in this light. In my view, the claim covers the racemate and the individual enantiomers.”
The 281 Patent

Two grounds of invalidity raised:

- Lack of novelty over disclosure of WO 89/07598
- Obviousness over EP 0 247 633A

598 disclosed the enantiomer as a free acid and pharmaceutically acceptable metal salts thereof. Also it stated:

- The term "pharmaceutically acceptable metal salt" contemplates salts formed with the sodium, potassium, calcium, magnesium, aluminum, iron and zinc ions.

- This anticipated claim 1

- Pumfrey also found the selection of the calcium salt of the enantiomer obvious over the generic disclosure of 633A:
  - The resolution of the racemate was common general knowledge at the date. It was becoming preferred in the industry generally, and this particular resolution did not, on the evidence, involve any work that was not common general knowledge. Seven salts are specifically described. How can it be inventive to use one?
Synergy and Obviousness

Glaxo Group Ltd's Patent [2004] EWHC 477 (Ch)
Salmeterol/Fluticasone combined inhaler (Seretide/Advair®)

“It is sometimes thought that a patent may be saved from a finding of obviousness if a combination otherwise obvious has some unexpected advantage, and, in particular, an advantage caused by an unpredictable co-operation between the elements of the combination. I do not consider that such an approach is in general justified. There is a limited class of cases in which the patentee has identified an advantageous feature possessed by some members only of a class otherwise old or obvious, has described the advantageous effect in his specification and has limited his claim to the members of the class possessing this advantageous feature. Such a claim may be justified on the basis of what is called selection. Unexpected bonus effects not described in the specification cannot form the basis for a valid claim of this kind.”
Conclusions

- **Polymorphs**
  - Define very carefully
  - Make sure that peak patterns are reproducible
  - Have a clear idea of what the prior art discloses

- **Formulations**
  - Understand the functioning of the invention and claim it!
  - Avoid recipe claims

- **Combinations**
  - Describe and claim – as early as possible (for SPCs)
  - Explain why combination is unobvious
  - Give good basis for later results showing synergy, etc

- **Selection**
  - Be very careful about “fall back” positions