

Achieving Total Patent Protection to Maximise the Patent Life Cycle: Multi-Jurisdictional Perspectives

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- What to claim
 - drug class
 - drug active
 - drug precursor
 - drug salts, polymorphs, enantiomers, purity profiles
 - drug formulations
 - drug combinations
 - drug uses, first and second
 - synthetic and manufacturing processes
 - method of treatment (USA)

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■ When to claim

- watch novelty and inventive step
 - what is made available to public by:
 - publications, patent filings?
 - clinical trials?
 - USA: 35 USC §102(b) may act as statutory bar if “the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country more than one year prior to the date of the application for patent in the United States.” (emphasis added)
- file to maximise term of protection
 - USA: Patent term may be adjusted as result of prosecution delay by USPTO (extension of term) or applicant (reduction of term)

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■ Scope and essential similarity

- Europe
 - Directive 2004/27/EC: all salts, esters, isomers, mixtures of isomers, complexes or derivatives “shall be considered to be the same active substance unless they differ significantly” in safety and/or efficacy
 - regulatory obstacle to generic variants lowered
 - adequate scope of patent and Supplementary Protection Certificate protection even more important now

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- Scope and essential similarity (cont.)
 - USA – Drug Approval Applications:
 - New Drug Applications (NDA's) – for innovator drugs requiring detailed showings of safety and efficacy
 - Abbreviated New Drug Applications (ANDA's) – for generic drugs that are the “same as” innovator drug; approved on basis of chemistry and bioequivalence data
 - Federal Food Drug and Cosmetic Act § 505(b)(2) – for drugs incorporating changes to innovator drug, e.g. different salt, enantiomer, etc. of active ingredient; approved by reliance on safety and effectiveness of approved innovator drug.

USA:

Therapeutic Equivalence-Related Terms (from Introduction, Section 1.2, of the FDA Orange Book)

Pharmaceutical Equivalents: Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration (e.g., chlorbutepoxide hydrochloride, 5mg capsules). Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, marking configuration, release mechanism, packaging, excipients (including color, flavor, preservatives), expiration time, and, within certain limits, labeling.

Pharmaceutical Alternatives: Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex, 250mg capsules; quinidine sulfate, 200mg tablets vs. quinidine sulfate, 200mg capsules). Data are generally not available for FDA to make the determination of label to capsule bioequivalence. Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.

Different salts and esters of the same therapeutic moiety are regarded as pharmaceutical alternatives. For the purposes of this publication, such products are not considered to be therapeutically equivalent. There are no instances in this List where pharmaceutical alternatives are evaluated or coded with regard to therapeutic equivalence. Anhydrous and hydrated entities, as well as different polymorphs, are considered pharmaceutical equivalents and must meet the same standards and, where necessary, as in the case of ampicillin/ampicillin trihydrate, their equivalence is supported by appropriate bioavailability/bioequivalence studies.

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- The “product-by-property” claim
 - UK
 - arbitrary parameters having little technical significance do not confer inventive step (Raychem's Patent)
 - France
 - essential to check that there is no uncertainty regarding the measurement of the parameters characterizing the claim (e.g. First Instance Court of Paris, May 12, 2000, Purac Biochem v. Xyrofin)

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- The “product-by-property” claim (cont.)
 - Germany
 - functional definitions may provide wider protective scope, but may cause problems proving infringement in litigation
 - USA
 - “product-by-process” claims more controversial!
 - Conflict in court decisions re: validity
 - Scripps Clinic v. Genentech* (Fed. Cir. 1991) – patentability of product does not depend on its method of production
 - Atlantic Thermoplastics Co. v. Faytex Corp.* (Fed. Cir. 1992) – “process terms in product-by process claims serve as limitations. . .”

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- Equivalents
 - UK
 - “Protocol questions”
 - Does the variant have any material effect upon the way the invention works? If not,
 - would it have been obvious to a man skilled in the art that the variant would work in the same way? If so,
 - would the skilled man in the art nevertheless have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention?

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■ Equivalents

– France

- 1. Do the claimed means implement a novel function? If so,
- 2. Does the variant perform the same function for the same result as the claimed means? If so,
- 3. Does the variant go directly and unambiguously against the teachings of the patent?

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■ Equivalents (cont.)

– Germany

- 1. Does the infringement solve the same object as the invention with objectively similarly effective means?
- 2. Could a skilled person have found such means based on his experience and knowledge?
- 3. Did the patent provide basis for considering that no equivalent replacement of the claimed feature, by such means, was intended? (BGH, “Custodiol I” and “Custodiol II”)

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■ Equivalents

- USA
 - *WarnerJenkinson v. Hilton Davis* (US S. Ct. 1997)
 - “known equivalents”
 - “insubstantial differences”
 - “separate patentability”
 - does device perform substantially same function, in substantially same way, to achieve substantially same result
 - But – DOE “is not a license to ignore or erase structural or functional limitations of the claim. . .” *Athletic Alternatives v. Prince* (CAFC 1996)
 - *Festo Corp. v. Shoketsu* (US S. Ct. 2002) – All claim amendments presumed to be narrowing, eliminating DOE; presumption rebuttable on showing amendment to claim element was “unforeseeable at time of application” or “for some other reason” not included in original claim

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Key patent litigation in US, UK, Germany and across Europe

■ *Zantac* (ranitidine hydrochloride Form 2)

- UK - no litigation
- France – no reported litigation
- Germany - no litigation

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Key patent litigation in US, UK, Germany and across Europe

- *Zantac* (ranitidine hydrochloride Form 2) (cont.)
 - USA – *Glaxo v. Novopharm* (Fed. Cir. 1997)
 - Form 1 and Form 2 ranitidine hydrochloride – patents on both forms
 - Form 1 patent expired July 1997
 - Novopharm filed ANDA claiming its product only contained Form 1
 - District Court and CAFC held Form 2 patent not infringed
 - Glaxo: only examine product described in ANDA; since Novopharm's ANDA allowed for 10% Form 2, don't need to prove Novopharm's tablets actually contain Form 2

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Key patent litigation in US, UK, Germany and across Europe

- *Zantac* (ranitidine hydrochloride Form 2)
 - USA – *Glaxo v. Novopharm* (Fed. Cir. 1997) (cont.)
 - CAFC: "In a case . . . Involving a compound capable of existing in various forms . . . Statute requires an infringement inquiry on what is to be sold following FDA approval."

The "inquiry in a [Hatch-Waxman] suit is . . . Whether, if the drug were approved based upon the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense."

"This inquiry is based on all the relevant evidence, including the ANDA."

"[A]ctual samples . . . Required by the FDA generally removes much of the uncertainty from a court's otherwise hypothetical inquiry."

Novopharm provided Glaxo samples, but Glaxo did not offer sample analyses at trial, therefore no infringement

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Key patent litigation in US, UK, Germany and across Europe

■ Losec (omeprazole)

- UK - formulation patent found obvious
- Germany - Supplementary Protection Certificate and formulation patent found invalid (confirmed by ECJ)
- France - Supplementary Protection Certificate expired April 15, 2004 and formulation patent under challenge
- USA - formulation patent found valid but not infringed by Schwarz Pharma (but by other generics) by District Court and CAFC
 - *In re Omeprazole Patent Litig. Astia Aktiebolag v. Andrex, et al.* (Fed. Cir. 2003)

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Key patent litigation in US, UK, Germany and across Europe

■ Paxil (paroxetine hydrochloride hemihydrate)

- UK
 - hemihydrate patent challenged only by Apotex and none of the generics purport to sell hemihydrate - no trial date
 - anhydrate patent challenged unsuccessfully by BASF, validity affirmed on appeal, then challenged successfully by Apotex - appeal pending
- France – no reported litigation
- Germany
 - hemihydrate patent: Request for interlocutory injunction rejected
 - UTM for anhydrate: cancelled by GPTO, confirmed by Federal Patent Court and German Supreme Court

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Key patent litigation in US, UK, Germany and across Europe

■ Paxil (paroxetine hydrochloride hemihydrate) (cont.)

- USA
 - *SmithKline Beecham Corp. v. Apotex Corp.*, 247 F.Supp.2d 1011 (N.D.Ill. 2003)
 - Apotex filed an ANDA for approval to market paroxetine hydrochloride anhydrate SB argued that Apotex's anhydrate converts to paroxetine hydrochloride hemihydrate
 - District Court finds that anhydrate converts to hemihydrate but found no infringement based on claim construction
 - The '723 patent notes that hemihydrate is not hygroscopic and thus has certain manufacturing benefits
 - District court limited claim 1 to "commercially significant" amounts of hemihydrate "High double digits to contribute any commercial value"

Key patent litigation in US, UK, Germany and across Europe

■ Paxil (paroxetine hydrochloride hemihydrate)

- USA (cont.)
 - *SmithKline Beecham Corp. v. Apotex Corp.*, 365 F.3d 1306 (Fed. Cir. 2004). (cont.)
 - SB did not establish Apotex will make "high double digits" amounts thus, Apotex does not benefit from hemihydrate.
 - District Court found that SB was responsible for seeds of hemihydrate
 - Thus, district court found that Apotex was not responsible for the hemihydrate in its product
 - The Federal Circuit agreed with SB's claim construction, and found Apotex's product infringed.

Key patent litigation in US, UK, Germany and across Europe

- Paxil (paroxetine hydrochloride hemihydrate)
 - USA (cont.)
 - *SmithKline Beecham Corp. v. Apotex Corp.*, 365 F.3d 1306 (Fed. Cir. 2004).
 - Ultimately, SB did not prevail in the litigation because the Federal Circuit found the claim invalid for public use under 102(b).
 - SB conducted clinical trials with the hemihydrate crystalline form in the United States in May-June, 1985, to establish that paroxetine hydrochloride worked as an antidepressant. SB filed its patent application in the United States in October, 1986, more than one year after the first use of the hemihydrate in the United States.
 - The Federal Circuit held that the clinical trials performed by SB were not an experimental because the claim did not literally recite any intended use, thus (according to the Court), SB had no right to experiment to determine whether P-HCL hemihydrate worked for its intended purpose.
 - The Federal Circuit agreed with SB's claim construction, and found Apotex's product infringed.

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Key patent litigation in US, UK, Germany and across Europe

- Paxil (paroxetine hydrochloride hemihydrate)
 - USA (cont.)
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Key patent litigation in US, UK, Germany and across Europe

■ Fosamax (alendronate)

- UK
 - composition patent found to lack novelty and second medical use (periodicity) patent found invalid as a method of therapy, at first instance and on appeal - permission to appeal to House of Lords refused
- France – no reported litigation
- Germany – not pending

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Key patent litigation in US, UK, Germany and across Europe

■ Fosamax (alendronate)

- USA - *Merck v. Teva* (D. Del. 2003)
 - patent covering weekly administration held valid and infringed by District Court
 - Teva stipulated infringement if patent valid
 - Teva argued collateral estoppel on factual findings underlying validity, based on British High Court's finding that counterpart EP was invalid. D. Del. found obviousness vs. inventive step standards different and denied
 - D. Del. found not obvious over other prior art; on appeal to CAFC

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Key patent litigation in US, UK, Germany and across Europe

■ Fosamax (alendronate)

- USA - *Merck v. Teva* (Fed. Cir. 2003)
 - patent covering method of using alendronate held valid and infringed by District Court and CAFC
 - Claim to method using alendronate acid; Merck FDA-approved product – alendronate sodium salt
 - Teva's ANDA: alendronate sodium salt; no infringement because claim is to alendronate acid, not salt
 - CAFC: Persons skilled in art recognize acid is active agent, and is administered in form of the salt; no evidence claimed method of treatment not achieved by the salt; claim infringed by acid, whether administered pure or as salt

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Key patent litigation in US, UK, Germany and across Europe

■ Synthon vs SKB - Paxil

- UK
 - patent covering paroxetine mesylate (PMS) found at first instance to be anticipated by teachings of Synthon patent application because judge concluded that these were the “same invention”
 - Court of Appeal rejected this reasoning and found patent valid on basis of established test of novelty - teachings would not give PMS as claimed
 - appeal to House of Lords pending
- DE
 - litigation stayed, pending decision by Dutch Court on cross-border injunction
 - competence and EPO decisions on validity

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Key patent litigation in US, UK, Germany and across Europe

■ *Synthon vs SKB* - Paxil

- USA - *SKB v. Synthon* (M. Dist. North Carolina)
 - PMS product for which Synthon sought FDA approval accused of infringement of counterpart US PMS patent
 - Synthon challenged validity – similar arguments as in UK
 - case settled before trial on confidential terms

Key patent litigation in US, UK, Germany and across Europe

■ USA - *Schering vs Geneva et al.*, D. New Jersey and CAFC

- Patent for metabolite of previously patented antihistamine (Claritin/loratadine) invalid as inherently anticipated, even though prior art did not disclose any compound identifiable as claimed invention
- Metabolite (DesCarboethoxyLoratadine – “DCL”) “necessarily” formed upon ingestion of previously patented antihistamine under normal conditions
 - *Continental Can v. Monsanto* (Fed. Cir. 1991) – “To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled by reference to extrinsic evidence. Such evidence must make clear that missing descriptive matter is *necessarily* present . . .” (emphasis added)
- Patent claims broadly construed to cover DCL in any form – whether metabolized within human body or synthetically produced in purified and isolated form
- Narrower claim (synthetically produced?) = different result?

New forms and polymorphs

- Purity/impurities and novelty
 - UK
 - SB's paroxetine hydrochloride anhydrate patent claims a process for making crystals substantially free of bound organic solvent by use of a displacing agent
 - *SB vs Apotex*: Apotex process found at first instance not to infringe: judge concluded that the resulting material substantially free of bound organic solvent was not produced by a displacement step
 - appeal pending
 - France
 - no reported litigation in the same matter
 - In another matter, a solution characterized by its active ingredient, its sterility and limpidity, was held lacking novelty since the active ingredient was known (First Instance Court of Paris, *Fisons v. Europhtha*, June 15, 1999)

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New forms and polymorphs

- Purity/impurities and novelty (cont.)
 - Germany
 - SB's anhydrate UTM cancelled for lack of novelty
 - USA
 - Litigation pending against various defendants in Philadelphia and cases consolidated for discovery.

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New forms and polymorphs

- Inevitable result
 - UK
 - “Showing that some types of implementation of a general teaching will produce a product within a subsequent claim may show that the subsequent claim is invalid for obviousness. By itself it does not prove anticipation” per Laddie J in *Inhale vs Quadrant*

New forms and polymorphs

- Inevitable result (cont.)
 - France
 - A process described in the prior art anticipates a product only if the skilled person could:
 - obtain the product when implementing the known process,
 - identify the obtained product with the methods available at this time
 - As an example of product claim which is not anticipated by a process because the prior art document does not provide all the parameters leading to the product: Court of Appeal of Paris, March 10, 2004, *Rhodia v. Asec*
 - Regarding inherency, French caselaw is in line with the EPO (G2/88 and G6/88): First Instance Court of Paris, 3^e Ch, March 14, 2000 (not published) *Abbott v. Wyeth Nutrition*:

« It does not anticipate claim 15 since, even though it covers a food product having the same composition as the one described in the claim, it does not anticipate the results described in the claim, i.e. the stimulation of repair and the regeneration of intestinal cells in infants and in adults ».

New forms and polymorphs

■ Inevitable result (cont.)

- Germany
 - What a skilled person necessarily finds when practising the prior art, is anticipated by said prior art (BGH, “Thrombozytenzählung”)

New forms and polymorphs

■ Inevitable result (cont.)

- USA – Inherent Anticipation
 - Prior art reference may anticipate when claim limitation(s) not expressly found in reference are nonetheless inherent in it. *MEHL/Biophile v. Milgraum* (Fed. Cir. 1999)
 - *Continental Can v. Monsanto* – must be “necessarily” present; “Inherency . . . May not be established by probabilities or possibilities. The mere fact that a certain thing *may* result . . . Is not sufficient.” (emphasis in original)
 - *MEHL/Biophile* – “Occasional results are not inherent.”

New forms and polymorphs

- *SB vs Synthon/Merck v Synthon*
 - UK - paroxetine mesylate patent/*Synthon vs SKB* - see above
 - France – see above
 - Germany – see above
 - USA – see above

New forms and polymorphs

- The cases of the “disappearing polymorph”
 - UK
 - paroxetine hydrochloride anhydrate patent - 407 patent gives paroxetine hydrochloride hemihydrate (more stable pseudo polymorph)
 - France – no reported litigation
 - Germany

New forms and polymorphs

- The cases of the “disappearing polymorph” (cont)
 - USA
 - Form 1 ranitidine – *Glaxo v. Novopharm*
 - Ritonavir/Norvir (Organic Process Res. & Dev. 2000, 4, 413-417)
 - From ritonavir discovery until NDA filing, only one crystalline form known
 - Attempts to identify others unsuccessful
 - 2 years after Abbott launched Norvir, some lots failed dissolution spec.
 - Investigation revealed new crystal form (Form II) than known one (Form I)
 - Form II didn't work in FDA-approved semi-solid formulation because less soluble
 - Form II spread within Abbott Chicago facility, and then to Italy – SEEDS!
 - Developed new formulation accommodating presence of Form II
 - Controlled process to make Form I again
 - paroxetine hydrochloride hemihydrate - SB vs Apotex
 - “SmithKline's experts applied the disappearing polymorph theory to show that Apotex's PHC anhydrate tablets inevitably convert to hemihydrate when combined with moisture, pressure and practically ubiquitous PHC seeds.”

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New manufacturing processes - impurities and novelty

- Know-how or patents?
 - enablement versus non-disclosure
 - US best mode requirement – 35 USC §112: “The specification shall contain a *written description* of the invention . . . In such full clear, precise and exact terms as *to enable* any person skilled in the art . . . To make and use the same, and shall set forth *the best mode contemplated by the inventor* of carrying out his invention.” (emphasis added)
 - biological/fermentation processes not easily reverse engineered or copied

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New manufacturing processes - impurities and novelty

- Simvastatin, Choline salicylate, Citalopram, Amlodipine
 - Simvastatin made by biological process - limited generic supplies available
 - Merck's "Dimeric contamination" patent revoked in Germany
 - Choline salicylate
 - Citalopram
 - EPO: Opposition proceedings on recrystallization patent
 - UK: settlement following inspection of Lagap's process
 - Amlodipine (amlodipine besylate/maleate)

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New manufacturing processes - impurities and novelty

- Simvastatin, Choline salicylate, Citalopram, Amlodipine (cont.)
 - US - *Pfizer v. Dr. Reddy's Labs.* (Fed. Cir. 2004)
 - Central issue was whether Patent Term Extension ("PTE"; 35 USC §156) applied to full scope of claim (amlodipine + acid addition salts), or whether limited to commercial product (Norvasc), amlodipine *besylate*
 - Dr. Reddy's sought to market amlodipine *maleate* and argued PTE applied only to amlodipine besylate so free to market amlodipine maleate
 - CAFC: "35 USC 156(f) makes clear that "drug product" means the active ingredient "including any salt or ester of the active ingredient"
 - "active ingredient" = amlodipine, whether as besylate or maleate salt
 - PTE extends to amlodipine and any salt or ester. ∴ Dr. Reddy's maleate product infringes

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New manufacturing processes - infringement

- France
 - Taxol case, First Instance Court of Paris, March 27, 2002, Aventis Pharma v. Bristol-Myers Squibb

New formulations

- Obviousness and scope
 - Formulation science is predominantly empirical and therefore susceptible to erroneous hindsight analysis
 - e.g. claim to drug active tablet formulated with known excipients
 - Relatively easy to get regulatory approval for sub-optimal non-literal infringements
 - e.g. formulation in which a claimed feature is missing or an excluded feature is added

New formulations

- Different active in a known formulation
 - Each drug active presents its own delivery problems, e.g. topical vs systemic, susceptibility to low/high/physiological pH, bioavailability/peak concentration/AUC requirements, etc
 - Known formulation solutions may be available but was there real expectation of success?
 - Was there a “teach away” from the known solution?
 - Enantiomers, pro-drugs and metabolites may all be novel and inventive but are they sufficiently advantageous for the market to pay more for them?

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New formulations

- Known active in a (compositionally defined) new formulation
 - Delayed or controlled release formulations
 - but will market pay for improved formulation?
 - US yes, UK no, France and Germany in many cases: yes
 - Depends on the improvement

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New formulations

- Known active in a functionally defined formulation
 - Second medical use
 - Characterisation by stability, delivery profile, bioavailability, avoidance of toxicity

New formulations

- Caselaw about infringement of patents covering numerical ranges
 - UK: leading authority (*Catnic*) was about the word “vertical”
 - In *Auchincloss* a range was interpreted as meaning the range and no more - but not considered by Court of Appeal
 - France
 - A value outside the claimed range excludes infringement if said range is:
 - essential for distinguishing the claim from prior art
 - or presented as exact and limitative
 - or essential for performing the function of the claimed means
 - Germany: leading authority (*Custodiol*) is about numerical range limits; recites *Auchincloss*. Equivalence possible, but practically limited to standard deviation from numerical value.

New formulations

- Caselaw about infringement of patents covering numerical ranges (cont.)
 - USA: USPTO and courts find claims anticipated where prior art teaches:
 - a species falling within claimed range – *Titanium Metals v. Banner* (Fed. Cir. 1985)
 - a range overlapping the claimed range – *Chester v. Miller* (Fed. Cir. 1990)
 - a range falling within the claimed range – *In re Mindick* (CCPA 1967)
 - a range sharing an end point with the claimed range – *In re Nehrenberg* (CCPA 1960)
 - Use of “about” or “approximately” may avoid strict numerical boundary, but cannot be used to render limitation meaningless
 - Hilton Davis v. Warner-Jenkinson* (Fed. Cir. 1997) – process performed at pH of 5 found equivalent to claimed pH range of “from approximately 6.0 to 9.0

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New metabolites

- Terfenadine, DCL/Loratadine
 - UK
 - Terfenadine: infringement/novelty squeeze not argued in House of Lords as parties agreed novelty only should be in issue
 - Patent held invalid
 - Loratadine: no UK cases
 - France
 - No litigation
 - However, a metabolite is likely to be held novel if it could not be identified in the past,
 - According to the rules about contributory infringement, the sale of the prodrug should be infringing only if there is a reference to the metabolite
 - Germany
 - Terfenadine: no infringement, since competitors' products were subject-matter of expired (older) patent on terfenadine.
 - Metabolite patent validity not attacked (probably valid)
 - No loratadine case in DE

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New metabolites

■ Terfenadine, DCL/Loratadine (cont.)

- USA
 - Terfenadine (Seldane)

Marion Merrell Dow v. Baker Norton (S.D. Florida 1996)

- Baker Norton sought FDA approval of generic Seldane (terfenadine) after MMD's basic patent expired
- MMD sued on '129 patent to terfenadine acid metabolite (TAM); patents taking generic terfenadine will produce TAM in vivo, inducing patients' infringement
- Dispute whether claimed "compound" includes in vivo conversion (MMD) or is limited to synthetic means (Baker Norton)
- Court construed claim to be limited to TAM made synthetically not metabolically
- Cancellation of claim including "essentially pure" in response to rejection of that claim and broader one without

New metabolites

■ Terfenadine, DCL/Loratadine (cont.)

- USA
 - Terfenadine (Seldane)

Marion Merrell Dow v. Geneva (D. Colorado 1994)

- Geneva sought FDA approval of generic terfenadine
- MMD sued on TAM patent; same in vivo infringement argument
- Geneva attacked validity: earlier '217 patent disclosed terfenadine, which when taken orally inherently metabolizes to TAM and therefore anticipates
- Court denied summary judgment of non-infringement and invalidity

Note: In 1997, Hoechst Marion Roussel and Baker Norton voluntarily discontinued distribution of all terfenadine-containing antihistamine products in U.S., on basis it caused serious and potentially fatal heart condition when taken with other medications. HMM replaced Seldane with Allegra.

New metabolites

■ Terfenadine, DCL/Loratadine (cont.)

- USA
 - Loratadine

Schering Corp. v. Geneva (Fed. Cir. 2003)

- Earlier patent to loratadine inherently anticipated later claims to its metabolite, DesCarboethoxyloratadine (DCL), based on inevitable in vivo conversion of loratadine to DCL
- CAFC noted that metabolites may be patentable, but not as “bare” compound claims; applicant may be able to claim purified isolated metabolite or composition containing the metabolite

New metabolites

■ Intermediates

- Synthetic intermediates - as part of process claim may provide scope to prevent importation of direct product of the process
- Metabolic intermediates - likely to present the same infringement/novelty problems that arose in Terfenadine

New metabolites

■ De minimis rule?

- UK
 - *Monsanto vs Merck*: 10^{-9} molar quantity of enol tautomer in vivo de minimis and not an infringement
 - but not considered by Court of Appeal
 - *SB vs Apotex*: Jacob J suggestion that preliminary injunction may not be granted unless alleged infringement contained more than 10% paroxetine hydrochloride hemihydrate
- France
 - No caselaw
 - However, infringement is unlikely if the product is present in a quantity too low to have any effect
- Germany - “Relevant technical effect” must be provided by claimed feature in the infringing product

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New metabolites

■ De minimis rule? (cont.)

- USA
 - *Deuterium Corp. v. U.S.* (U.S. Cl. Ct. 1990) – “This court questions whether any infringing use can be *de minimis*. Damages for extremely small infringing use may be *de minimis*, but infringement is not a question of degree.”
 - *Embrex v. Service Eng'g Corp.* (Fed. Cir. 2000) – Defendant’s two experiments, in course of designing around patented in ovo injection found to be directed to commercial purpose, not “for amusement to satisfy idle curiosity, or for strictly philosophical inquiry” and thus not *de minimis* infringement.
 - *SmithKline v. Apotex* (Fed. Cir. 2003) – small amounts of patented paroxetine hydrochloride hemihydrate in paroxetine hydrochloride anhydrate tablets infringed SmithKline’s patent.

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New therapies/indications

- Carvedilol, “Knochenzellenpräparat”
 - Carvedilol: use of beta blocker for congestive heart disease
 - DE: Federal Patent Court found no new indication (Boehringer Mannheim’s patent)
 - Biocyte: claims to umbilical cord stem cells in cryopreservative revoked by EPO
 - Knochenzellenpräparat:
 - DE: Federal Patent Court found dosage regime (“Therapy plan”) basically patentable (but, in this case, not novel).

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Second medical use claims and disguised therapeutical methods

- Specific/class/functional definitions
 - Second medical use claim result of prohibition in EPC of claims covering methods of therapy
 - typical form: use of known compound **X** for the preparation of a medicament for the treatment of disease **Y**
 - claims can cover use of class of compounds, specific compounds and/or effects such as blood levels or toxicity

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Second medical use claims and disguised therapeutical methods

- Mode of administration and means of delivery
 - Claims can be limited to mode of administration, e.g. simultaneous or sequential delivery of a combination
 - Claims can be limited to a means of delivery, e.g. oral formulation

Second medical use claims and disguised therapeutical methods

- Dosage regime
 - Claims can be limited to dosage regimens and/or infusion regimens
 - e.g. 75 mg - 300 mg every 12 to 18 hours
 - but possibly not valid in UK because of Taxol decision
 - probably valid in DE, "Knochenzellenpräparat"

Second medical use claims and disguised therapeutical methods

■ Taxol, Viagra, Vioxx, rapamycin

- Taxol
 - UK: Court of Appeal found claim to use of Taxol for the preparation of a medicament for the administration of a defined dose of taxol over a period of 3 hours for the treatment of cancer to be a method of therapy
 - EPO: Opposition Division did not find claim invalid on this ground
- USA
 - *Bristol-Meyers Squibb v. Boehringer Ingelheim* (D. New Jersey 2000): Preambles of method of treatment claims reciting purpose limitations; claims invalid over prior art, because it carried out claimed method steps
 - *Bristol-Meyers Squibb v. Benvenue Labs.* (Fed. Cir. 2001): Preamble merely expresses a purpose and intended result; steps of claim same regardless of achieving purpose in preamble; affirmed invalidity

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Second medical use claims and disguised therapeutical methods

■ Taxol, Viagra, Vioxx, rapamycin

- Viagra
 - UK: Court of Appeal found claim covering use of PDE_v inhibitors for the preparation of a medicament for the treatment of male erectile dysfunction invalid for obviousness
 - EPO: Opposition Division came to same conclusion - appeal pending

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Second medical use claims and disguised therapeutical methods

- Taxol, Viagra, Vioxx, rapamycin
 - Viagra (cont.)
 - USA: proceedings pending in District Court
 - Pfizer v. GSK/Bayer* (D. Del.)
 - GSK/Bayer copromoting Levitra
 - Pfizer sued on claim to method of treating erectile dysfunction comprising using an effective amount of a PDE-5 inhibitor (broad claim!)

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Second medical use claims and disguised therapeutical methods

- Taxol, Viagra, Vioxx, rapamycin
 - Viagra (cont.)
 - USA: proceedings pending in District Court
 - Pfizer v. Lilly/ICOS* (D. Del.)
 - Lilly/ICOS selling Cialis
 - Pfizer sued on same claim

Cases not consolidated but parties ordered to coordinate discovery

PTO Commissioner ordered reexamination of all Pfizer claims;
Lilly/Icos also requested reexamination

D. Del. stayed both litigations pending outcome of reexamination

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Second medical use claims and disguised therapeutical methods

- Taxol, Viagra, Vioxx, rapamycin
 - Vioxx
 - USA – no reported cases
 - Rapamycin
 - UK: Court of Appeal found claim to use of rapamycin for the preparation of a medicament for inhibiting organ transplant rejection not infringed but valid - no basis on which it would have been obvious that derivative SDZ RAD would work
 - USA – no reported cases

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Second medical use claims and disguised therapeutical methods

- Infringement and regulatory considerations
 - European Union: currently applicant under abridged procedure required to have harmonised summary of product characteristics - if therapeutic indications include one covered by a second medical use claim, then risk of infringement
 - from 20 November 2005 EC Regulation 726/2004 permits SMPC to omit indications or dosage forms which are still covered by patents

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