Royal Society of Chemistry, Law Group

Recent Chemistry Case Law 2014

Kempner & Partners

Hospira UK Limited

-v-

Genentech Inc

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Trastuzumab

- Monoclonal antibody used in adjuvant chemotherapy against cancers that overexpress the HER2 gene
- Successfully commercialised as Herceptin by Genentech
- SPC for trasuzumab expired on 28 July 2014
- Two follow-on patents in force after expiry of SPC:
  - EP 1 210 115 (dosage regimen)
  - EP 1 308 455 (composition)

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Patents Court

- Validity of 115 and 455 patents challenged by Hospira
- Heard before Birss J in March 2014

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The 115 Patent

- Very broad description, including use against many cancers and other indications, but very narrow claims
- Claim 1 limited to :
  - Use to treat breast cancers overexpressing HER2
  - with initial dose of 8mg/Kg, and
  - Subsequent doses of 6mg/Kg,
  - Administered at 3 week intervals

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The Common General Knowledge

- Shared by clinician and pharmokineticist in team who would work together
- Trastuzumab used in conjunction with cytotoxic agents such as paclitaxel
- Use to treat breast cancers overexpressing HER2
- The FDA label for Herceptin
- Target serum concentration of 20µg/ml
- Safe to administer up to 8mg/Kg
- The benefit of convenience

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Questions about Construction

- Is the mere proposal to use a treatment, without the disclosure of efficacy, sufficient?
- Must there be clinical trial results in the patent specification?
- Clinical trials are expensive, but a mere proiposal is not a contribution to the art.
- The requirements for sufficiency must be balanced against the rules of novelty and inventive step
- Plausibility

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Obviousness

- The FDA label discloses:
  - initial 4mg/Kg with subsequent 2mg/Kg at weekly intervals
  - paclitaxel administered in a 3 weekly schedule
  - steady state serum concentration between weeks 16 and 32 with troughs of 79 and peaks of 123µg/ml
- Would a 3 weekly regimen occur to a clinician, and if so, would he try it?
- Pharmokinetics shows trough concentration of 20µg/ml from 500mg administered 3 weekly

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Obviousness – Decision

- A pharmacokinetics expert in the team would not regard 8mg/Kg followed by 3 weekly 6mg/kg as inventive, and would see no reason not to undertake a clinical trial
- The clinician in the team would see no reason not to undertake a trial with 3 weekly dosing, would expect it to work, and would be encouraged to do so by the great benefit of increased convenience
- 115 Patent held to be obvious with regard to the FDA label in the light of common general knowledge

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Sufficiency

- If claim 1 of 115 is not obvious, is it insufficient?
- The assertion that the invention will work across the scope of the claim must be plausible or credible
- There is no pharmacokinetics on 3 weekly dosing in the patent, so would the FDA label support doing a trial?
- Held that if claim 1 did involve an inventive step, the team would not conduct a trial based on the information in the patent and cgk, therefore the patent is invalid for insufficiency

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The 455 patent

- Concerned with the purification of trastuzumab for therapeutic use
- Claim 1 defines a composition of trastuzumab with <25% “acidic variants” (mainly with asparagine at position 30 deamidated to aspartate)
- The patent explains that such a composition can be made by a special reverse wash ion exchange method, but claim 1 is not limited to product made in this way.
- Only the reverse wash method of purification is described or exemplified in the patent

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The 455 patent

- Describes the use of affinity chromatography to extract antibodies from the mixture derived from cell culture
- The product from the affinity column is purified by the reverse was method
- The product after the reverse wash has a lower level of acidic variants (ca.13%) than the starting material (ca.25%)
- States that reverse wash improves the yield/purity ratio, but quotes no figures, and does not state that <25% acidic variants cannot be obtained without reverse wash step

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The Common General Knowledge

- Protein can be degraded by deamidation of asparagine residues to aspartate
- Protein purification techniques such as ion exchange, affinity and size-exclusion chromatography
- A trade off between purity and yield
- As the scale of a chromatographic separation increases, the resolution decreases

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Claim Construction

- Claim 1 is to "a composition for therapeutic use"
- Does this require full manufacturing scale?
- Dependent claims to compositions with <20%, <13% and about 1 to 18% acidic variants

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Novelty

- Lack of novelty requires the prior art to make an enabling disclosure (Lord Hoffmann in *Synthon*)
- Andya discloses a composition made by reconstituting lyophilised trastuzumab containing 82% trastuzumab
- Quantity sufficient for therapeutic use
- Method disclosed is slow and troublesome, but it would yield a composition with claim 1 (and claims 2 and 4)
- Andya does not anticipate claim 3 (<13% acidic variant)
- Claim 3 is not invalid for lack of novelty, but claims 1, 2 and 4 are

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Obviousness

- The 455 patent claims trastuzumab with a specified impurity levels *per se*
- Would it be obvious to want to make such products?
- Could they be made without invention?
- The reverse wash method taught by 455 is irrelevant
- The reverse wash method is the subject of another Genentech patent, EP 1 308 456, which is in force

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Obviousness Attacks

- Waterside
- Andya
- Common general knowledge
- Common general knowledge plus Protein A

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Obviousness Attacks – Waterside

- Slides presented at a conference by Genentech relating to analysis of trastuzumab manufactured in CHO cells at full production scale for Phase III trials
- Analytical chromatograms on cation exchange columns showed that trastuzumab could be separated from the Asn 30 acidic variant
- Discloses trastuzumab for therapeutic use
- No level of acidic variants stated

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Obviousness Attacks – Waterside

- Skilled team would understand from waterside that trastuzumab for therapeutic use could be made by method described
- It would be obvious to make it with low level of impurity
- Waterside teaches that any level of impurity can be achieved by the known technique described
- Purification method described in 455 is not the only way
- All relevant claims held invalid for lack of inventive step

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Arguments against Obviousness over Waterside

- Ion exchange purification would be difficult at production scale
- Genentech did not remove the acidic variants
- Variants were not generally removed
- **But:**
- Position 30 is in an area that affects antibody binding
- Acidic variant has lower activity, so larger amounts would need to be administered

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Obviousness – cgk plus Protein A

- It was obvious to make trastuzumab in CHO cells
- 455 discloses that such product falls within claim 1 without further purification (24.2% acidic variants)
- **But**:
- Impurity levels disclosed in 455 include levels of 25% to 29% acidic variants
- A composition within claim 1 was not inevitable, and hospira had no experimental evidence
- Birss J held that Hospira had not proven its case based on this argument, so it failed.

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Present Position

- 455 Patent revoked
  - No appeal sought
- 115 Patent revoked
  - Permission to appeal refused by High Court
  - Permission to appeal granted following application to Court of Appeal

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