Protecting ‘singles’, ‘combinations’ and ‘loose combinations’

Michael Pears , Patent Attorney
Lucy Sharples, Trainee Patent Attorney

Overview

1. Current position on Article 3(a)
2. Examples of how case law is being applied and general principles
3. Pending referrals at CJEU
4. Protecting "loose" combinations
5. Thoughts and conclusions

Refresher of Article 3(a) – product is protected by a basic patent in force

- Not enough for Product to infringe a patent for it to be protected
  - Patent to A alone does not "protect" A+B
  - Medeva (C-322/10) – active ingredients of a combination must be "*specified in the wording of the claims of the basic patent*"
  - Express definition is not, however, necessary
  - Lilly v HGS (C-493/12) – functional definitions may suffice
- Spectrum of specificity

Infringement test ⟷ **Express definition in claims**

Teva v Gilead (C-121/17)

- Gilead's SPC for Truvada®
  - Combination of tenofovir disoproxil and emtricitabine
- Patent EP 915894
  - Claim 27: "A pharmaceutical composition comprising a compound according to any one of claims 1-25 [Claim 25 recites TD] … and optionally other therapeutic ingredients"
- Teva sought invalidation, which led to referral to CJEU

Teva v Gilead (C-121/17)

"…a product composed of several active ingredients…is 'protected by a basic patent in force'…where, **even if the combination of active ingredients…is not expressly mentioned in the claims of the basic patent, those claims relate necessarily and specifically to that combination**.

For that purpose, from the point of view of a person skilled in the art and on the basis of the prior art at the filing date or priority date of the basic patent:

- [a] the combination of active ingredients must **necessarily, in the light of the description and drawings of that patent, fall under the invention** covered by that patent; and
- [b] each of those active ingredients must be **specifically identifiable**, in the light of all the information disclosed by that patent."

Royalty Pharma (C-650/17)

- Royalty Pharma's SPC application for Januvia®
  - Sitagliptin
- Patent EP 1084705
  - Claim 2: "DP IV-inhibitor for use in lowering blood glucose level…for alleviation of diabetes mellitus…"
- Refused by German Patent and Trade Mark Office (DPMA), which led to referral to CJEU

Royalty Pharma (C-650/17)

"…a product is 'protected by a basic patent in force'…**if it corresponds to the general functional definition used by one of the claims…and**

- **it necessarily comes within the scope of the invention covered by the basic patent** …,
- provided that it is **specifically identifiable**, in the light of all the information disclosed by that patent, by a person skilled in the art, based on that person's general knowledge in the relevant field at the filing date or priority date of the basic patent, and on the prior art at that date.

…a product is not 'protected by a basic patent in force…if, although covered by the functional definition given in the claims of that patent, **it was developed after the filing date…following an independent inventive step**."

Part 1/2 of test – questions remain

- Product must necessarily … **fall under/come within the scope of the invention**
    - What is required by this?
        - Single active ingredients – product must meet functional definition (see para 39 of C-650/17)
        - Combinations – product must be a "*specification required for the solution of the technical problem disclosed by the patent*" (see para 48 of C-121/17)
            - A and B (not just A) must be required for solution
            - Impact on "optional" elements in claims?
            - Circumvent via divisional application to A+B? Probably not

Part 2/2 of test – questions remain

- Product must be **specifically identifiable**
  - Express definition not necessary, but what is?
  - Actual knowledge at priority date of active ingredient, e.g. from description or prior art / CGK
  - What if active ingredient not created as of priority date?

Para 49: *"…account must be taken **exclusively** of the **prior art at the filing date or priority date** of that patent, such that the product must be **specifically identifiable by a person skilled in the art in the light of all the information disclosed by that patent**."*

Para 50: *"Were it to be accepted that such an assessment could be made taking into account results from **research which took place after the filing date or priority date** of the basic patent, an SPC could enable its holder **unduly to enjoy protection for those results** though they were not yet known at the priority date or filing date of that patent, what is more outside any procedure for the grant of a new patent"*

  - What does 'developed … following an independent inventive step' mean?
  - What about active ingredients created after priority date by routine development?

How has the test been applied on a national level?

Teva v Gilead – UK High Court and Court of Appeal

Claim wording	"and other therapeutic ingredient"
Product	Tenofovir disoproxil & Emtricitabine (both small molecules)

"Fall under the invention"

- "Fall under the invention" ≠ extent of protection test
- Combination must embody the technical contribution of the patent / claim must require two components

"Specifically identifiable"

- "and other therapeutic ingredient" is not sufficient
- Emtricitabine was not mentioned as a member of any structural or functional group of compounds
- Not known in the art to be an anti-HIV agent

How has the test been applied on a national level?

Royalty Pharma – German Federal Patent Court

Claim wording	"DP IV-inhibitor"
Product	Sitagliptin (small molecule)

"Fall under the invention"

- Satisfied as meets functional definition

"Specifically identifiable"

- Must be considered specifically identifiable without fictitious knowledge of product
- Results of research obtained after the priority or filing date of the basic patent must not be taken into account
- Existence of later compound patent suggests not "specifically identifiable"

How has the test been applied on a national level?

Wyeth and The General Hospital Corp – French Supreme Court

Patent	EP 1848414
Claim wording	"an irreversible EGFR inhibitor"
Product	osimertinib (small molecule)
Later patent?	Yes (filed 6 years later – AZ)

"Fall under the invention"

- Satisfied as meets functional definition

"Specifically identifiable"

- Product was unknown to the skilled person at filing date and skilled person could not deduce it directly and unambiguously from the patent
- Structural element that makes osimertinib an irreversible inhibitor (Michael acceptor) first described after patent was filed
- The fact later patent cited earlier patent does not mean that there is no "independent inventive step"

How has the test been applied on a national level?

Ono Pharmaceuticals – French Supreme Court

Patent	EP 1537878 (Ono Pharmaceuticals *et al*)	
Claim wording	"anti-PD-1 antibody that inhibits the PD-1 immunosuppressive signal"	
Product	nivolumab	pembrolizumab
Later patent?	Yes (filed 3 years later – Ono Pharmaceuticals *et al*)	Yes (filed 5 years later - Merck)

"Fall under the invention"

- Satisfied as both antibodies met functional definition

"Specifically identifiable"

- Time taken to develop antibodies does not indicate "independent inventive step"
- Relevant questions:
  - Were methods to develop mAbs known to skilled person and does patent describe how to screen those that perform function of invention?
  - Could skilled person on reading patent and CGK obtain by routine operations all antibodies fulfilling function covered by patent?

How has the test been applied on a national level?

Dana Farber Cancer Institute – French Court of Appeal

Patent	EP 1210424 (Dana Farber Cancer Institute)
Claim wording	"antibody that selectively binds to [particular PD-1 polypeptide]"
Product	avelumab
Later patent?	Yes (filed 11 years later by Merck)

"Fall under the invention"

- Satisfied as antibody met functional definition

"Specifically identifiable"

- Antibody generation against given antigen was routine at filing date
- Inventive step of subsequent patent recognised not because of ability to bind PD-L1 but because of cross-species reactivity of avelumab

How has the test been applied on a national level?

Dana Farber Cancer Institute – Portuguese Supreme Court

Patent	EP 1210428 (Dana Farber Cancer Institute)
Claim wording	"anti-B7-4 antibody that inhibits the interaction of B7-4 and PD-1"
Product	Atezolizumab
Later patent?	Yes (filed 8 years later by Roche)

✓ **"Fall under the invention"**

- Satisfied as antibody met functional definition

✗ **"Specifically identifiable"**

- Atezolizumab was one of an indeterminate number of possible antibodies that satisfy functional definition
- Atezolizumab had an Fc modification
- Basic patent must clearly and unambiguously enable skilled person to identify specifically the product as of the filing date

How has the test been applied on a national level?

Georgetown University - modified HSV-1 virus

Patent	EP 1776957 (Georgetown University)
Claim wording	Claim 1: "a HSV that replicates in dividing cells and exhibits attenuated replication in non-dividing cells, …that comprises one or more nucleotide sequences encoding GM-CSF…[and elicits] a systemic antitumour immune response…specific for melanoma cells" Claim 2: "HSV is incapable of expressing a functional ICP34.5 gene product and a ribonucleotide reductase"
Product	"talimogene laherparepvec" (Imlygic®), a modified HSV-1 for the treatment of melanoma Modifications of ICP34.5 and ICP47 and insertion of GMCSF into ICP34.5 locus
Later patent?	Yes (filed 2.5 years later by Biovex)

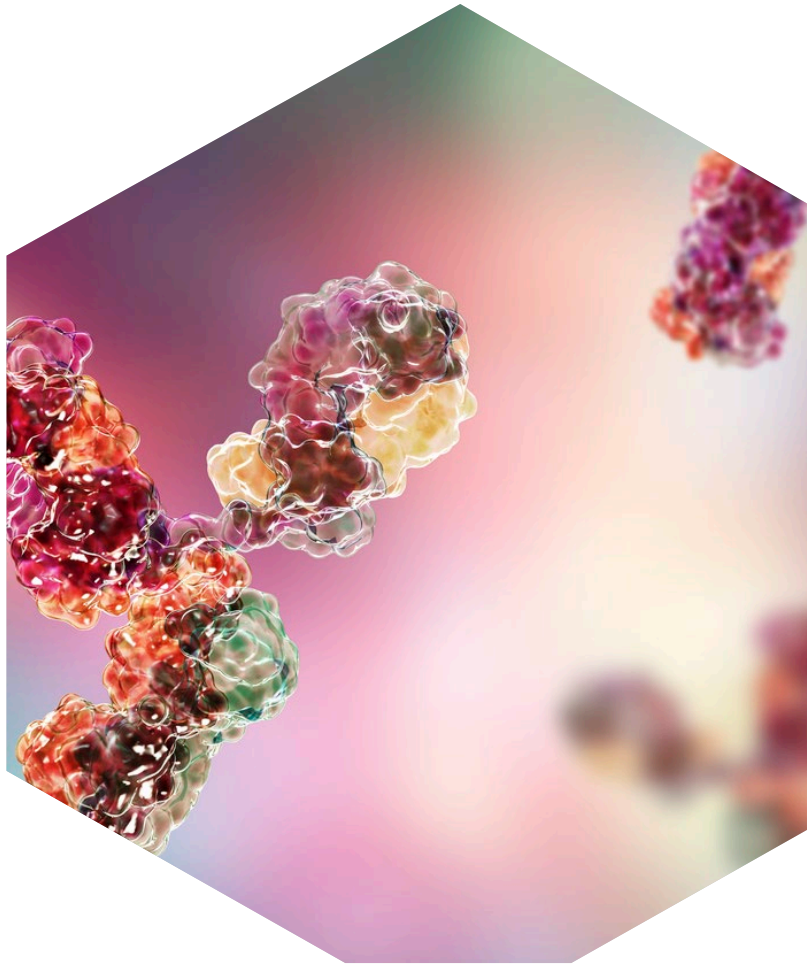
How has the test been applied on a national level?

Georgetown University - modified HSV-1 virus

- SPCs refused in FR, SE, NL and IE: -
    - No information in basic patent on deletion of ICP47 gene or on any potential therapeutic benefits of that deletion
    - Prior art that mentioned deletion of ICP47 gene dismissed - considered that skilled person could not conclude from the reference that deletion of ICP47 would result in a product that had functional requirements of claim.
    - Skilled person could not therefore identify product
    - Combination of ICP34.5 and ICP47 gene deletions was subject of later filed patent
- SPCs granted in UK and DE

General principles on satisfying Article 3(a)

- For '**singles**', first part of test (falls under invention) appears to be met if product satisfies functional features of claim
- Cf for '**combinations**', where a more substantive analysis may be needed
- Cannot assume knowledge of product to evidence "**specifically identifiable**"
- Must show **how skilled person could have arrived at product without inventive skill at priority/filing date**:
  - evidence/examples of structural features of broad functionally defined product
  - explanations of how skilled person could arrive at product routinely
- **Later-filed patents that specifically describe products may be problematic** (unless product inventive for a reason other than functionality in earlier patent? – e.g. antibodies)



Does the two-part test apply when product expressly claimed?

Teva v Gilead (C-121/17)

- See answer:

"Article 3(a)…must be interpreted as meaning that a product composed of several active ingredients…is 'protected by a basic patent in force' within the meaning of that provision where, **even if the combination of active ingredients of which that product is composed is not expressly mentioned in the claims of the basic patent, those claims relate necessarily and specifically to that combination**. For that purpose…"

- See para 37:

"Therefore, a product cannot be considered to be protected by a basic patent in force within the meaning of Article 3(a) of Regulation No 469/2009 unless the product which is the subject of the SPC **is either expressly mentioned in the claims of that patent or those claims relate to that product necessarily and specifically**."

But then two lines of opposing CJEU case law?

Availability of single and combination SPCs based on same patent

BASIC PATENT	MARKETING AUTHORISATIONS	SPCs
Independent claim to - active ingredient A	Monotherapy A	Product A
Dependent claim to - active ingredient A and - known active ingredient B	Combination therapy A + B	Product A + B?

But then two lines of opposing CJEU case law?

Availability of single and combination SPCs based on same patent

- Contradictory standards for determining SPC eligibility under Articles 3(a)/(c)

  3(a) - the product is protected by a basic patent in force

  3(c) - the product has not already been the subject of a certificate

"Core inventive advance" test	"Literal /specifically identifiable" test
• Actavis (I) – C-443/12 • Actavis (II) – C-577/13 Articles 3(a) and/or 3(c) preclude the grant of a combination SPC in where the "core inventive advance" or "subject matter of the invention" of the patent relates to A, but not to the combination of A+B **No SPC to A+B**	• Teva – C-121/17 • Royalty Pharma – C-650/17 Rejected core inventive advance test Combination is "protected" under Article 3(a) if expressly mentioned or satisfies two-part test **SPC to A+B**

Referral by the Finnish Court to CJEU (C-119/22)

- Merck's type 2 diabetes treatment, Janumet® (a combination of sitagliptin and metformin)

BASIC PATENT	MARKETING AUTHORISATIONS	SPCs
EP 1412357 The patent claims: - sitagliptin, and - pharmaceutical composition comprising sitagliptin and metformin	Monotherapy (Januvia®) authorised Combination therapy (Janumet®) authorised	1st SPC for sitagliptin 2nd SPC for a combination of sitagliptin and metformin

- Teva challenged the validity of combination SPC under Articles 3(a) and 3(c)
- Questions referred to CJEU on interpretation of Article 3(c)

Referral by the Finnish Court to CJEU (C-119/22)

The Finnish Market Court referred **4 questions** to CJEU:

1. *What **criteria** must be applied to determine when a product has not already been granted an SPC within the meaning of Article 3(c)[…]?*
2. *Must the assessment of the condition set out in Article 3(**c**) of the SPC Regulation be regarded as being **different** from the assessment of the condition set out in Article 3(**a**) of that regulation, and if so, in what way?*
3. *Must the statements on the interpretation of Article 3(**a**) of the SPC Regulation in the judgments of the Court in Case C-121/17 (**Teva**) and Case C-650/17 (**Royalty Pharma**) be regarded as **relevant** to the assessment of the condition in Article 3(**c**) of the SPC Regulation and, if so, in what way?[…]*
4. *Are the concepts **core inventive advance**', '**central inventive step**' and/or '**subject matter of the invention**' of the basic patent relevant to the interpretation of Article 3(c) of the SPC Regulation and, if any or all of those concepts are relevant, how are they to be understood for purposes of interpreting Article 3(c) of the SPC Regulation? For the purposes of applying those concepts, does it make any difference whether the product in question consists of a single active ingredient ('mono-product') or a combination of active ingredients ('combination product') and, if so, in what way?[…]*

Referral by the Irish Court to CJEU (C-149-22)

- Merck's cholesterol lowering therapy, Inegy® (a combination of ezetimibe and simvastatin)

BASIC PATENT EP 0720599	MARKETING AUTHORISATIONS	SPCs
The patent claims: - ezetimibe - combination of ezetimibe with a cholesterol biosynthesis inhibitor (specific reference to simvastatin, among others)	Monotherapy (Ezetrol®) authorised Combination therapy (Inegy®) authorised	1st SPC for ezetimibe 2nd SPC for a combination of ezetimibe and simvastatin

- Following infringement action, Clonmel Health counter-claimed for revocation of the combination SPC under Articles 3(a) and (c)
- Questions referred to CJEU on interpretation of Articles 3(a) and 3(c)

Referral by the Irish Court to CJEU (C-149-22)

The Supreme Court referred **4 questions** to CJEU:

1A. For the purpose of the grant of a SPC, and for the validity of that SPC in law, under Article 3(a) …, does it suffice that the product … is expressly identified in the patent claims, and covered by it; or is it necessary for the grant of an SPC that the patent holder, who has been granted a MA, also demonstrate ***novelty or inventiveness*** *or that the product* ***falls within a narrower concept*** *described as the invention covered by the patent?*

1B. If the latter, the invention covered by the patent, ***what must be established*** *by the patent holder and marketing authorisation holder to obtain a* ***valid SPC****?*

2. Where, as in this case, the patent is for a particular drug, ezetimibe, and the claims in the patent teach that the application in human medicine may be for the use of that drug alone or in combination with another drug, here, ***simvastatin, a drug in the public domain****, can an SPC be granted under Article 3(a) of the Regulation only for a product comprising ezetimibe, a monotherapy, or can an SPC* ***also be granted for any or all of the combination products*** *identified in the claims in the patent?*

Referral by the Irish Court to CJEU (C-149-22)

The Supreme Court referred **4 questions** to CJEU:

*3. Where a monotherapy […] is granted an SPC, or any combination therapy is first granted an SPC for drugs A and B as a combination therapy, which are part of the claims in the patent, though **only drug A is itself novel** and thus **patented**, with other drugs being already known or in the public domain; is the grant of **an SPC limited to the first marketing** of either that monotherapy of drug A or that first combination therapy granted an SPC, A+B, so that, following that first grant, **there cannot be a second or third grant** of an SPC for the monotherapy or any combination therapy apart from that first combination granted an SPC?*

*4. If the **claims** of a patent cover **both a single novel molecule and a combination** of that molecule with an existing and known drug[…] does Article 3(c) of the Regulation limit the grant of an SPC;*

(a) only to the single molecule if marketed as a product;

(b) the first marketing of a product covered by the patent whether this is the monotherapy of the drug covered by the basic patent in force or the first combination therapy; or

(c) either (a) or (b) at the election of the patentee irrespective of the date of market authorisation?

And if any of the above, why?

Expected referral by the Swedish Court

- AstraZeneca's diabetes therapy, Xigduo® (combination of dapagliflozin and metformin)

BASIC PATENT EP 1506211	MARKETING AUTHORISATIONS	SPCs
The patent claims: - C-aryl glucoside type (formula I) compound (can be used alone or in combination with other antidiabetic/hypolipidemic agents) (Claim 1) - the specific combination of dapagliflozin and metformin (Claim 7)	Monotherapy (Forxiga®) authorised Combination therapy (Xigduo®) authorised	1st SPC for dapagliflozin 2nd SPC for a combination of dapagliflozin and metformin

- Swedish Intellectual Property Office rejected the 2nd SPC, AZ appealed but appeal was dismissed by the Patent and Market Court
- Swedish Supreme Court ruled that Patent and Market Court made serious error by refusing application without making its own referral to CJEU
- Case handed back to the Patent and Market Court

Implications for protecting combinations

- Hopefully, CJEU clarifies how Article 3(a) and 3(c) should be applied soon!
- In the meantime:
  - Gather data to show A+B is inventive in its own right so constitutes another invention / embodies a separate inventive advance
  - Include combinations in subsequent patent filings?
  - Include as many examples of A and B in claims as possible (at least *Teva v Gilead* test may not apply if A+B expressly mentioned)
  - Revisit claims prior to grant to ensure any combinations expressly mentioned

“Loose” combinations

- “Fixed-dose” combinations (co-formulated) vs “loose” combinations (formulated separately)
- Are SPCs available for “loose” combinations?
- Article 3(b) - **valid authorisation to place the product on the market as a medicinal product** has been granted
- What if marketing authorisation refers to only one active ingredient as a component of the *authorised product* and lists the other active ingredient(s) in the context of the *authorised use* of that product?
    - E.g. small molecule formulated for oral administration and antibody formulated for parenteral administration

"Loose" combinations – Roche Glycart

UK Patent Decision O/711/22

Patent	EP 2464382 (Roche Glycart AG)
Claim wording	*"Use of an afucosylated anti-CD20 antibody with an amount of fucose of 60% or less of the total amount of oligosaccharides (sugars) at Asn297 for the manufacture of a medicament for the treatment of cancer in combination with bendamustine, characterised in that said cancer is a CD20 expressing cancer and in that said antibody comprises an amino acid sequence of …"*
Product for SPC	Obinutuzumab and bendamustine
Marketing authorisation	Type II variation to marketing authorisation for Obinutuzumab (GAZYVARO®) – addition of authorised use for treating follicular lymphoma in combination with bendamustine

- MA considered a valid authorisation for obinutuzumab alone, not obinutuzumab and bendamustine
- Hearing Officer referred to previous UK High Court decision in *Yeda* (cetuximab and irinotecan)
- Also considered consistent with CJEU decision in *Santen* (C-673/18)

"Loose" combinations – Newron

UK High Court [2023] EWHC 1471 (Ch)

Patent	EP 1613296 (Newron Pharmaceuticals SPA)
Claim wording	*"The use of a first agent selected from safinamide from 0.5 to 1, 2, 3, 4 or 5 mg/kg/day in combination with levodopa/PDI for the preparation of a medicament as a combined product for simultaneous, separate or sequence use for the treatment of Parkinson's Disease"*
Product for SPC	Safinamide for use in combination with levodopa/PDI
Marketing authorisation	Safinamide (Xadago®) (said to be add-on therapy to levodopa)

- MA considered a valid authorisation for safinamide alone, not the combination
  - Title, first recital and Article 1 of MA all recite "XADAGO – safinamide"
  - Only reference to levodopa in Section 4.1 "clinical particulars" of Annex I of MA (SmPC)

- Some meritorious inventions do not qualify for extended protection

- Therapeutic use of a product cannot be imported into its definition

Protecting “Loose” combinations

- Obtain SPCs to single active ingredient that will be the subject of the marketing authorisation
  - SPC to A will provide protection for “loose” A+B

- Where the patentability of an invention resides in the combination of A+B, then include following claims types:
  - A+B for use in treating X
  - A for use in treating X wherein the patient is also administered B
  - B for use in treating X wherein the patient is also administered A

- Patient subgroup claims may enable you to define the “product” as A alone or B alone, and so satisfy Articles 3(a) and 3(b). Provided Articles 3(c) and 3(d) are satisfied!

Thoughts and conclusions

- We should expect to use the two-part test to demonstrate that “singles” and “combinations” are “protected” at least where active ingredients not expressly mentioned in the claims
- Proving "specifically identifiable" will require evidence/explanations
- For ("loose") combination products, try to secure broad protection for single active ingredient (e.g. SPC for A to provide protection for A+B)
    - For "loose" combination products, try to include patient subgroup claims (at drafting stage and revisit prior to grant) to enable product to be defined as A alone
- Combination products will likely require data showing A+B inventive in its own right (regardless of whether expressly mentioned in claims?)

Thank you – any questions?

Potter Clarkson
UK, Sweden, Denmark
W potterclarkson.com | E info@potterclarkson.com