

Guidelines for Examining Pharmaceutical Patents

Tahir Amin

Director and Intellectual Property Solicitor

I-MAK

tahirmamin@gmail.com

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INITIATIVE FOR MEDICINES ACCESS & KNOWLEDGE

Pharmaceutical Patenting Trends

- The number of patents for new chemical entities is decreasing annually - *U.S Government Accountability Office Report (Nov, 2006)*
- The number of patents for new forms, uses, dosages, etc of known substances have increased and is a strategy for prolonging the patent life of old inventions.



Common forms of Pharmaceutical Product Patents

- New chemical entities
- Derivatives
- Salt/esters/ethers
- Crystalline solids (polymorphs/solvates/hydrates)
- Metabolites
- Combinations
- Compositions and formulations



Derivatives

- A compound that is formed from a similar compound *or* a compound that can be imagined to arise from another compound, if one atom is replaced with another atom or group of atoms.
- S3d in India considers derivatives of known substances to be the *same substance*, unless they differ significantly in properties re efficacy.



Derivatives - (cont'd)

- E.g Oseltamivir (Carbocyclic compounds - US 5763483) derives from the earlier compound Zanamivir (WO 9113620).

Gilead changed the oxygen pyran ring in '620 with a $-\text{CH}_2-$ moiety in order to make a carbocyclic compound (which makes it easier to make salts for the compound and achieve bioavailability).



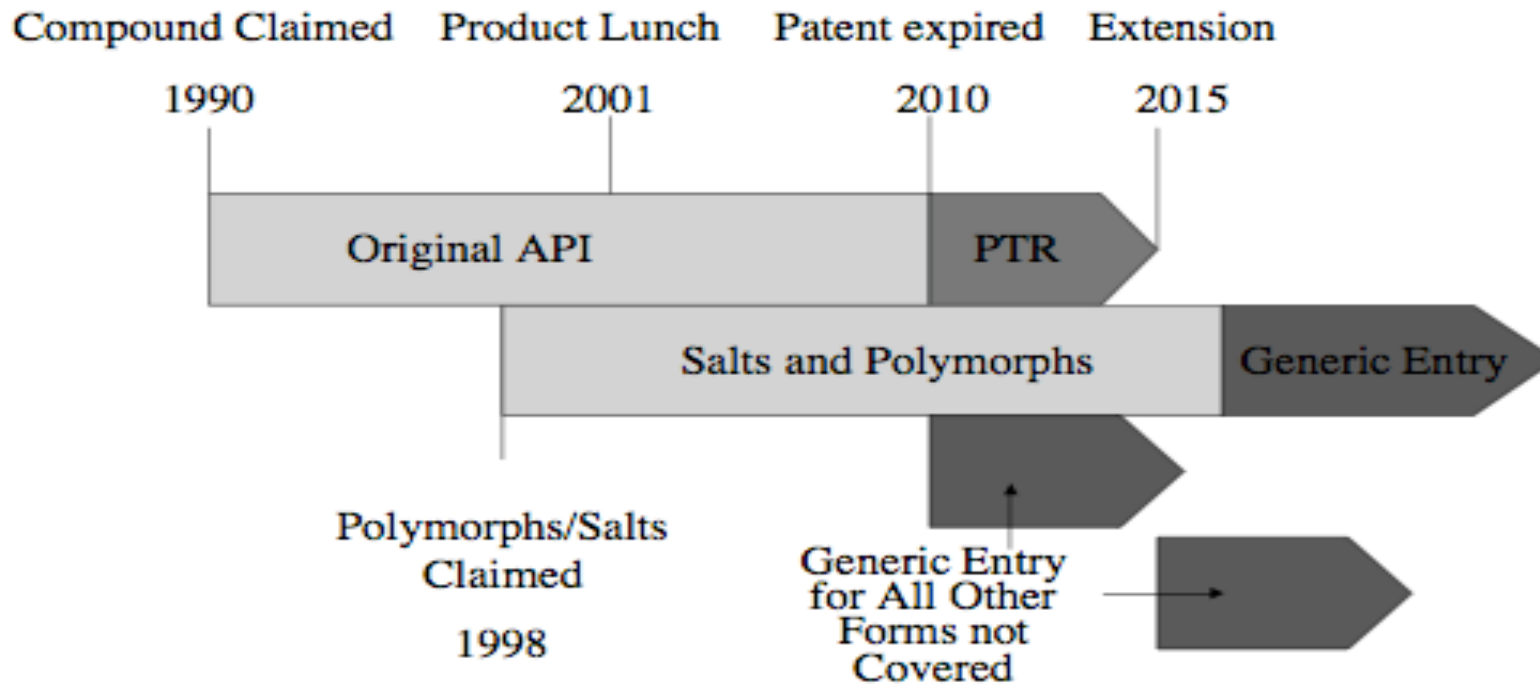
Salts/Esters/Ethers

- Selection of salts (and their crystalline forms) and esters to change the physico-chemical properties of a known compound i.e. solubility, stability, hygroscopicity, stability and/or bioavailability of a known compound has been common knowledge in the industry for over 30 years. This practice is at the heart of extending the life of known substances.
- It is usually obvious to predict the claimed advantages a salt/ester will give over the base compound - given the pre-existing knowledge of their respective properties and the ability to pre-determine/expect how the compounds will react and the end properties they will achieve. E.g rule of thumb for salt selection in industry i.e weak base use a weak acid.



Salts/Esters/Ethers - (cont'd)

How can Salt and Polymorph Patents Provide Additional Patent Protection?



PTR: Patent Term Restoration = half of the investigational period + all of the FDA review period

Ref: Lucas J and Burgess P., PharmVOICE, Feb., 2004

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Salts/Esters/Ethers - (cont'd)

- E.g of salt selection Tenofovir Disoproxil Fumarate (TDF) - WO 99/05150
- Tenofovir base compound patented in 1986 - now expired. Gilead patented ester derivative of Tenofovir (Tenofovir Disoproxil (TD)) in 1996 and claims the fumarate salt in 1997 on the basis that it shows unexpected advantages (stability) compared to the free base and other salts.



Salts/Esters/Ethers - (cont'd)

- Applicants claiming advantages/better therapeutic response should be required to show data proving why a particular salt selection achieves this over the base compound and other salts of similar properties.
- E.g TDF - the applicant only provides a comparison with another salt (citrate) to show 'unexpected advantages' but no other salts.



Crystalline Solids/Polymorphs

- Crystalline forms/polymorphs/solvates/hydrates are inherent in the original form and are not invented/created. They are discovered by commonly known x-ray diffraction techniques.
- Crystalline forms can differ significantly in properties but rarely for therapeutic effect. They usually are only useful for controlling purity, yield for streamlining the manufacturing process or for strategic reasons to keep competitors out.
- Crystalline solids should be considered lacking novelty/inherently anticipated or inventive step.



Crystalline Solids/Polymorphs - (cont'd)

- E.g Lopinavir crystalline forms (European Application No. 01924250) claiming greater than 90% purity. Applicant argued that there could be no reasonable expectation of success for obtaining the crystalline forms. The application was rejected on the ground that it lacked inventive step/unexpected advantages over Abbott Laboratories earlier patent for the amorphous form.
- Under s3d in India, as the specification fails to show any efficacy it should be rejected.



Metabolites

- Where a pharmaceutical compound generates an active metabolite once metabolised in the body.
- Metabolites are not invented/created with human intervention but occur naturally. Can be considered derivatives of the original compound.
- E.g Bristol Myers attempt to use the metabolite of the already patented Ternfenadine (antihistamine drug) to block competition was held an unlawful extension of patent rights.
- Therefore, should be considered inherently anticipated.



Combinations

- The combination of known active ingredients should not be considered inventive unless there is a non-obvious synergy between the compounds.
- Any synergy should be specifically disclosed and claimed in the specification to demonstrate inventive step.
- India's s3(e) does not classify as inventions admixtures of active ingredients which only amount to an aggregation of the known properties, but which do not have any synergy.



Compositions/Formulations

- Includes patenting the known active compound in different dosage forms such as tablets, capsules or aqueous solutions formulated using different excipients e.g glidants (flow enhancers), binders, lubricants, sweeteners and fillers.
- Although some compositions/formulations may provide an unexpected/surprising therapeutic effect such as improving transport of the active drug to the site - many are trivial improvements to aid manufacture or for masking bitter tastes.



Compositions/Formulations - (cont'd)

- Obtaining new formulations is a well known art in the industry - there is a plethora of literature on suitable excipients/agents for achieving particular results. Therefore, unless there is some unexpected therapeutic advantage through a new formulation/composition - such patents should be considered obvious in light of prior art/common industry knowledge.
- India's s3(e) - mere admixtures of ingredients resulting only in aggregation of properties, but no synergy are not inventions.



Other Types of Pharmaceutical Patents

- Methods/processes for medicinal/therapeutic treatment of humans (s3(l) India)
- New properties/uses for known substances

