Enablement for Derivatives of Compositions of Matter

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Overview

- Statutory Basis - 112 1st paragraph.
- How examiners interpret claim language and disclosure as related to invention
- Definition of Various Derivatives of Compounds
- Inquiries for Enablement of Derivatives of Compounds

Enablement Statute

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of **the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same** and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Legal Inquiry for Lack of Enablement

- When considering the legal inquiry for enablement for the derivatives of compounds, the examiner considers the relevant factors advanced in In re Wands to establish a prima facie case of lack of enablement.

- Specific technical reasons why the examiner doubts the invention is enabled are always required when establishing a prima facie case of lack of enablement.

Definition of Derivatives

- **derivative** /de·riv·a·tive/ (de-riv´ah-tiv)

  In chemistry, a **derivative** is a compound produced from an original compound either directly or by modification or partial substitution of the original compound core *or* a compound that can be imagined to arise from another compound, if one atom is replaced with another atom or group of atoms. The latter definition is common in organic chemistry. In biochemistry, the word is used about compounds that at least theoretically can be formed from the original compound.

Source : Wikipediahttp://en.wikipedia.org/wiki/Derivative_(chemistry) (2008)

Types of Compound Derivatives

Most frequently, compounds are set forth in the claims of patent applications along with one or more derivatized forms of the compounds claimed. Some of the most common derivatized forms of compounds seen in patent applications include:

Salts

Isomers

Analogues

Metabolites/Prodrugs

Crystals/Polymorphs

Solvates/Hydrates

Definitions for Specific Compound Derivatives

- **Salts** : Ionic compounds in which cations and anions combine to form electrically neutral products.
- **Isomers** : Compounds with the same molecular formula but different structural formulae. The two types of isomers are structural isomers and stereoisomers.

http://en.wikipedia.org/wiki/Salt_(chemistry)
http://webhost.bridgew.edu/fgorga/Stereochem/default.htm

Definitions for Specific Compound Derivatives

- **Analogues (Analogs) :** Compounds in which one or more individual atoms have been replaced, either with a different atom, or with a different functional group. Another use of the term in chemistry refers to a substance which is similar in structure and/or function to another substance.

http://en.wikipedia.org/wiki/Analog_(chemistry)

Definitions for Specific Compound Derivatives

- **Metabolites** : Any substance produced by metabolism or by a metabolic process.

  http://cancerweb.ncl.ac.uk/cgi-bin/omd?metabolite

- **Prodrug** : **A compound resulting from modification of a biologically active compound that will liberate the active form via biotransformation.**

  Banker et al., Modern Pharmaceutics, 4th Ed., p 596 (2002)

Definitions for Specific Compound Derivatives

- **Crystal : A crystal is a solid in which the constituent atoms, molecules, or ions are packed in a regularly ordered, repeating pattern extending in all three spatial dimensions.**

  http://en.wikipedia.org/wiki/Crystal(line)

- **Polymorph : Crystals which have the same chemical composition but different internal structure, including different unit cell dimensions and different crystal packing.**

  Byrn et al.; Solid State Chemistry of Drugs, 2nd Ed. , p 143 (1999).

Definitions for Specific Compound Derivatives

- **Solvates :** Crystalline solid adducts containing solvent molecules within the crystal structure giving rise to unique differences in physical and pharmaceutical properties of the drugs..

Vippagunta et al., Advanced Drug Delivery, 48, p 15-16 (2002)

- **Hydrates :**Crystalline solid adducts containing water molecules within the crystal structure.

Vippagunta et al., Advanced Drug Delivery, 48, p 15-16 (2002)

Factors Considered to Determine Enablement for Derivatives of Compounds

- **Factors considered by examiners when determining whether there is sufficient evidence to satisfy the enablement requirement for claim limitations (derivatives of compounds) include, but are not limited to:**

- **(A) The breadth of the claims;**
- **(B) The nature of the invention;**
- **(C) The state of the prior art;**
- **(D) The level of one skilled in the art;**
- **(E) The level of predictability in the art;**
- **(F) The amount of direction provided by the inventor;**
- **(G) The existence of working examples; and**
- **(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.**

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

Use of the Wands Factors to Establish a Prima Facie Case of Lack of Enablement

- Examiners cite the specific Wands factors that are particularly relevant to the enablement analysis on a case-by-case basis.
- Accordingly, if the evidence of record establishes that making certain types of derivatives is not enabled and the claims under review are of a scope allowing for the inclusion of these derivatives, a prima facie finding of lack of enablement is proper.

Claim Interpretation Applied to Derivatives of Compounds During the Examination Process (Breadth of the Claims)

- **MPEP 2111.01**
- **The USPTO (examiner) construes claims in applications as broadly as their terms reasonably allow in light of the specification. See *In re American Academy of Sciences Tech Center* , 367 F.3d 1359, 70 USPQ2d 1827 (Fed. Cir. 2004).**
- **Broadest reasonable interpretation in light of the specification often means the plain meaning of the term unless the specification defines the term otherwise.**

Wands Factors Often Relevant to Enablement of Derivatives of Compounds

- The nature of the invention and the state of the prior art
- The level of predictability in the art
- The amount of direction provided by the inventor
- The quantity of experimentation needed to make or use the invention based on the content of the disclosure

The nature, predictability and the state of the prior art: Salts

- Preparation of salts of compounds are often routine and predictable in organic chemistry and the pharmaceutical arts.
- While salts may be routine to make, the use of derivatives must be considered as well.
- Salts of compounds are rarely an enablement issue.

The nature, predictability and the state of the prior art: Isomers

- There are two types of isomers: structural isomers and stereoisomers.
- Two compounds are considered structural isomers is they have the *same* molecular formula but *different* connections between atoms (bonding).
- Two compounds are considered stereoisomers if they have the *same* molecular formula, the *same* connections between atoms, but *different* arrangements of the atoms in three dimensional space.
- Enablement usually resides in the recognition of the isomer and the successful resolution of the racemate.

The nature, predictability and the state of the prior art: Analogues

- Compounds of this class are usually improved versions of a ‘pioneer’ drug with pharmacological, pharmacodynamic or biopharmaceutical advantages over the original compound
- Direct analogue design involves straightforward molecular modifications, such as the synthesis of homologues, vinylogues, isosteres, modified ring systems and twin drugs (homodimers).
- As a rule, the basic scaffold is conserved or only slightly modified.

The nature, predictability and the state of the prior art: Analogues

- Structural analogues may be compounds originally prepared from a novel lead but for which biological assays revealed totally unexpected pharmacological properties.
- Observation of a new activity can be purely fortuitous but can also result from planned systematic investigations.
- Structural analogues often originate from those serendipitous discoveries that often happen during clinical investigations.
- Structural analogues can also result from a systematic application of multi-target screening large series of structurally similar compounds.

The nature, predictability and the state of the prior art: Analogues

The three categories of drug analogues

Nature of the analogue*	Degree of relationship with the original structure	Production and design	Originality and patentability	Result of the design	Likelihood of drug success
S + F: direct analogue	Isosterism Functional exchange	Molecular variations Parallel synthesis	Low	'Me-too'	Medium to high
S: structural analogue	Bioisosterism Fragment exchange	Traditional medicinal chemistry	Medium	Patentable copy	Low
F: functional analogue	Pharmacophore identification Scaffold hopping	Fortuitous discovery Screening Computer-aided design	High	Original back-up	Variable

*S = structural, F = functional, S + F = direct.

According to the degree of molecular modifications achieved, the alterations made in drug analoging can focus on exchanges of atoms or small groups (isosterism), exchanges of fragments of molecules (bioisosterism) or on total replacement of the original molecule by a new one (scaffold hopping).

Drug Discovery Today
Volume 11, Issues 7-8, April 2006, Pages 348-354

The nature, predictability and the state of the prior art: Crystalline/Polymorphic Forms of Compounds

- Most drugs are used in crystalline form.
- The arrangement of molecules in a crystal determine its physical properties.
- Physical properties of a drug affect its performance.
- Compounds that crystallize as polymorphs exhibit a wide range of different physical and chemical properties including melting point, solubility, density, hardness, crystal shape and spectral properties.

Byrn et al.; Solid State Chemistry of Drugs, 2nd Ed. , p 143 (1999).

The nature, predictability and the state of the prior art: Crystalline/Polymorphic Forms of Compounds

- **Pharmaceutical processing (temperature, pressure, relative humidity) encountered during drying, granulation , milling and compression affect physical properties of crystals making consistency in products difficult.**

- **Pharmaceutical processing (temperature, pressure, relative humidity) encountered during drying, granulation , milling and compression may affect crystalline structure, making consistency in products based on structural order difficult to determine and physical properties difficult to maintain.**

Byrn et al.; Solid State Chemistry of Drugs, 2nd Ed. , p 143 (1999).

The nature, predictability and the state of the prior art: Crystalline/Polymorphic Forms of Compounds

Characterization of crystals/polymorphs introduce problems which include but are not limited to :

- The degree of disorder introduced into the lattice structure during pharmaceutical preparation of the drug
- The difficulty in calculating the amount of a single crystal or polymorphic form from a mixture of crystalline forms
- The challenges to Identify the solid form of the active ingredient in formulated products
- The transient nature and instability of various polymorphic and crystalline forms of active agents

Vippagunta et al. , Crystalline solids, Advanced Drug Delivery Reviews 48 p. 3-26 (2001)

The nature, predictability and the state of the prior art: Metabolites/ Prodrugs

- **Metabolites may be activated in vivo into the active form of a drug by the attachment, rearrangement or removal of some functional group(s) attached to the compounds core. The compound may or may not be modified structurally.**
- **The biological (in vivo) transformation may facilitate transport to the active site or activation of the drug's therapeutic properties.**
- **Prodrugs are compounds which are structurally modified which undergo subsequent changes in their physicochemical properties.**
- **The conversion of a metabolite or a prodrug may occur via a variety of reactions, the most common being hydrolytic or enzymatic cleavage.**

The nature, predictability and the state of the prior art: Metabolites/ Prodrugs

- **Many aspects of drug metabolism are of interest to medicinal chemists and should be considered when determining the efficacy of metabolites and prodrugs, such as:**
  - **The chemistry and biochemistry of metabolic reactions involved in the conversion of the metabolite or prodrug into the active form of the compound.**
  - **The changes in the compound based upon biotransformation of the metabolite or prodrug.**
  - **Predictions of drug metabolism based on quantitative structure metabolism relationships, modeling of enzyme sites and expert systems has advanced substantially in the last decade.**

- **Testa et al, Pure Appl. Chem., Vol. 76, No. 5, pp 907-914 (2004)**
- **Banker et al, Modern Pharmaceutics, 4th Ed., pp 516-517 (2002)**

The nature, predictability and the state of the prior art: Metabolites/ Prodrugs

- **Metabolites and prodrugs are compounds which have been or will be modified which will be subsequently modified in vivo (via metabolic reaction) to provide biologically active compounds.**
- **Physiochemical properties of the parent compound are altered to prepare metabolites/prodrugs which influence acidity, basicity, lipophilicity, drug permeability,dosage choice, toxicity, stability and localization of the parent compound.**
- **The most serious consideration of the metabolite/prodrug is the change to the compound core because a prodrug is most often a new drug and therefore requires extensive and costly studies to determine safety and efficacy.**

- **Testa et al, Pure Appl. Chem., Vol. 76, No. 5, pp 907-914 (2004)**
- **Banker et al, Modern Pharmaceutics, 4th Ed., pp 516-517 (2002)**

The nature, predictability and the state of the prior art: Solvates/Hydrates

- It has been estimated that approximately one-third of pharmaceutically active substances are capable of forming hydrates.
- Solvates differ in crystal packing and molecular conformation as well as lattice energy.
- Crystalline states of compounds vs. pharmaceutical compositions may require consideration of phase transformation during formulation of compositions.

- **Vippagunta et al. , Crystalline solids, Advanced Drug Delivery Reviews 48 p. 3-26 (2001)**

The nature, predictability and the state of the prior art: Solvates/Hydrates

- **Predicting the formation of solvates and hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of the compound is challenging.**

- **The reactions and processing involved in the preparation of solvates and hydrates cannot be generalized for a series of related compounds since each solid compound responds uniquely to solvate or hydrate formation**

- **Pharmaceutical processing (temperature, pressure, relative humidity) encountered during drying, granulation , milling and compression affect crystalline structure, which may make consistency in products based on structural order difficult to determine and physical properties difficult to maintain.**

Byrn et al.; Solid State Chemistry of Drugs, 2nd Ed. , p 143 (1999).

The nature, predictability and the state of the prior art: Solvates/Hydrates

- **Each solid compound responds uniquely to the possible formation of solvates and hydrates and generalizations cannot be made for a series of related compounds**

- **Pharmaceutical processing (temperature, pressure, relative humidity) encountered during drying, granulation , milling and compression affect crystalline structure, making consistency in products based on structural order difficult to determine and maintain.**

- **Consideration of hydration/dehydration of active agents requires consideration of conditions during processing, proper packaging, acceptable temperature ranges for shipping and storage, making selection of the specific solid form of the drug critical.**

Vippagunta et al. , Crystalline solids, Advanced Drug Delivery Reviews 48 p. 3-26 (2001)

Direction provided by the inventor and the existence of examples

- Questions of enablement may arise when :

- **There are no adequate representations advanced in the specification teaching how to make and use the derivatives such as analogues, prodrugs, metabolites, solvates and hydrates.**

- **The disclosure fails to direct the skilled artisan to relevant prior art teachings which would correlate modification of a compound in a manner which could be extrapolated to compounds set forth in a patent application's claims.**

- **When the disclosure does not set forth in full, clear and exact terms the identity and location of modifications to the compound.**

Patents Issued with Derivatives listed below in the Claims since 2000

- Prodrugs 9204 Patents
- Metabolites 4340 Patents
- Polymorphs 1291 Patents
- Crystals 12,639 Patents
- Solvates 11043 Patents

Thank You!

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