

Patents and the Polymorph

Washington, DC
(Henry Stuart publ., Feb. 2004)

Economic Importance

- Revenue loss to innovator firms:

\$51,508,000,000

- Revenue gain to generic firms:

\$19,117,000,000

(Figures are for upcoming ten years, discounted at 7%)

- New rule is expected to increase ¶ (iv) patent certifications by 50%
- How to succeed within this new framework?

= Overview =

- How to draft polymorph patents for the Orange Book

- Expressly permitted patents
 - Drug Substance & Drug Product
 - Product-by-process
 - Method of Use

- Conditionally permitted patents
 - Polymorphic forms

- Certain patents may need to be re-issued to qualify
 - Manufacturing Intermediates, Packaging, Metabolites

- What happens when a patent is listed?

- 30-month Stay, 180-day exclusivity
- Declaratory Judgment resolution

Drug Substance & Product

- Declaration ¶ 2.1: “Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?”
- “the final rule does not open the door to submission of any patents claiming formulations ... [not] described in the NDA.”
 - *If at least one patent claim is listable, the entire patent becomes so.*

Drug Substance & Product

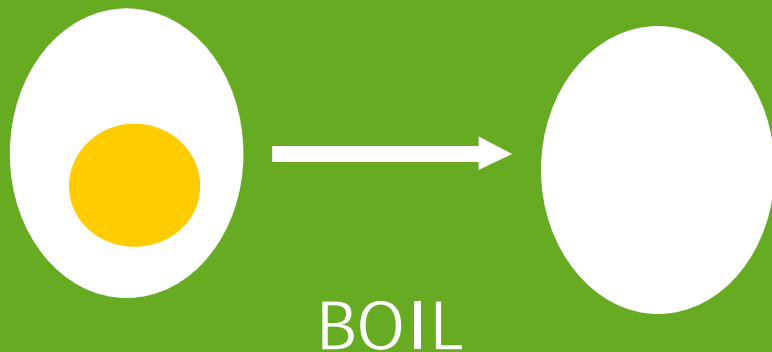
■ Combinations

- FDA Office of Combination Products
- “Exclusion of a patent claiming a drug substance in conjunction with another active ingredient or method of using the combination”
- This was considered, but ultimately was not adopted.
 - *If at least one patent claim is listable, the entire patent becomes so.*

Drug Substance & Product

Product-by-process

- Example: eating hard-cooked eggs to treat low serum albumin.
 - *N.B.*: Raw eggs may contain bacteria

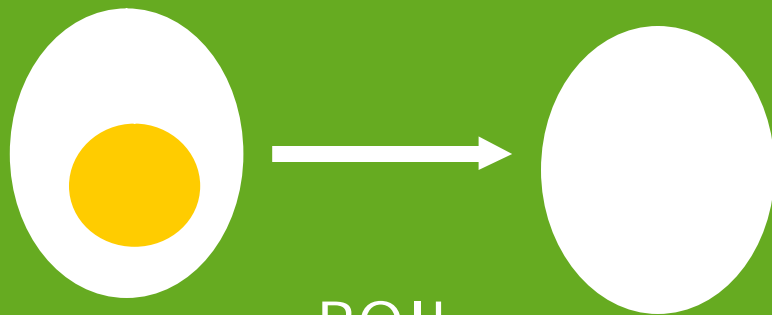


ASSUMING THAT THIS HAS BEEN KNOWN FOR A LONG TIME, NEITHER THE BOILING PROCESS NOR THE EGG IS PATENTABLE

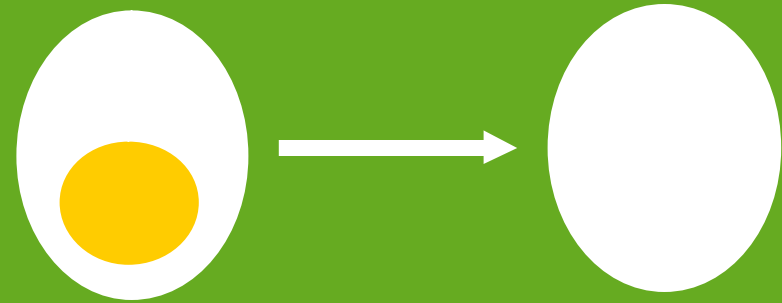
Drug Substance & Product

Product-by-process

- New combination of process and product
 - Both process and product might be “old”



BOIL



MICRO-WAVE

Faster, cheaper

Drug Substance & Product

- “when the PTO issues a patent, the PTO necessarily determines that **some aspect** of the patent claims is ‘novel.’ We want to make sure that the NDA applicant ... is identifying **the product claim** as **the** novel aspect.” Comments at 18.
 - *Cf.*: It is illegal for PTO to determine that “**some aspect**” of the claim is or is not novel; the claim must be evaluated as a whole.
 - *Cf.*: Every **product claim** is novel; it is illegal for PTO to issue any claim which is not.

Method of Use

- Must claim “a use that is described in the NDA”; “method of use that is in the labeling”
 - *Cf.* off-point patents need not be certified
- Declaration ¶ 4:
 - Does the patent claim one or more approved methods of using the approved drug?
 - Identify the use with specific reference to the approved labeling for the drug product
- Issues: drafting and certification consequences

Certification Consequences

- “I attest that ... this submission complies with the requirements of the regulation. I verify under penalty of perjury...”
 - No “good faith belief” qualifier, nor exception for subsequent change in law or fact.
 - If patent claim does not verbatim copy use code
 - Where will Doctrine of Equivalents be in the future?
 - If newly-discovered prior art unexpectedly limits claim scope

Methods - Listing Implications

- Estoppel may be found in court.
 - “The [] requirement to identify claims was intended to ... help prevent arguments as to whether a particular claim claimed the approved drug product.”
- Tension
 - Avoid estoppel by comprehensive listing of claims – and risk “erroneous” listing
 - Avoid perjury potential with an overly-conservative listing – and be estopped from enforcing legal rights.

Methods – Generic Strategy

- Section (viii) Certification
 - “when an ANDA applicant has sought to duplicate the labeling for which the innovator has submitted the patent, and not to specifically omit, or ‘carve out’ labeling, we require the ANDA applicant to submit a certification”
 - Purepac v. Thompson
 - Consider claiming the “carved-up” label
 - Property & Infringement value

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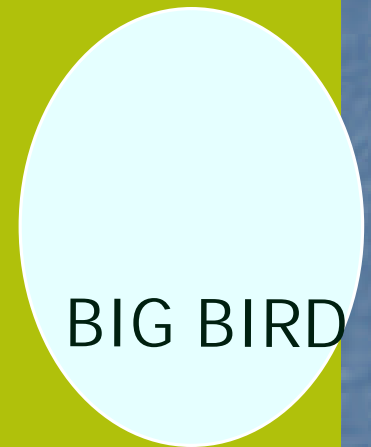
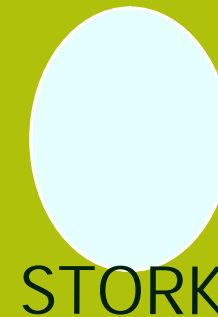
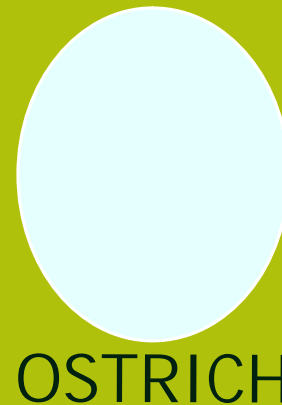
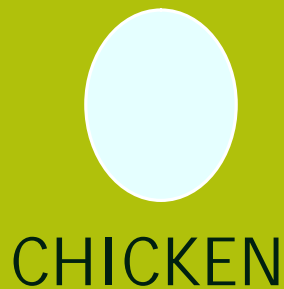
- Manufacturing Intermediates, Packaging, Metabolites

■ What happens when a patent is listed?

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Polymorphic Forms

- Different physical form, yet equivalent to NDA active ingredient
 - crystalline structures, waters of hydration, solvates, amorphous forms
 - Example : hard-cooked eggs



Polymorphic Forms

- Listed if bioequivalence data exists
- Issues:
 - Having data
 - Timing of data
 - Effect of data
- Having data
 - Manufacturing and packaging process controls, product specifications, analytical methods are required
 - What if Holder doesn't manufacture / sell the polymorph?

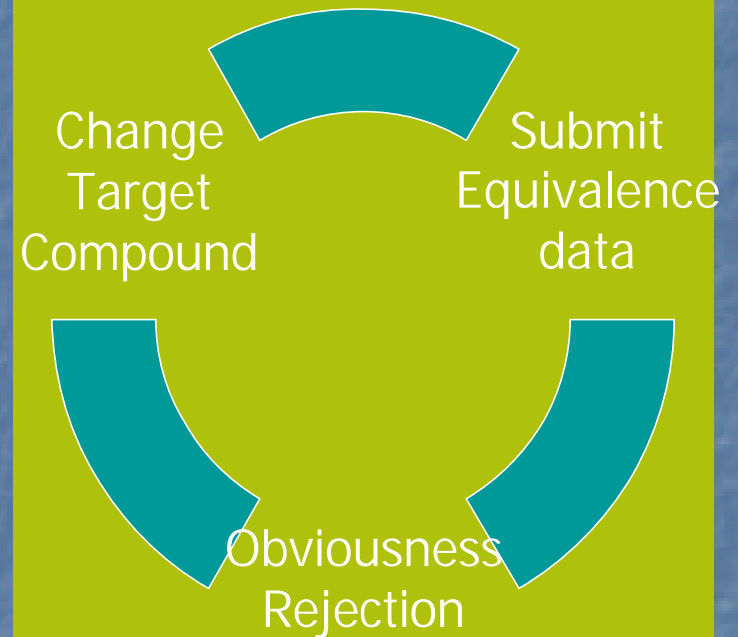
Polymorphs

- The test data must exist when a polymorph patent Declaration is submitted to FDA.
 - *Cf.* Patent must be submitted to FDA w/in 30 days after PTO issues it.

Polymorphs

- *Potential Solution: several-month delay between Notice of Allowance and patent Issue date*
 - *Cf. PTO can revoke a Notice of Allowance*

- Bioequivalence data may show that the polymorph is legally an obvious (read: minor or inconsequential) variant of the innovator
 - Can make it difficult to obtain / retain a patent claim covering the polymorph
 - Patent attorney **must** be given this bioequivalence data



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Packaging

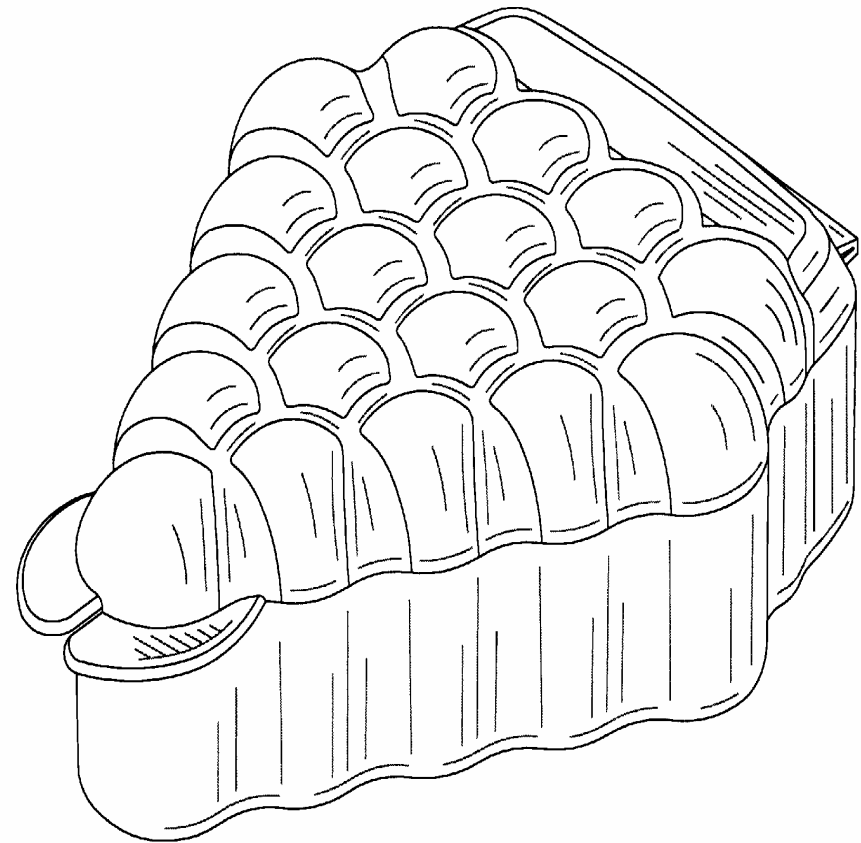
- “patents must not be submitted for bottles or containers and other packaging, as these are not dosage forms.”

U.S. Patent

Aug. 26, 2003

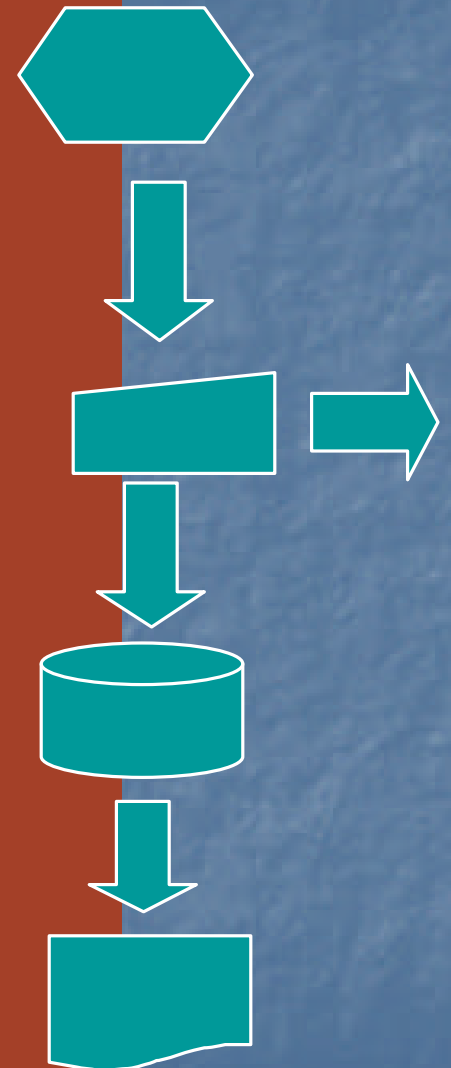
Sheet 1 of 4

US D478,784 S



Business Methods

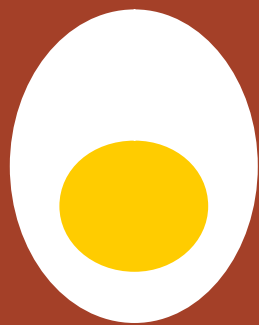
- Patient registries, titration / dosage schedules...
 - Celgene's thalidomide
 - Roche's 13-*cis* retinoic acid
- Relate claim verbiage to matter with which FDA is comfortable



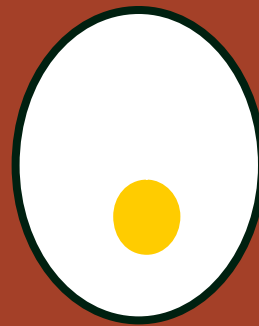
Manufacturing Intermediate

“We consider reagents to be ‘in-process materials’ rather than drug”

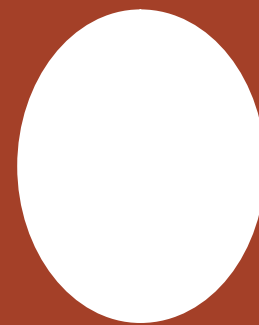
How does one list a “soft-cooked egg” patent?



RAW



SOFT-COOKED



HARD-COOKED

Metabolites

- “The final rule prohibits submission of patents claiming metabolites”
 - Declaration ¶ 2.5: “Does the patent claim a metabolite of the approved active ingredient?”

Metabolites

- If a patent claims an approved use of an approved drug to administer a metabolite, the patent may be listable - yet invalid.
 - Schering Corp. v. Geneva Pharma., Inc. (Fed. Cir., Aug. 1 2003) (loratadine metabolite is inherently created *in vivo*; the metabolite is therefore not new; the metabolite patent claim is thus invalid).

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30-Month Stay

- One full opportunity per ANDA or 505(b)(2)
- One - Change from prior practice
 - *Cf. In re Omeprazole*: the statute does not limit the number of stays available
 - *Cf. Continuation with a terminal disclaimer (cf. Paxil®, Fosamax®)*
 - Only one - subsequent ¶ (iv) certifications need not be noticed
- full opportunity
 - 45 day response period
 - Amending a ¶ (iv) to a ¶ (iii) certification before 45 day period runs, before suit commences.
 - Notice
 - ¶ (ii), ¶ (iii) certifications and § 505(j)(2)(A)(viii) flings do not require notice, thus may fail to provide a full opportunity for a stay
 - ? What if notice is given in fact ?

180-Day Exclusivity

- “Each patent listed in the Orange Book may form the basis for a claim to 180-day exclusivity. Thus an increase or decrease in listed patents as a result of this final rule could affect the number of exclusivity periods.”
 - With only one stay, there is less incentive to list patents - and each listed patent is an aid to a potential generic company.
 - Consider drafting patents to **preclude** listing

Declaratory Judgments

- Holder need not sue on ANDA filing.
- If Holder waits to sue until after generic is launched, infringement may be “willful”
 - treble damages, attorneys fees, permanent injunction, personal liability
- Declaratory judgment
- Jurisdiction requires:
 - 1) Current infringing activity § 271(e)(2)
 - 2) Reasonable apprehension of being sued

Declaratory Judgments

- Dr. Reddy's v. Pfizer (New Jersey)
 - Sertraline declaratory judgment petition dismissed on 11 July 03
 - 1) Pfizer alleged that it needed more time to assess whether infringement exists.
 - 2) Dr. Reddy's failed to show reasonable apprehension of suit
 - Ananth Iyer of Express Pharma Pulse (Bombay) predicted this in an article published in the spring.
- Resolving patent disputes prior to ANDA product launch not always possible

Declaratory Judgments

- *Cf.*: “a firm’s inability to predict whether it will or will not be sued for patent infringement is a matter outside the scope of this final rule. * * * some patent infringement suits may be initiated after the 45 day period available to obtain a 30-month stay has expired. * * * the NDA holder or patent owner can bring suit at a later time, but loses the opportunity to obtain a 30-month stay”
- *Cf.*: “an NDA holder who defers filing a lawsuit on a later-filed patent until a 30-month stay has elapsed may feel that the subsequent litigation is still ‘timely’”

To-Do

- Currently-Listed method patents
 - Use of new declaration form “is particularly advisable for method-of-use patents”
 - “voluntary submission of new patent declarations will not bring patents within the scope of the final rule with respect to notice and 30-month stays.”
 - But with respect to perjury and estoppel...

To-Do

- => Review existing method patents and consider filing claim-identifying Declarations
 - Patents listed in the Orange Book as of August 17, 2003 are “grandfathered” in and enjoy benefits of the old rule (e.g., multiple 30-month stays, etc...)
 - *Cf.* in Glaxo v. Apotex, Glaxo asked the FDA (on 1 July 2003) to de-list 3 patents from the Orange Book.

To-Do

- Patent Prosecution
 - Large-size Belt

To-Do

“Our long experience with administering the Hatch-Waxman Amendments convinces us that ... any advantage a party can find in manipulating the regulatory program will be pursued. Despite our conviction that the final rule will substantially reduce such manipulation, we do not believe we can completely prevent attempts at ‘creative compliance’ by the parties.”

Comments at 52.

for further research...

- available on-line at www.LicensingLaw.Net/Library:
 - A color copy of this presentation together with the Federal cases cited; and
 - A paper on antitrust implications of patent listing, together with the Federal cases cited



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