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# Orange Book Use Codes: Impact of Caraco v. Novo Nordisk

Pursuing, Avoiding or Defending Against Counterclaims to Correct Method-of-Use Patents

TUESDAY, JUNE 5, 2012

1pm Eastern | 12pm Central | 11am Mountain | 10am Pacific

Today's faculty features:

David S. Bloch, Partner, **Winston & Strawn**, San Francisco

Thomas L. Irving, Partner, **Finnegan Henderson Farabow Garrett & Dunner**, Washington, D.C.

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# Method-Of-Use Patents and *Caraco v. Novo Nordisk*

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# Disclaimer

- I have been actively involved in the *Novo Nordisk v. Caraco* case since 2007. I tried the case in the Eastern District of Michigan alongside Winston's Jim Hurst, Chuck Klein, and John Hsu.
- I also participated in the entire appellate process alongside Jim, Chuck, and Steffen Johnson.
- Because I remain one of the lawyers of record for Caraco in the litigation, I cannot comment on Caraco's or Novo's current legal strategies.

# History

- Three Main OAD Classes as of Oct. 1996:
  - *Insulin Secretagogues*
    - Sulfonylureas (e.g., glipizide, glyburide)
    - Meglitinides (e.g., repaglinide, nateglinide)
  - *Insulin Sensitizers*
    - Biguanides (e.g., metformin)
    - TZDs (e.g., troglitazone)
  - *Glucose Absorption Inhibitors* (e.g, Acarbose)

# Repaglinide

- Novel secretagogue (meglitinide class) developed by Boeringher Ingelheim. Compound patented by BI: U.S. Patent No. RE37,035, expiring March 2009.
- BI licensed repaglinide (including the `035 patent) to Novo Nordisk.
- During clinical trials, Novo applied for and received U.S. Patent No. 6,677,358, expiring in 2018.
- Novo sells repaglinide as Prandin, with 3 approved uses:
  - Monotherapy
  - Combination therapy with TZDs
  - Combination therapy with metformin
- Novo listed both the `035 and `358 patents in the Orange Book.
- Novo's use code for the `358 patent: "Use of repaglinide in combination with metformin to lower blood glucose."

# The `358 Patent: “NIDDM Regimen”

- 1. A pharmaceutical composition comprising repaglinide and metformin together with a suitable carrier.
- 2. A pharmaceutical composition of claim 1 provided in the form of a tablet.
- 3. A pharmaceutical composition of claim 1 provided in the form of a capsule.
- 4. A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin.
- 5. A kit for use in the treatment of a patient having non-insulin dependent diabetes mellitus (NIDDM), said kit comprising an amount of repaglinide formulated for administration to said patient and an amount of metformin formulated for administration to said patient.

# The `358 Patent: "NIDDM Regimen"

- 1. A pharmaceutical composition comprising repaglinide and metformin together with a suitable carrier.
- 2. A pharmaceutical composition of claim 1 provided in the form of a tablet.
- 3. A pharmaceutical composition of claim 1 provided in the form of a capsule.
- 4. A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin.
- 5. A kit for use in the treatment of a patient having non-insulin dependent diabetes mellitus (NIDDM), said kit comprising an amount of repaglinide formulated for administration to said patient and an amount of metformin formulated for administration to said patient.

# Caraco's ANDA

- ANDA for Prandin submitted in 2005.
  - Paragraph III certification to `035 patent: will wait to market until March 14, 2009.
  - Paragraph IV certification to `358 patent: patent is invalid or not infringed – obvious, and no intention to market combination.
- Novo sued Caraco and Sun in the Eastern District of Michigan, 2005.
  - Caraco is accused of inducing infringement of claims 4 (method) and 5 (kit).

# Label changes and Citizen Petitions

- In response to a proposed Caraco ANDA amendment, FDA suggested a split certification. Caraco duly submitted a split certification carving out all references to repaglinide-metformin combination therapy.
- Caraco also submitted a Citizen Petition confirming that any section viii filer carving out claim 4 must also file a Paragraph IV certification to claim 5.
- FDA agreed, holding that a split certification is proper. Novo asked FDA to reconsider this decision.

# Novo changes its use code

- In April 2009, Novo changes its use code description from "use of repaglinide in combination with metformin to lower blood glucose" to "a method for improving glycemic control in adults with type 2 diabetes."
  - Novo claims that it made the change to respond to an FDA-required change to Prandin's "Indications" section a year earlier.
- As a consequence, FDA denied Novo's request to reconsider Caraco's Citizen Petition ruling as "moot" and denied Caraco's split certification request.

# The Hatch-Waxman counterclaim

- 21 U.S.C. Section 355 (j)(5)(C)(ii)(I) provides:
  - If an owner of the patent or the holder of the approved application under subsection (b) for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) on the ground that the patent does not claim either-- (aa) the drug for which the application was approved; or (bb) an approved method of using the drug.

# The Hatch-Waxman counterclaim

- 21 U.S.C. Section 355 (j)(5)(C)(ii)(I) provides:
  - If an owner of the patent or the holder of the approved application under subsection (b) for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) on the ground that the patent does **not** claim either-- (aa) the drug for which the application was approved; or (bb) an approved method of using the drug.

# Caraco states a claim

- In May 2009, Caraco sought leave to amend its answer and counterclaims to assert a counterclaim under the Hatch-Waxman Act and a claim for patent misuse based on the same underlying facts. Novo opposed the motion.
- Citing *Mylan*, legislative history, and post-enactment commentary, the District Court held in August 2009 that Caraco had properly stated claims under the Hatch-Waxman Act: "The scope of a counterclaim under § 355(j)(5)(C)(ii) allows for Caraco's challenge to the Use Code U-968 which comes from the Form FDA 3542 filed by Novo on May 06, 2009." 2009 WL 2768955 (E.D. Mich.).

# Novo is ordered to correct its use code

- Less than a month later (9/24/09), Caraco won a motion for summary judgment. Key holdings:
  - "The `358 patent which is the subject of this patent action does not cover repaglinide; it covers repaglinide only in combination with metformin."
  - "Novo filed the new U-968 use code on May 6, 2009, shortly after the `035 patent expired, as a significantly broadened replacement for use code U-546 that it previously submitted for the `358 patent."
  - "Novo's defense to Caraco's motion is a farrago of misstated and irrelevant facts and misstated law."
  - "Novo is not a private FDA. Novo, by the change in the use code narrative is attempting to extend the life of an expired patent."
- By a separate injunction, the District Court ordered Novo "to correct within twenty (20) days from the date of this Order and Injunction its inaccurate description of the `358 patent by submitting to FDA an amended Form FDA 3542 that reinstates its former U-546 listing for Prandin and describes claim 4 of the `358 patent … as covering the 'use of repaglinide in combination with metformin to lower blood glucose.'"



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# Novo's Federal Circuit appeal

- Novo promptly appealed the District Court's decision to the Federal Circuit and won a swift stay of the decision.
- The parties then briefed whether the Hatch-Waxman counterclaim was available to Caraco and (Caraco contends) whether the District Court properly ordered Novo to change its use code.
- The Federal Circuit ruled in April 2010 that the Hatch-Waxman counterclaim was not available to Caraco. Key points:
  - "[T]he Hatch-Waxman Act authorizes a counterclaim only if the listed patent does not claim any approved methods of using the listed drug."
  - "[T]o preserve the Act's careful balance and to enforce the language of the statute, the explicit definition of 'the patent information' as 'the patent number and the expiration date' controls."

# Dissents and denials en banc

- A strongly worded dissent from Judge Dyk argued that "The amendment was designed to permit the courts to order correction of information published in the Orange Book, yet under the majority's opinion, erroneous Orange Book method of use information cannot be corrected."
  - "[T]he majority's crabbed view of the statute sanctions an unjustified manipulation of the Orange Book."
- Caraco sought *en banc* review but lost, though with a favorable dissent from Judge Gajarsa: "Because the majority's statutory construction of the counterclaim provision abrogates the HWA and frustrates the clear intent of Congress, I dissent from the court's denial of Caraco's request for rehearing en banc."

# Meanwhile, in Detroit ….

- Caraco and Novo conducted an 11-day bench trial between June and August 2010.
- The Federal Circuit denied rehearing about halfway through trial.
- In January 2011, the District Court found that the `358 patent was invalid for obviousness and unenforceable due to inequitable conduct.
- Novo appealed the trial verdict.

# Judge Cohn's conclusions

- "While Novo argued vigorously to sustain the '358 patent, at the end of the day the record simply does not support its arguments. Rather, **the record shows, quite clearly, that the patent should never have issued. The idea to combine repaglinide with metformin was natural. Moreover, the results of the combination were not at all unexpected.**"
- "**Novo knew the obstacles to obtaining a patent, as seen by the several rejections. Knowing what was needed to be shown to establish patentability, in what would be Novo's final attempt before the Patent Office, Novo omitted material information. The only inference which can be drawn from its conduct was that it was done with the intent to deceive the examiner and obtain a patent.** Perhaps market forces drove Novo to do what it did; the Court can only speculate. In the end, however, the patent cannot be sustained."

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# Meanwhile, in D.C. …

- Caraco appealed the Federal Circuit's use code ruling to the United States Supreme Court.
- Caraco asked the Supreme Court to seek the views of the Solicitor General, which it did.
- The Solicitor General urged the Supreme Court to take the case: "Under the Federal Circuit's decision, a brand-name manufacturer can effectively preclude generic competition by submitting an overbroad description of its method-of-use patent to FDA. **Congress enacted the counterclaim provision at issue here to combat precisely that sort of manipulation.** The court's ruling significantly impairs ANDA applicants' ability to secure FDA approval for their products, and hence deprives consumers of the full benefit of generic competition."
- The Supreme Court took the case and heard oral argument in December 2011.

# The Supreme Court's decision

- On April 17, 2012, the Supreme Court rendered a unanimous decision reversing the Federal Circuit, in an opinion authored by Justice Kagan. The highlights:
  - **What does the `358 patent cover?** "Novo currently holds a patent for one of the three FDA-approved uses of repaglinide—its use with metformin. But Novo holds *no* patent for the use of repaglinide with TZDs or its use alone."
  - **Did Novo change its use code based on FDA guidance?** "[T]he FDA, in calling for new labeling, neither requested nor required Novo to amend its use code."

# The Supreme Court's decision

- **Is Novo's new use code overbroad?**
  - **"**[T]he statute's text and context demonstrate that the counterclaim is available not only (as in *Mylan*) when the patent listing is baseless, but also (as here) when it is overbroad."
  - "[Judge Dyk] would have read the phrase 'the patent does not claim ... an approved method of using the drug' to include situations where, as here, the use code wrongly indicates that the patent covers one or more particular approved methods of use."
  - "[W]here (as here) a brand files an overbroad use code, a generic company cannot use paragraph IV litigation to [obtain a judgment of non-infringement]."
  - The Supreme Court repeatedly characterized Novo's use code as "overbroad" and stated that it "wrongly indicates" the scope of Novo's patent.
- **What's wrong with an overbroad use code?** "An overbroad use code … throws a wrench into FDA's ability to approve generic drugs as the statute contemplates. So it is not surprising that the language Congress used in the counterclaim provision sweeps widely enough to embrace that filing."



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# The Supreme Court's decision

- **What is the counterclaim for?** "The statutory scheme … contemplates that one patented use will not foreclose marketing the generic drug for other unpatented ones. … [T]he counterclaim naturally functions to challenge the brand's assertion of rights over whichever discrete use (or uses) the generic company wishes to pursue. That assertion, after all, is the thing blocking the generic drug's entry on the market. The availability of the counterclaim thus matches the availability of FDA approval under the statute: A company may bring a counterclaim to show that a method of use is unpatented because establishing that fact allows the FDA to authorize a generic drug via section viii."
- **What's wrong with Novo's reading of the counterclaim?** "Novo's reading of 'patent information,' like its reading of 'not an,' effectively deletes the term 'correct' from the statute."
- **What's the bottom line?** "We accordingly hold that Caraco may bring a counterclaim seeking to 'correct' Novo's use code 'on the ground that' the `358 patent 'does not claim … an approved method of using the drug'—indeed, does not claim two."

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# Where are we now?

- At a minimum, it is now clear that the Hatch-Waxman Act's counterclaim provision allows a generic to challenge a brand pharmaceutical company's overbroad use code.
- Caraco and Novo differ as to whether the Supreme Court's decision only resolved that issue, or whether it also resolved whether Novo's use code was overbroad (and thus whether the District Court's injunction was proper).
  - This question is being briefed to the Federal Circuit now.
- Separately, Novo's appeal of Caraco's trial win (which had been stayed pending resolution of the Supreme Court "use code" appeal) will now proceed forward in the ordinary course.

# *Orange Book Use Codes: Impact of Caraco v. Novo Nordisk*

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June 5, 2012, with
gratitude to Stacy Lewis

# Disclaimer

- These materials are public information and have been prepared solely for educational and entertainment purposes to contribute to the understanding of U.S. intellectual property law and practice. These materials reflect only the personal views of the speakers and are not individualized legal advice. It is understood that each case is fact-specific, and that the appropriate solution in any case will vary. Therefore, these materials may or may not be relevant to any particular situation. Thus, Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., EISAI, and the speakers cannot be bound either philosophically or as representatives of their various present and future clients to the comments expressed in these materials. The presentation of these materials does not establish any form of attorney-client relationship with Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., EISAI, and the speakers. While every attempt was made to insure that these materials are accurate, errors or omissions may be contained therein, for which any liability is disclaimed.

# Statutory Framework

- It shall be an act of infringement to submit
  - (A) an application under section 505(j) of the [FDA Act] or described in section 505(b)(2) of that Act for a drug claimed in a patent or the use of which is claimed in a patent . . .

  if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use or sale of a drug . . . claimed in a patent before the expiration of such patent.

  35 U.S.C. § 271(e)(2) (emphasis added)

# What Hatch-Waxman Requires

- The FDA cannot authorize a generic drug that would infringe a brand manufacturer's patent.
  - For example, a claim of the patent of the NDA holder reads:
    - A method of treating bladder cancer comprising . . . .
  - If the ANDA is for treating bladder cancer, . . .
  - If the ANDA is for treating colon cancer, . . .

# What Hatch-Waxman Requires (con't)

- To facilitate the approval of generic drugs as soon as patents allow, the Hatch-Waxman Amendments require a brand manufacturer to submit its patent numbers and expiration dates, §355(b)(1) (called Orange Book listing)

- A patent is listed in the Orange Book if the patentee could reasonably assert that the patent is valid, enforceable, and would be infringed, if copied.

- Form 3542.

Department of Health and Human Services
Food and Drug Administration

# PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

***For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use***

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
*See OMB Statement on Page 3.*

NDA NUMBER

NAME OF APPLICANT/NDA HOLDER

***The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.***

TRADE NAME

| ACTIVE INGREDIENT(S) | STRENGTH(S) |
|---|---|
| DOSAGE FORM | APPROVAL DATE OF NDA OR SUPPLEMENT |

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

**For hand-written or typewriter versions of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

***FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.***

***For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.***

## 1. GENERAL

| | | |
|---|---|---|
| a. United States Patent Number | b. Issue Date of Patent | c. Expiration Date of Patent |
| d. Name of Patent Owner | Address *(of Patent Owner)* | |
| | City/State | |
| | ZIP Code | FAX Number *(if available)* |
| | Telephone Number | E-Mail Address *(if available)* |
| e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) | Address *(of agent or representative named in 1.e.)* | |
| | City/State | |
| | ZIP Code | FAX Number *(if available)* |
| | Telephone Number | E-Mail Address *(if available)* |

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

***For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.***

## 2. Drug Substance (Active Ingredient)

| | | |
|---|---|---|
| **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? | ☐ Yes | ☐ No |
| **2.2** Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA? | ☐ Yes | ☐ No |
| **2.3** If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). | ☐ Yes | ☐ No |
| **2.4** Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**. | | |
| **2.5** Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.) | ☐ Yes | ☐ No |
| **2.6** Does the patent claim only an intermediate? | ☐ Yes | ☐ No |
| **2.7** If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) | ☐ Yes | ☐ No |

**FDA will not list the patent in the Orange Book as claiming the drug substance if:**

- **the answers to 2.1 and 2.2 are "No," or,**
- **the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,**
- **the answer to 2.3 is "Yes" and there is no response to 2.4, or,**
- **the answer to 2.5 or 2.6 is "Yes."**
- **the answer to 2.7 is "No."**

## 3. Drug Product (Composition/Formulation)

| | | |
|---|---|---|
| **3.1** Does the patent claim the approved drug product as defined in 21 CFR 314.3? | ☐ Yes | ☐ No |
| **3.2** Does the patent claim only an intermediate? | ☐ Yes | ☐ No |
| **3.3** If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) | ☐ Yes | ☐ No |

**FDA will not list the patent in the Orange Book as claiming the drug product if:**

- **the answer to question 3.1 is "No," or,**
- **the answer to question 3.2 is "Yes," or,**
- **the answer to question 3.3 is "No."**

**METHOD OF USE**

## 4. Method of Use

***Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information:***

| | | |
|---|---|---|
| **4.1** Does the patent claim one or more approved methods of using the approved drug product? | ☐ Yes | ☐ No |
| **4.2** Patent Claim Number(s) *(as listed in the patent)* | Does (Do) the patent claim(s) referenced in **4.2** claim an approved method of use of the approved drug product? ☐ Yes | ☐ No |
| **4.2a** If the answer to **4.2** is "Yes," identify the use with specific reference to the approved labeling for the drug product. | Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* | |

# Method of Use

- Patent must claim one or more approved methods of using the approved drug product:
  - Method of treatment or prevention.
  - Method of using the approved drug to administer an active metabolite.

***For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.***

## 2. Drug Substance (Active Ingredient)

| | | | |
|---|---|---|---|
| **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? | ☐ Yes | ☐ No |
| **2.2** | Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA? | ☐ Yes | ☐ No |
| **2.3** | If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). | ☐ Yes | ☐ No |
| **2.4** | Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**. | | |
| **2.5** | Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.) | ☐ Yes | ☐ No |
| **2.6** | Does the patent claim only an intermediate? | ☐ Yes | ☐ No |
| **2.7** | If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) | ☐ Yes | ☐ No |

**FDA will not list the patent in the Orange Book as claiming the drug substance if:**

- **the answers to 2.1 and 2.2 are "No," or,**
- **the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,**
- **the answer to 2.3 is "Yes" and there is no response to 2.4, or,**
- **the answer to 2.5 or 2.6 is "Yes."**
- **the answer to 2.7 is "No."**

## 3. Drug Product (Composition/Formulation)

| | | | |
|---|---|---|---|
| **3.1** | Does the patent claim the approved drug product as defined in 21 CFR 314.3? | ☐ Yes | ☐ No |
| **3.2** | Does the patent claim only an intermediate? | ☐ Yes | ☐ No |
| **3.3** | If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) | ☐ Yes | ☐ No |

**FDA will not list the patent in the Orange Book as claiming the drug product if:**

- **the answer to question 3.1 is "No," or,**
- **the answer to question 3.2 is "Yes," or,**
- **the answer to question 3.3 is "No."**

## 4. Method of Use

***Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information:***

| | | | |
|---|---|---|---|
| | or more approved methods of using the approved drug product? | ☐ Yes | ☐ No |
| | *as listed in the patent)* — Does (Do) the patent claim(s) referenced in **4.2** claim an approved method of use of the approved drug product? | ☐ Yes | ☐ No |
| **4.2a** | If the answer to **4.2** is "Yes," identify the use with specific reference to the approved labeling for the drug product. | Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* | |

**USE**

# Section 4.2 - Information and Instructions

- "For each approved use of the drug claimed by the patent, identify by number the claim(s) in the patent that claim the approved use of the drug. An applicant may list together multiple patent claim numbers and information for each approved method of use, if applicable. However, each approved method of use must be separately listed within this section of the form."

# Section 4.2a - Information and Instructions

- "Specify the part of the approved drug labeling that is claimed by the patent."

- Contrast with 21 CFR 314.53(b), which states: "…method of use and *related* patent claim" and "…identify…labeling that *corresponds*."

- Use of Auditor's Notes.

# What Hatch-Waxman Requires

- FDA regulations require a description of any method-of-use patent, known as a use code.
  - See 21 CFR §§314.53(c)(2)(ii)(P)(3).

| 4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description. | Use: *(Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)* |
|---|---|

**FDA will not list the patent in the Orange Book as claiming the metho[illegible] if:**

- **the answer to question 4.1 or 4.2 is "No," or**
- **if the answer to 4.2 is "Yes" and the information requested in 4.2a**

**USE CODE**

## 5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

☐ Yes

## 6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

***Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.***

| 6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)* | Date Signed |
|---|---|
| | |

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/ holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

| | |
|---|---|
| ☐ NDA Applicant/Holder | ☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official |
| ☐ Patent Owner | ☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official |

| | |
|---|---|
| Name | |
| Address | City/State |
| ZIP Code | Telephone Number |
| FAX Number *(if available)* | E-Mail Address *(if available)* |

# Question 4.2b

- [P]rovide the information on the indication or method of use for the Orange Book "Use Code" description.

- Use: (Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)

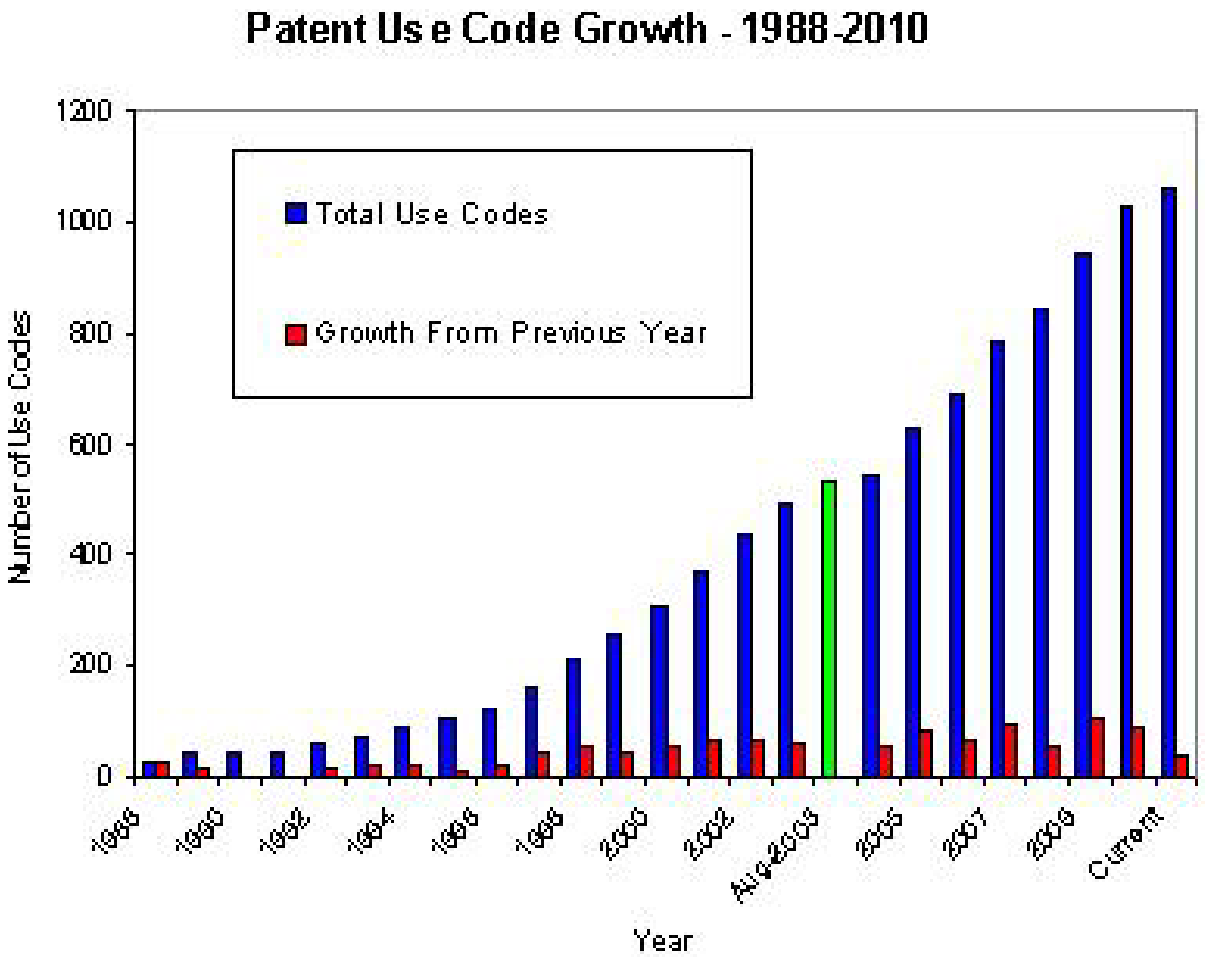
# Use Code

- The use code designates a method of use patent that claims the approved indication or use of a drug product.

- Each approved use claimed by the patent should be separately identified in this section.

- Claim construction in 240 characters or less.
  - Auditor's Notes
  - *See* Phillips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005)(en banc).

# “Old” or “new”?




http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2010/07/analysis-shows-patent-use-codes-have-doubled-since-august-2003--by-kurt-r-karst-httpwwwhpmcomvattorneycfmrid22.html

# Drafting the Use Code

- FDA has not expressly addressed what the use code should be when the patent claim is different than the approved indication.

- Use code should contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent claims a use for which the 505(b)(2) or ANDA applicant is **not** seeking approval.

# Drafting the Use Code (con't)

- But the Supreme Court has now spoken in Caraco:
  - *"Held: A generic manufacturer may employ the counterclaim provision to force correction of a use code that inaccurately describes the brand's patent as covering a particular method of using a drug."*

# Drafting the Use Code (con't)

- It can all start with drafting and prosecuting the patent application.

- Caraco: use code was broader in scope than issued patent claims.

# Ex. 1: Drafting the Use Code: the Claims

- Patent claims:
  - 1. A method of treatment which comprises administering to a patient in recognized need thereof a compound which blocks Inhibitor A instead of Inhibitor B.
  - 2. The method of claim 1, wherein said recognized need is for treatment of lung cancer.
  - 3. The method of claim 1, wherein said recognized need is for treatment of brain cancer.

# Drafting the Use Code: the Specification

- Specification:
  - The compounds of this disclosure are useful for the treatment of certain cancers, such as brain cancer, lung cancer, breast cancer, cancer of the colon, liver cancer, prostate cancer, and throat cancer.

# Drafting the Use Code: The Label

- The Label: Mechanism of Action
  - The compound Tumor Kill blocks Inhibitor A instead of Inhibitor B. Once blocked, those inhibitors regulate the expression of genes that control differentiation. The exact mechanism of action of Tumor Kill in the treatment of lung cancer and brain cancer is unknown.

# Drafting the Use Code: the Label (con't)

- The Label: Indications and Usages
  - Tumor Kill Tablets are indicated for the treatment of lung cancer and brain cancer.

# The Use Code

- The Use Code:
  - A method of treatment which comprises administering to a patient in recognized need thereof a compound, such as Tumor Kill, which blocks Inhibitor A instead of Inhibitor B.

# Alternative Use Code

- A Use Code alternative:
  - A method of treatment of brain or lung cancer which comprises administering to a patient in recognized need thereof Tumor Kill.
  - Existing use codes are in Orange Book Addendum http://www.accessdata.fda.gov/scripts/cder/ob/docs/pattermsall.cfm

# ANDA

- ANDA filer:
  - –Seeks approval of Tumor Kill for treatment of brain cancer.

# What happens?

- NDA holder takes the position that it tailored the use code descriptor to an approved product.

- Issues of skinny labeling?
  - No skinny labeling opportunity seen here because breadth of the claims is commensurate with Use Code and approved indications, i.e., brain and lung cancers.

# Ex. 2: Drafting the Use Code: the Claims

- Patent claims:
  - 1. A method of treatment which comprises administering to a patient in recognized need thereof a compound which blocks Inhibitor A instead of Inhibitor B.
- No claim specific to brain cancer treatment.
- A claim specific to lung cancer treatment.

# Drafting the Use Code: the Specification

- Specification:
  - The compounds of this disclosure are useful for the treatment of certain cancers, such as lung cancer, breast cancer, cancer of the colon, liver cancer, prostate cancer, and throat cancer.
  - Brain cancer does not appear in spec.

# Drafting the Use Code: The Label

- The Label: Mechanism of Action
  - The compound Tumor Kill blocks Inhibitor A instead of Inhibitor B. Once blocked, those inhibitors regulate the expression of genes that control differentiation. The exact mechanism of action of Tumor Kill in the treatment of lung cancer and brain cancer is unknown.

# Drafting the Use Code: the Label (con't)

- The Label: Indications and Usages
  - Tumor Kill Tablets are indicated for the treatment of lung cancer and brain cancer.
  - Note that brain cancer was approved by FDA but no patent claim specifically reciting treatment of brain cancer issued.

# The Use Code

- The Use Code:
  - A method of treatment which comprises administering to a patient in recognized need thereof a compound, such as Tumor Kill, which blocks Inhibitor A instead of Inhibitor B.

# ANDA

- ANDA filer:
  - Seeks approval of Tumor Kill for treatment of brain cancer.
  - Assume Inhibitor A is blocked but Inhibitor B is not.
  - Seeks to skinny label out lung cancer.

# What happens?

- A section viii statement allows the FDA to approve a generic drug for unpatented uses so that it can quickly come to market.

# Seeking Approval?

- If label has more than one indication, but patent claim (or exclusivity) covers only one of those indications?

- ANDA applicant seeks approval only on those indications that are not covered by patent or exclusivity.

- In that case Section viii, noted above, applies instead of Paragraph IV.
  - No notice to NDA holder;
  - No 30-month stay;
  - No 180-day exclusivity for first generic manufacturer.

# What happens?

- Is the Use Code too broad?
  - It is exactly what was patented.
  - Is the Use Code an approved method of using?
  - Per Caraco, the patent covers multiple methods of use.

# What happens? (con't)

- NDA holder/patent owner takes the position that it tailored the use code to the approved product.
- The approved indication utilizes a compound which blocks Inhibitor A instead of Inhibitor B.
- The NDA holder/patent owner asserts it obtained such broad indication coverage.
- The ANDA indication also utilizes a compound which blocks Inhibitor A instead of Inhibitor B.

# 21 C.F.R. § 314.94(a)(8)(iv)

- Labeling (including the container label and package insert) proposed for the drug product must be the same as the labeling approved for the reference listing drug [RLD], except for [certain differences] . . . .

- Such differences between the applicant's proposed labeling and labeling approved for the [RLD] may include . . . **omission of an indication or other aspect of labeling protected by patent** or accorded exclusivity under [FDC Act § 505(j)(5)(D)].

- But in Ex. 2, how can ANDA filer omit lung cancer? Use Code covers mechanism of action of approved products.

# Skinny Labeling

- In the report accompanying the 1984 Hatch-Waxman Amendments, Congress stated that a generic applicant:

> need not seek approval for all of the indications for which the [Reference Listed Drug ("RLD")] has been approved. For example, if the [RLD] has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the application could seek approval for only the angina pectoris indication.

# No Skinny Labeling

- In Example 2, the RLD has been approved for both brain and lung cancer and both indications fall within the scope of Claim 1:

1. A method of treatment which comprises administering to a patient in recognized need thereof a compound which blocks Inhibitor A instead of Inhibitor B.

# No Skinny Labeling (con't)

- NDA holder/patentee takes the view that the indication sought in the ANDA is a patented use and hence the ANDA filer must file a paragraph IV, not an section viii.

# NDA Holder's Option if There is a Caraco Use Code Issue

- File good-faith Citizens Petition asking FDA to refrain from approving any generic versions of the drug for treating brain cancer (Ex. 2 above) until the ANDA holder establishes that the generic version would be as safe and effective as the clinically proven innovative method of treatment.

- If a labeling carve-out would render the proposed generic drug product less safe or effective than the RLD, then the Agency will not permit a labeling carve-out.

# NDA Holder's Option if There Is a Caraco Use Code Issue (con't)

- File good-faith Citizens Petition asking FDA to refrain under section viii from approving any generic versions of the drug for treating brain cancer (Ex. 2 above) subject to the ANDA holder filing a paragraph IV certification??

# Rapamune® (sirolimus) Example of Successful Citizens Petition

- FDA approved efficacy supplements for formulations of Rapamune® that provided for cyclosporine withdrawal procedures in patients at low to moderate risk for rejection.

- This new cyclosporine withdrawal labeling received 3 years of marketing exclusivity.

# Rapamune® (sirolimus) Example of Successful Citizens Petition (con't)

- *Indications and Usage* for Rapamune®
  - It is recommended that Rapamune® be used initially in a regimen with cyclosporine and corticosteroids. In patients at low to moderate immunologic risk cyclosporine should be withdrawn 2 to 4 months after transplantation and Rapamune® dose should be increased to reach recommended blood concentrations. . . . The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended.

# Rapamune® (sirolimus) Example of Successful Citizens Petition (con't)

- Wyeth filed a citizen's petition requesting that FDA refrain from approving any generic versions of Rapamune® before expiration of the exclusivity period.

- FDA decision:
  - Agency cannot approve an ANDA for a generic product with labeling omitting the cyclosporine withdrawal language because that would make the product less safe and effective than Rapamune® for its nonprotected indication.

# Too Broad Outside of Hatch-Waxman Counterclaim?

- FDA forwards challenge and requests that NDA holder reply, either confirming that the use code is correct as listed, or amending the use code in response to the challenge.
  - Orange Book not amended "[u]nless the application holder withdraws or amends its patent information in response to the FDA's request."

- If not amended, despite disagreement on correctness, ANDA filer must make appropriate certifications and then make Caraco challenge in counterclaim.
- *See* 21 C.F.R. § 314.53(f),

# Cardizem® (diltiazem hydrochloride) Example

- Prescribing Information (Label)
  - Treatment of hypertension
  - Management of chronic stable angina

# Sample Orange Book Page
# Cardizem® Extended Release Capsule

## Patent Data

| Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code |
|---|---|---|---|---|---|---|
| 020062 | 001 | 4894240 | JAN 16,2007 | | | |
| 020062 | 001 | 5002776 | MAR 26,2008 | | | |
| 020062 | 001 | 5286497 | MAY 20,2011 | | | |
| 020062 | 001 | 5364620 | NOV 14,2011 | | | U-3 |
| 020062 | 001 | 5439689 | AUG 08,2012 | | | U-107 |
| 020062 | 001 | 5470584 | MAY 20,2011 | | | |

# Cardizem® (diltiazem hydrochloride) Example (con't)

- U.S. 5,364,620
  - Method of treating or controlling blood pressure in a subject suffering from mild to moderate hypertension
  - Method of controlling or preventing angina attacks or reducing the incidence of angina attacks
- U-3: Treatment of hypertension
- Was Use Code too narrow?

# Cardizem® (diltiazem hydrochloride) Example (con't)

- U.S. 5,439,689
  - Method of treating cardiovascular disorders
  - Specification: "treatment of cardiovascular disorders such as angina, arrhythmias, and hypertension"
- U-107: Treatment of hypertension and angina pectoris

# Other Use Codes

- U-279: METHOD OF USE OF THE APPROVED PRODUCT
- U-308: CLAIMS A SOLID ORAL FORMULATION INCLUDING TABLETS AND GRANULES OF OLANZAPINE USEFUL FOR TREATING ANY NUMBER OF LISTED CONDITIONS, INCLUDING SPECIFIC PSYCHOLES, EMPLOYING OLANZAPINE AS PER THE INDICATIONS OF THIS NDA
- U-362: USE OF APPROVED FORMULATIONS TO TREAT ALL APPROVED DISEASE INDICATIONS
- Post-Caraco??????

# Statutory Language Analysis In Warner-Lambert

- "[I]t is clear that the phrase 'the use' in §271(e)(2)(A) refers to the use for which the FDA has granted an NDA. That is, as we indicated above, the *only* use for which an ANDA applicant can seek approval."
    - Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1356 (Fed. Cir. 2003).

# Statutory Language Analysis In Allergan

- "Under Warner-Lambert, Allergan is precluded from suing Alcon and B&L under section 271(e)(2) for inducing infringement of the [patents-in-suit] because Alcon and B&L are not seeking FDA approval for the uses claimed in the patents and because the uses claimed in the patents are not FDA-approved."
    - Allergan, Inc. v. Alcon Labs., Inc., 324 F.3d 1322, 1334 (Fed. Cir. 2003).

- How does Example 2 above fare post-Caraco?

# Infringement in the Pharma Context

- Direct infringement typically occurs when generic drug prescribed and administered.
- Induced infringement typically occurs when proposed labeling instructs users of generic drug to perform patented method.
- "[T]he pertinent question is whether the proposed label instructs users to perform the patented method."
  - AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1060 (Fed. Cir. 2010) (emphasis added).
- Attempted skinny label in Ex. 2: should not work to remove mechanism of action.

# No Special Infringement Test under § 271(e)(2)

- "[A] court must employ a traditional infringement analysis, focusing on all of the elements of infringement.... The only difference in the analysis of a traditional infringement claim and a claim of infringement under section 271(e)(2) is the timeframe under which the elements of infringement are considered."
  - Allergan, Inc. v. Alcon Labs., Inc., 324 F.3d 1322, 1331 (Fed. Cir. 2003) (emphasis added).

- The innovator/NDA-holder should fare well in Ex. 2 post-Caraco.

# Bayer Schering Pharma v. Lupin Ltd. *(Yasmin®)(drospirenone/ethinyl estradiol)*

- Federal Circuit decided April 16, 2012, affirming district court ruling granting motion to dismiss.
- Patent claimed simultaneously achieving three effects (contraception, anti-acne, anti-water retention).
- Indications and Usage section of label mentioned only contraception.
- "Pharmacodynamics" section of label discussed other effects observed in preclinical studies.
- Bayer argued that the FDA approved use of Yasmin® to obtain all three effects.

## Bayer Schering Pharma v. Lupin Ltd. *(Yasmin®)(drospirenone/ethinyl estradiol) (con't)*

- Federal Circuit focused on whether FDA approved Yasmin® for all three effects.
  - "While the label [mentions anti-acne and anti-water retention] based on animal studies, neither that passage nor anything else on the label provides any safety or efficacy information associated with the possible use of Yasmin® in patients who are in need of those effects." Slip Op. at 13
  - "[T]he label, taken in its entirety, fails to recommend or suggest to a physician that Yasmin® is safe and effective for inducing the claimed combination of effects in patients . . . ." Slip Op. at 16.

## Bayer Schering Pharma v. Lupin Ltd. *(Yasmin®)(drospirenone/ethinyl estradiol) (con't)*

- Not inconsistent with making ANDA holder file paragraph IV certification in Example 2 above.
- Bayer Schering does not present a Use Code issue.
- Example 2 did not claim simultaneously treating lung cancer and brain cancer.
- Example 2 claimed mechanism of action, assumed to be applicable for either brain or lung cancer, and both brain and lung cancer treatment by Tumor Kill were approved.

# Bayer Schering Pharma v. Lupin Ltd. *(Yasmin®)(drospirenone/ethinyl estradiol) (con't)*

- Dissent asserts panel majority erred by failing to conduct a standard infringement analysis and by failing to credit the factual assertions in the complaint given that posture of the case (motion to dismiss).

- "The court errs in ruling as a matter of law that the FDA-approved label for Yasmin® does not encompass the three effects stated in the label and claimed in the [patent-in-suit]. Bayer's complaint contains well pleaded and well-supported factual allegations and states a plausible claim of infringement." Slip Op. at 9.

- Motion for rehearing due by mid-May 2012; none was filed.

# Use Code Strategies and Tactics

- Orange Book listings
  - Broad use codes, counterclaim challenges more possible? Design-arounds less possible?
  - Indication-only codes, counterclaim challenges less possible? Design-arounds more possible?

- US PTO Prosecution
  - Obtain broad claims.
  - Obtain claims directed to mechanism of action.

# Will There Be Enhanced Antitrust And FTC Scrutiny Of Use Codes?

- Responsibility of brand manufacturers to submit use codes.
- FDA assumes correct; procedure for notifying FDA of alleged inaccurate listing, but up to brand manufacturer to withdraw or amend.
- But post-Caraco, will use codes receive increased scrutiny of generic manufacturers AND the Department of Justice and Federal Trade Commission?
- The Use Codes of either Example 1 or Example 2 should withstand scrutiny.

# New Rules?

- Will Congress and/or the FDA, through its regulations, pick up the Use Code gauntlet hurled down by Justice Sotomayor in her concurring opinion?
  - Justice Sotomayor: “Precisely because the regulatory scheme depends on the accuracy and precision of use codes, I find FDA’s guidance as to what is required of brand manufacturers in use codes remarkably opaque…. Absent greater clarity from FDA concerning what is required of brand manufacturers in use codes, Congress’ fears of undue litigation may be realized.”

# Thank You!

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