

# Information on Unapproved Drug Marketing Applications: The Public Has a Right to Know

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## A Forum on Transparency at the US Food and Drug Administration Panel 2 – Correcting Misinformation

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# Introduction

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- **The FDA's long-standing policy is that it does not release its analyses of data submitted for NDAs or supplemental NDAs or disclose agency complete response letters notifying drug manufacturers of the non-approval decisions and the reasons for such actions.**
- **By contrast, the FDA routinely releases to the public its detailed analyses and findings related to data supporting the approval of a drug's first NDA and, upon request by at least three individuals, of supplemental NDAs for new uses of already marketed drugs.**

# Case Example 1

## FDA Approval of Valdecoxib (Bextra)

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- Valdecoxib is one of the NSAIDs known as selective cyclooxygenase-2 inhibitors that was marketed in the U.S. by Pfizer and Pharmacia under the brand name Bextra.
- January 2001: J.D. Searle submitted an NDA to the FDA for approval to market valdecoxib for 4 indications:
  - Osteoarthritis
  - Rheumatoid arthritis
  - Dysmenorrhea
  - Acute pain
- November 2001: The FDA approved valdecoxib only for the first three indications.

# Case Example 1

## FDA Approval of Valdecoxib (Bextra) (2)

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- **December 2001:** Public Citizen requested from the FDA a copy of the approval package for Bextra.
- **Early 2002:** the FDA posted on its website a complete copy of the requested approval package, but a few days later, at the request of Searle, the FDA removed the information from its website.
- **May 2002:** A medical journal article and a related industry press release were published touting Bextra for treating acute pain associated with dental surgery.

# Case Example 1

## FDA Approval of Valdecoxib (Bextra) (3)

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- **2004: Public Citizen FOIA lawsuit; the FDA released some of the information redacted from the agencies approval package, which showed that the FDA had denied approval of Bextra for treating acute pain because of safety concerns.**

# Public Health Benefits of Increased Transparency on Unapproved NDAs

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- *2017 Blueprint for Transparency at the U.S. Food and Drug Administration:* “[C]linical community can benefit from the insight, expertise, and analyses of FDA reviewers, and researchers can learn from the failures of previous medical products in subsequent research programs.”
- Lack of transparency is particularly troubling in cases where the FDA has found a currently marketed drug to be ineffective or unsafe for a newly proposed indication.
- Disclosure of the FDA’s findings in such cases would promote public health by encouraging healthcare providers to avoid prescribing drugs for unapproved (off-label) uses that the agency has deemed to be potentially dangerous or ineffective.

# Public Health Benefits of Increased Transparency on Unapproved NDAs (2)

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- Disclosure of complete response letters is all the more important given the current permissive framework allowing the promotion of already marketed drugs for unapproved uses.
- Congress is considering legislation that would further expand the scope of such off-label promotion.
- Such erosions of restrictions on off-label marketing make it vital that healthcare professionals be informed of off-label uses that were deemed by the FDA to be too dangerous or ineffective for patients.

# Public Health Benefits of Increased Transparency on Unapproved NDAs (3)

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- Finally, a new policy of transparency whereby the FDA discloses data related to rejected applications for new drugs and new indications for already approved drugs also would be consistent with the Belmont Report's basic ethical principle of beneficence governing human subjects research

# Feasibility: The FDA Should Follow Europe's and Canada's Lead

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- In 2004, the European Union (EU) required that the European Medicines Agency (EMA) make publicly accessible “information about all refusals [of human drug marketing applications] and the reasons for them.”
- Health Canada followed suit in 2015 when it announced that it would make available to the public all regulatory decision summaries, which contain the rationale for the agency's decisions on drug marketing applications. This decision notably included, for public release, “final negative decisions and cancellations” for all marketing applications for new drugs and new indications for existing drugs.

# Case Example 2: Marketing Application for Paliperidone (Invega) for Acute Manic Episodes

- **September 2008: Johnson and Johnson submitted an application to the EMA for an additional indication for its antipsychotic drug paliperidone (Invega): the treatment of acute manic episodes associated with bipolar I disorder.**
- **The company withdrew its application in December 2008, 85 days into the EMA's CHMP review of the application. The company stated that it withdrew the application because of "the Rapporteur's and Co-Rapporteur's Assessment Reports indicating that the data provided to date were not sufficient to support approval for this indication"**
- **The EMA subsequently issued a press release announcing the company's withdrawal of its application, posted the company's letter requesting the withdrawal and published a Q&A fact sheet on the application, describing the studies used to support the application and linking to the company's letter to explain why the withdrawal was made.**

## **Case Example 2: Marketing Application for Paliperidone (Invega) for Acute Manic Episodes (2)**

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- The company went on to publish the three studies in peer-reviewed journals, without disclosing to readers that its EMA application for approval of Invega for bipolar disorder was withdrawn because the data in these studies were deemed insufficient to support such an approval.**
- Off-label use of second-generation antipsychotics, such as Invega, for psychiatric conditions for which they are not approved is widespread.**
- Physicians may have been prescribing Invega for bipolar disorder with no knowledge of this regulatory history.**

# Conclusion

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- **The FDA must join the EMA and Health Canada in allowing the public to know when a drug is deemed unsafe or ineffective for a certain use. Even notwithstanding the public health benefits that disclosure of such information would reap, the public has a right to know when, how, and why the nation's largest public health agency reaches major decisions on the products it regulates.**