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

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Much of the information upon which the Food and Drug Administration (FDA) relies when making pivotal regulatory decisions with regard to regulated products is kept secret.

One prominent example of the FDA's lack of transparency concerns new drug applications (NDAs), including supplemental NDAs, that have been rejected by the agency or withdrawn by the company. The FDA's long-standing policy is that it does not release its analyses of data submitted for such applications or disclose agency complete response letters describing non-approval decisions and the reasons for such actions, nor does the agency even notify the public that such rejections or withdrawals have occurred.[1]

By contrast, the FDA 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.[2]

Case Example 1: *FDA approves valdecoxib (Bextra) for only three of four requested indications*

Valdecoxib is one of the non-steroidal anti-inflammatory drugs (NSAIDs) known as selective cyclooxygenase-2 inhibitors that was marketed in the U.S. by Pfizer and Pharmacia under the brand name Bextra[3] before it was removed from the market in 2005 because of safety concerns.[4] In January 2001, G.D. Searle (then a subsidiary of Pharmacia) submitted an NDA to the FDA for approval to market valdecoxib for four indications: (1) relief of the signs and symptoms of osteoarthritis; (2) relief of the signs and symptoms of adult rheumatoid arthritis; (3) treatment of primary dysmenorrhea (menstrual pain); and (4) prevention and treatment of acute pain, including opioid-sparing and prevention of operative pain.[5] In November 2001, the FDA approved valdecoxib only for the first three indications.

In December 2001, Public Citizen requested from the FDA a copy of the approval package for Bextra.[6] In early 2002, the FDA posted on its website a complete copy of the requested approval

[1] 21 C.F.R. 314.430 (c) and (b)
[2] 21 U.S.C. §355(l)(2).
[3] Pharmacia Corporation. Drug label: valdecoxib (BEXTRA). November 2001. https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21341lbl.pdf. Accessed January 12, 2018.
[4] Smith A. Pfizer pulls Bextra off the market. *CNN*. April 7, 2005. http://money.cnn.com/2005/04/07/news/fortune500/bextra/. Accessed January 12, 2018.
[5] Food and Drug Admininistration. Medical review for valdecoxib. November 7, 2001. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-341_Bextra_medr_P3.pdf. Accessed January 12, 2018.
[6] Public Citizen. Public Citizen Health Research Group v. the Food and Drug Administration: Complaint for declaratory and injunctive relief. February 26, 2004. https://www.citizen.org/system/files/case_documents/acf5cf.pdf. Accessed January 12, 2018.

package, but a few days later — before Public Citizen staff saw the information — at the request of Searle, the FDA removed the information from its website.[7] At a later date, FDA re-posted the approval package but redacted all information related to the drug's safety and efficacy in treating acute pain, claiming that the removed information contained trade secrets and/or confidential information that were not disclosable.[8]

In May 2002, a medical journal article[9] and a related press release[10] were published touting Bextra for treating acute pain associated with dental surgery. The article, published in the Journal of the American Dental Association, was co-sponsored by Pfizer and Pharmacia and three of its five authors were employees of Pharmacia.[11]

Public Citizen subsequently submitted a Freedom of Information Act (FOIA) request for the unredacted approval package and, in response to a lawsuit filed by Public Citizen in 2004,[12] the FDA released some of the information redacted from the agency's approval package,[13] which showed that the FDA had denied approval of Bextra for treating acute pain because of safety concerns. In particular, safety data from a trial that tested valdecoxib as an adjunct to narcotic analgesia following coronary artery bypass graft surgery revealed an excess of serious adverse events, including death, in subjects receiving valdecoxib.[14]

Need for, and benefits of, increased transparency on unapproved drug marketing applications

The 2017 *Blueprint for Transparency at the U.S. Food and Drug Administration*[15] builds on the work of the FDA's 2010 Transparency Task Force, which recommended that the agency, among other things, release complete response letters to shed light on why drug marketing applications were refused.[16]

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[7] *Ibid*.
[8] *Ibid*.
[9] Daniels SE, Desjardins PJ, Talwalker S, et al. The analgesic efficacy of valdecoxib vs. oxycodone/acetaminophen after oral surgery. *J Am Dent Assoc*. 2002; 133(5):611-621.
[10] Public Citizen. Comments on First Amendment issues. September 13, 2002. https://www.citizen.org/our-work/health-and-safety/comments-first-amendment-issues. Accessed January 12, 2018.
[11] Ibid.
[12] Public Citizen. Public Citizen Health Research Group v. the Food and Drug Administration: Complaint for declaratory and injunctive relief. February 26, 2004. https://www.citizen.org/system/files/case_documents/acf5cf.pdf. Accessed January 12, 2018.
[13] Public Citizen. Public Citizen HRG v. FDA (Bextra). https://www.citizen.org/our-work/litigation/cases/public-citizen-hrg-v-fda-bextra. Accessed January 12, 2018.
[14] Food and Drug Admininistration. Medical review for valdecoxib. November 7, 2001. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-341_Bextra_medr_P3.pdf. Accessed January 12, 2018.
[15] FDA Transparency Working Group. Blueprint for Transparency at the U.S. Food and Drug Administration. March 13, 2017. http://www.jhsph.edu/departments/health-policy-and-management/_pdf/FDA_Transparency.pdf. Accessed January 12, 2018.
[16] Food and Drug Administration. Transparency Task Force. FDA Transparency Initiative: Draft proposals for public comment regarding disclosure policies of the U.S. Food and Drug Administration. May 2010.

The *Blueprint* report noted several potential benefits from releasing such information, including that "[t]he clinical 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."[17]

Keeping the public in the dark about unapproved drug marketing applications prevents patients, researchers, and healthcare providers from gaining insight into why a drug's application was not approved.[18] This 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. This is especially important given the endemic practice within the pharmaceutical industry of illegally marketing drugs for off-label uses.[19]

Disclosure of complete response letters is all the more important given the current permissive framework allowing the promotion of marketed drugs for unapproved uses. Existing FDA guidance already permits drug and medical device manufacturers to market their products to physicians for unapproved uses through the dissemination of scientific or medical journal articles and reference publications.[20] And Congress is considering legislation[21] 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.

Failing to provide information on unapproved NDAs also gives companies free rein to craft their own self-serving narratives as to why their product applications were turned down. Disclosing all complete response letters would allow the public, healthcare professionals, and other interested

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https://wayback.archive-it.org/7993/20161022134022/http://www.fda.gov/downloads/AboutFDA/Transparency/PublicDisclosure/GlossaryofAcronymsandAbbreviations/UCM212110.pdf. Accessed January 12, 2018.

[17] FDA Transparency Working Group. Blueprint for Transparency at the U.S. Food and Drug Administration. March 13, 2017. http://www.jhsph.edu/departments/health-policy-and-management/_pdf/FDA_Transparency.pdf. Accessed January 12, 2018.

[18] *Ibid.*

[19] From 1991 through 2015, a total of 373 settlements were reached between the federal and state governments and pharmaceutical manufacturers, for a total of $35.7 billion. The unlawful promotion of drugs, mostly off-label marketing, was the single violation that resulted in the largest financial penalties. See: Public Citizen. Twenty-Five Years of Pharmaceutical Industry Criminal and Civil Penalties: 1991 Through 2015. March 31, 2016. https://www.citizen.org/our-work/health-and-safety/twenty-five-years-pharmaceutical-industry-criminal-and-civil-penalties-1991-through-2015. Accessed January 12, 2018.

[20] Food and Drug Administration. Good reprint practices for the distribution of medical journal articles and medical or scientific reference publications on unapproved new uses of approved drugs and approved or cleared medical devices. January 2009. https://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm. Accessed January 12, 2018.

[21] H.R.1703 - Medical Product Communications Act of 2017. Introduced March 23, 2017. https://www.congress.gov/bill/115th-congress/house-bill/1703/text. Accessed January 12, 2018.

stakeholders access to an unbiased rendering of the reasons for the FDA's rejection of a drug marketing application.

Finally, a new policy of transparency whereby the FDA discloses the existence of, and 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.[22] The beneficence principle establishes an ethical obligation to minimize possible harms and maximize potential benefits. In the event that a drug marketing application is rejected because the FDA determines that the drug's harms outweigh its benefits for a particular use, both the drug company and the FDA have an ethical obligation to make this determination public in order to avoid future clinical trials of the drug (or, in some cases, a similar drug in the same class) that would unnecessarily expose human subjects to harm.

Feasibility: The FDA should follow Europe's and Canada's lead

A policy whereby the FDA releases complete response letters and the underlying analyses leading to the agency's decision not to approve a drugmaker's application is certainly feasible. 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."[23] The EU law stipulated[24] that after any EMA decision rejecting a sponsor's drug application or where the sponsor has withdrawn its application before the EMA has completed its assessment, the agency must publish, among other things, a public assessment report containing the agency's analyses and conclusions related to the clinical data in the application.[25]One can search the EMA's website for all public assessment reports, with specific searches available for drugs that have been refused marketing authorization or that have been suspended or withdrawn after approval.[26]

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

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[22] Department of Health Education and Welfare. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. April 18, 1979. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/. Accessed January 12, 2018.

[23] Official Journal of the European Union. Regulation (EC) No 726/2004 of the European Parliament and of the Council. Article 12(3). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF. Accessed January 12, 2018. Article 12.

[24] *Ibid.* Article 11.

[25] European Medicines Agency. Procedural advice on publication of information on negative opinions and refusals of marketing authorization applications for human medicinal products. May 2, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004188.pdf. Accessed January 12, 2018.

[26] European Medicines Agency. European public assessment reports. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125. Accessed January 12, 2018.

on drug marketing applications.[27] 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.[28] All regulatory decision summaries are publicly searchable on Health Canada's website.[29]

Case Example 2: Withdrawal of Application of paliperidone *(Invega) for Bipolar I Disorder*

In September 2008, Johnson and Johnson submitted an application to the EMA for an additional indication for its antipsychotic drug paliperidone: the treatment of acute manic episodes associated with bipolar I disorder.[30] The company submitted three studies of paliperidone in such patients in support of its application.[31] The company withdrew its application 85 days into the EMA's Committee for Medicinal Products for Human Use (CHMP) review of the application "based on the feedback from the early [EMA] evaluation indicating that the data provided were not sufficient to support approval for this indication and the company's view that it was not in a position to adequately address this issue at that time.[32]

The EMA subsequently issued a press release announcing the company's withdrawal of its application,[33] and then 1) posted the company's letter requesting the withdrawal[34] and 2)

[27] Health Canada. Notice: Regulatory decision summaries and submissions under review. March 13, 2015. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/rds-sdr/drug-med/rds-sur-notice-phasei-avis-sdr-pce-eng.php. Accessed January 12, 2018.
[28] *Ibid.*
[29] Health Canada. The Drug and Health Product Register. https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary.php. Accessed January 12, 2018.
[30] EMA. Press release: Janssen-Cilag International N.V. withdraws its application for an extension of indication for Invega (paliperidone). http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014689.pdf. Accessed January 9, 2018.
[31] EMA. Questions and answers on the withdrawal of the application for a change to the marketing authorization for Invega. January 22, 2009. http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2010/01/WC500059541.pdf. Accessed January 9, 2018.
[32] EMA. Press release: Janssen-Cilag International N.V. withdraws its application for an extension of indication for Invega (paliperidone). http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014689.pdf. Accessed January 9, 2018.
[33] EMA. Press release: Janssen-Cilag International N.V. withdraws its application for an extension of indication for Invega (paliperidone). http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014689.pdf. Accessed January 9, 2018.
[34] Janssen-Cilag. Letter to EMA announcing withdrawal of application to add a new indication for the treatment of acute manic episodes associated with bipolar I disorder. December 15, 2008. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/01/WC500059542.pdf. Accessed January 9, 2018.

published a Q&A fact sheet on the application,[35] describing the studies used to support the application and linking to the company's letter to explain why the withdrawal was made.

We could not find a publicly available record indicating whether the company had submitted a similar sNDA to the FDA. The FDA did refer in passing – in an unrelated medical review document on another NDA published 6 months after the EMA announcement[36] – to pre-NDA meetings with the company to discuss the bipolar disorder application.

The company went on to publish in peer-reviewed journals the three studies that tested paliperidone in patients with bipolar disorder,[37,38,39] 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.[40] Physicians may have been prescribing Invega for bipolar disorder with no knowledge of this regulatory history. It should be noted that Johnson and Johnson, Invega's maker, was forced to reach a $2.2 billion settlement with the federal government in 2013 over, in part, allegations of off-label promotion of its antipsychotics Invega and Risperdal.[41]

Conclusions: Right to know

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.

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[35] EMA. Questions and answers on the withdrawal of the application for a change to the marketing authorization for Invega. January 22, 2009. http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2010/01/WC500059541.pdf. Accessed January 9, 2018.

[36] FDA Medical Review. Invega NDA 22264-000. June 8, 2009. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000medr.pdf. Accessed January 9, 2018.

[37] Vieta E, Nuamah IF, Lim P, et al. A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. *Bipolar Disord*. 2010;12(3):230-243.

[38] Berwaerts J, Lane R, Nuamah IF, et al. Paliperidone extended-release as adjunctive therapy to lithium or valproate in the treatment of acute mania: a randomized, placebo-controlled study. *J Affect Disord*. 2011;129(1-3):252-260.

[39] Berwaerts J, Xu H, Nuamah I, Lim P, Hough D. Evaluation of the efficacy and safety of paliperidone extended-release in the treatment of acute mania: a randomized, double-blind, dose-response study. *J Affect Disord*. 2012;136(1-2):e51-e60.

[40] Boodman SG. Off-Label Use Of Risky Antipsychotic Drugs Raises Concerns. *KHN* and *The Washington Post*. March 12, 2012. https://khn.org/news/off-label-use-of-risky-antipsychotic-drugs/. Accessed January 10, 2018.

[41] U.S. Department of Justice. Johnson & Johnson to Pay More Than $2.2 Billion to Resolve Criminal and Civil Investigations. November 4, 2013. https://www.justice.gov/opa/pr/johnson-johnson-pay-more-22-billion-resolve-criminal-and-civil-investigations. Accessed January 10, 2018.