# Memorandum on Differences between Carpenter/Zucker/Avorn data and Nardinelli et al Data, and Re-Analysis of Data Adjusting for These Differences, and Robustness and Sensitivity Checks on Analyses

May 17, 2008


SUMMARY:

- There are discrepancies in safety-based withdrawals that represent two Nardinelli et al omissions, while other discrepancies involve matters of interpretation (for which the FDA's own coding has changed). In a wide variety of sensitivity analyses, the association between just-before-deadline approvals and safety-based withdrawals persists.
- Nardinelli et al's data on postmarket safety differ materially from data that (1) the agency has posted elsewhere on its website, (2) that the agency provided to other authors and that were presented at FDA-sponsored conferences, and (3) from the published medical literature.
- There are significant discrepancies in the coding of standard/priority ratings. Although we coded our data from the FDA web site, these discrepancies represent probable coding errors on our part.
- There are also significant discrepancies between our data on black-box warnings and the Nardinelli et al data. Nardinelli et al's data on black-box warnings are assembled without a clear or rigorous methodology.

**THE RELATIONSHIPS OBSERVED PERSIST EVEN WHEN USING THE NARDINELLI ET AL DATA POSTED ON APRIL 7, 2008 (see Sections 4 and 5, Sections 11-16).**

- Withdrawals: If Nardinelli et al's 314 NMEs are used, and their pre-deadline approval measure is used, the relationships between pre-deadline approvals and safety-based withdrawals are larger and more statistically robust than reported in the original *NEJM* paper (OR = 5.89, $p = 0.01$ from exact logistic regression; OR = 6.09, $p = 0.006$ from random-effects logistic regression).

- Black Box Warnings: If Nardinelli et al's 314 NMEs are used, and their pre-deadline approval measure is used, the relationships between pre-deadline approvals and black-box warnings are slightly smaller and more statistically robust than reported in the original *NEJM* paper (OR = 3.41, $p = 0.02$ from exact logistic regression; OR = 4.53, $p = 0.009$ from random-effects logistic regression).

- Dosage-Form Disc. If Nardinelli et al's 314 NMEs are used, and their pre-deadline approval measure is used, the relationships between pre-deadline approvals and dosage-form discontinuation are similar to and more statistically robust than reported in the original *NEJM* paper (OR = 3.85, $p = 0.007$ from exact logistic regression; OR = 5.73, $p = 0.003$ from random-effects logistic regression).

# Memorandum Order of Contents (by Sections)

EXECUTIVE SUMMARY
May 17, 2008

After reviewing our data and correcting for factual errors, we can state with confidence that our major findings remain intact as do their implications. In particular, post-PDUFA NMEs are far more likely to be approved in the two months before the user-fee deadline than at other times, and these just-before-deadline approvals are significantly more likely to encounter postmarket safety issues once on the market. Odds ratios for the association between just-before-deadline approvals and our three postmarket safety measures remain large (> 3) and statistically significant using a variety of tests.

Our first and main measure of post-marketing safety problems was safety-based withdrawals, and we stand by our results. Seven of the eleven withdrawals in our sample were just-before-deadline approvals (alatrofloxacin, rofecoxib, cerivastatin, grepafloxacin, troglitazone, trovafloxacin, and valdecoxib). We did not originally code alosetron (Lotronex) as a safety-based withdrawal because the drug was returned to market in 2002 before the end of our study period. Levomethadyl (Orlaam) became unavailable because of reduction in supply by the manufacturer and was therefore not listed as a withdrawal in our data, nor was it listed as such in FDA publications through fall 2005; see below). Even if we add alosetron and levomethadyl to the analyses it does not change the original findings; in fact, use of the FDA's sample of NMEs and the pre-deadline measure of the FDA yields larger and more statistically significant associations between deadline approvals and safety-based withdrawals than were reported in the original article (see the embedded table). The final difference in drug withdrawals, Tegaserod (Zelnorm), was withdrawn just last March, long after our paper was already in the review process.

| Re-Analysis of Withdrawals and Dosage Form Discontinuations, Using Nardinelli et al's 314 NMEs and their Deadline Approval Measure | | |
|---|---|---|
| Postmarket Safety Measure | Cross Tabulation | Odds Ratios from Exact Logistic Regression (ELR) and Random-Effects Logistic Regression (RLR) |
| Carpenter/Zucker/Avorn (CZA) Withdrawal Measure | 7 of 88 deadline approvals are withdrawn; 4 of 226 non-deadline approvals. | ELR: OR = 5.89, P = 0.01<br>RLR: OR = 6.09, P = 0.006 |
| CZA Withdrawal Measure, add Alosetron | 7 of 88 deadline approvals are withdrawn; 5 of 226 non-deadline approvals. | ELR: OR = 4.52, P = 0.03<br>RLR: OR = 4.61, P = 0.01 |
| CZA Withdrawal Measure, add Levomethadyl | 7 of 88 deadline approvals are withdrawn; 5 of 226 non-deadline approvals. | ELR: OR = 4.90, P = 0.02<br>RLR: OR = 5.05, P = 0.01 |
| CZA Withdrawal Measure, add Alosetron and Levomethadyl | 7 of 88 deadline approvals are withdrawn; 6 of 226 non-deadline approvals. | ELR: OR = 3.91, P = 0.04<br>RLR: OR = 3.99, P = 0.02 |
| Dosage-Form Discontinuations | 16 of 88 deadline approvals are discontinued; 20 of 226 non-deadline approvals. | ELR: OR = 2.98, P = 0.008<br>RLR: OR = 3.13, P = 0.005 |
| Note: ELR controls for submission year. RLR controls for submission year, epidemiological covariates, and includes 135 random effects grouped by NME primary indication. | | |

The data posted by Nardinelli et al on April 7, 2008 is a new dataset never before published or posted. It differs materially from data elsewhere on the FDA website, from data that the agency has published elsewhere or has provided to other authors, and from published medical literature. There are serious problems with the publicly available FDA data on withdrawals. For example, the agency's Drugs@FDA site does not list two very important withdrawn drugs, bromfenac (Duract) and mibefradil (Posicor). Another drug included in the FDA's data of April 2008, levomethadyl (Orlaam) was not mentioned in published FDA material (and material generated by CDER) more than two years after Nardinelli et al report that it was withdrawn. The FDA's own notice[1] describes it as not being a safety-based withdrawal. Still, as

[1] See http://www.fda.gov/CDER/drug/shortages/orlaam.htm, reproduced and discussed below. See also Jim Rosack, "Med Check," *Psychiatric News* 38 (19) (October 3, 2003) http://pn.psychiatryonline.org/cgi/content/full/38/19/36 [accessed April 16, 2008].

the table above suggests, recoding levomethadyl acetate as a withdrawal still does not change our original findings.

The results for our third measure – one or more dosage-form discontinuations – also hold up and are virtually identical to those in the published paper.

The Nardinelli letter mentions two other issues with our data. The first is the difference in standard and priority coding. We have recoded our drugs according to Drugs@FDA and now identify 132 priority drugs, just as Nardinelli et al report for their April 2008 data. Most of the drugs that we coded as standard that Drugs@FDA lists as priority were drugs with review times of 14 months or more, so the recoding does not affect our measure, as these are not pre-deadline approvals under any version of PDUFA.

Nardinelli et al also extrapolate from our Figure 1 and state that our data on approval times differ from theirs. This is not a matter of data but a matter of rounding. Our original coding was based on dividing the number of days of approval by 30, which produced a number of drugs that had met the review deadlines but had numerical review times that appeared to put them past the deadlines. For instance, L-Glutamine (Nutrestore; NDA # 21667) was submitted on August 8, 2003 and approved on June 10, 2004, which generates a review time of 10.23 months, which we rounded down to produce the patterns in Figure 1. This had the effect of rendering NMEs that went into the tenth month of review being coded as ninth-month approvals, which accounts for the difference. If timing calculations of Nardinelli et al is preferred, *our finding about the concentration (or "piling") of approval decisions near the deadline approvals is even stronger***.**

It is for postmarket black-box warnings that the greatest discrepancies persist remain. The main difference between our data on black box warnings (BBW) and that of Nardinelli et al is the date at which coding was stopped; 17 of the 29 drugs with BBWs in the FDA data, or 58% of the BBWs in their sample, were added in the last two years. Our analysis included data through August 2005. This points to the increased use of BBWs (and reliance upon class relabeling in particular) by the FDA in recent years, which suggests that *BBWs may not be as consistent a measure of postmarket safety problems as they once were*.

In reviewing all the drugs in our data set and the Nardinelli et al dataset with boxed warnings, we have identified errors in the data provided by Nardinelli et al as well as in our own data:

- In their April 2008 posted data, Nardinelli et al have missed at least five (5) postmarket BBWs added to approval NMEs (adefovir, emtricitabine, entecavir, tenofovir, tiprinavir), and has coded as many as three other drugs as having BBWs added which contained no significant safety information . One clear example is the FDA's coding of saquinavir; an important NIH publication (for which two FDA officials consulted) did not list this drug as having a black box warning in February 2002, over a year after the FDA says that a BBW was added (see below).
- We incorrectly coded three (3) NMEs as having postmarket BBWs added. Although the boxed warning changed in all three cases, we agree that these should not have been coded as imparting major new safety information. We also omitted five (5) BBWs thatshould have been coded as having imparted important new safety information. In some cases this is because we had coded the NME as withdrawn before the BBW was added. [Another drug (celecoxib) received its BBW on July 29, 2005, likely before the drug was listed on the KUMC web database.] Dr. Carpenter assumes sole responsibility for these errors.
- For a number of other drugs, there are reasonable differences of judgment between our coding, the FDA's coding, and that of published medical literature on whether the drugs had significant postmarket black-box warnings added.

(3) Correcting for these errors, and using either (a) Nardinelli et al's April 2008 data, or (b) combined data before August 2005 or before the post-Vioxx set of BBW relabelings, we still find large (> 3) and statistically significant odds ratios in the vast majority of replications (see http://people.hmdc.harvard.edu/~dcarpent/fdaproject/nejmresponse20080517.pdf ), and the first two rows of results in the following table.]

(4) Even if we accept all of Nardinelli et al's determinations that a given drug had a safety-based withdrawal or a postmarket BBW, and we add only those drugs that we appropriately identified as having postmarket safety problems (adefovir, alatrofloxacin, emtricitabine, entecavir, tenofovir, tipranavir, tolcapone, and trovafloxacin), there is still an appreciable (OR > 2) and statistically significant difference between just-before-deadline approvals and the combined withdrawal-or-warning measure (see http://people.hmdc.harvard.edu/~dcarpent/fdaproject/nejmresponse20080517.pdf, the last row of results in following table, and Section 12.3 below).

| Re-Analysis of Black Box Warning Measure and Combined "Withdrawal or Warning" Measure, using Nardinelli et al's 314 NMEs and their Deadline Approval Measure | | |
|---|---|---|
| **Postmarket Safety Measure** | **Cross Tabulation** | **Odds Ratios** from Exact Logistic Regression (ELR) and Random-Effects Logistic Regression (RLR) |
| Carpenter/Zucker/Avorn (CZA) BBW Measure, recode 6 CZA omissions, drop 3 CZA miscodes, accept saquinavir.* (21 total BBWs) | 12 of 88 deadline approvals are BBWs added; 9 of 226 non-deadline approvals. | ELR: OR = 3.85, P = 0.007<br>RLR: OR = 5.73, P = 0.003 |
| Carpenter/Zucker/Avorn (CZA) BBW Measure, recode 6 CZA omissions, recode 2 close cases, drop 3 CZA miscodes, accept saquinavir.* (19 total BBWs) | 10 of 88 deadline approvals have BBWs added; 9 of 226 non-deadline approvals. | ELR: OR = 3.41, P = 0.03<br>RLR: OR = 4.52, P = 0.009 |
| **Withdrawal or Warning Measure**, recode 6 CZA omissions, drop 3 CZA miscodes, accept saquinavir.* | 15 of 88 deadline approvals have SBWs or BBWs; 12 of 226 non-deadline approvals. | ELR: OR = 3.93, P = 0.002<br>RLR: OR = 5.10, P = 0.001 |
| **Withdrawal or Warning Measure**, recode 6 CZA omissions, recode 2 close cases, drop 3 CZA miscodes, accept saquinavir.* | 13 of 88 deadline approvals have SBWs or BBWs; 12 of 226 non-deadline approvals. | ELR: OR = 3.58, P = 0.009<br>RLR: OR = 4.20, P = 0.003 |
| **Withdrawal or Warning Measure**, accept <u>all</u> FDA positive codes of withdrawals or BBWs, extend data up through December 2007 | 21 of 88 deadline approvals have SBWs or BBWs; 21 of 226 non-deadline approvals. | ELR: OR = 2.29, P = 0.03<br>RLR: OR = 3.42, P = 0.01 |
| Note: ELR controls for submission year. RLR controls for submission year, epidemiological covariates, and includes 135 random effects grouped by NME primary indication. *Saquinavir represents a possible FDA error (see Section 2.3 below), but we code it as a BBW for sake of demonstration. Results are stronger if saquinavir is coded as not having a postmarket BBW (see Section 8.2 and Section 9 below). | | |

Thus, even after addressing the issues raised by Nardinelli et al, our main findings remain valid. We did code standard and priority drugs differently from FDA, a discrepancy for which we assume responsibility but which does not materially affect our conclusions. Our determination of the presence of black-box warnings also differs from that of Nardinelli et al, and while some of these discrepancies stem from our coding errors, at least as many are the result of errors in the data of Nardinelli et al. In many other cases it is debatable which classification is more accurate. However, even after adjusting for these differences, our findings remain robust,

statistically significant, and consistent with our earlier findings. Our paper did not conclude that FDA should be freed of all deadlines. More research is needed about how best to make the American drug approval process as efficient, reliable, and credible as possible.

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# 1. Examination of Differences for Safety-Based Withdrawals, and Re-Analysis of Data

## 1.1 Coding Rules for Approval Times and Postmarket Safety Problems.

We completed our coding in the summer of 2005, and did not code any postmarketing event after August 1, 2005. The first version of this paper was submitted to the *New England Journal of Medicine* in January 2006. Except for correction of known coding errors, we did not update the data after August 1, 2005, or after the first submission of this manuscript to the journal.

Approval Times and Pre-Deadline Approval Status: We coded data from FDA approval letters and new drug applications on the FDA web site. To get a measure of the approval time for a drug, we divided the approval time in days by 30 to produce an "approval time" measure denominated in months. Our original coding was based on dividing the number of days of approval by 30 (in separate data that was sent to us by former FDA official Ed Hass, a similar measure with similar denominator was used). This produced a number of drugs that had met the review deadlines but had numerical review times that appeared to put them past the deadlines. For instance, L-Glutamine (Nutrestore; NDA # 21667) was submitted on August 8, 2003 and approved on June 10, 2004, which generates a review time of 10.23 months – so we rounded down to produce the patterns Figure 1.

In addition, we used a rounding-down rule. If a drug was approved within two weeks of the deadline for days, we coded it as a pre-deadline approval. Our intuition here is that if a drug went just a few days (or a week or two) past the deadline but was approved, there was likely to have been pressure on the FDA to approve it as close to the

deadline as possible. Significantly, *we re-analyzed our results without the rounding-down rule and they were stronger*. Evidence of this robustness of our results to the dropping of the two-week round-down rule is presented below. When everything else is kept the same, our observed associations are stronger (larger ORs, smaller p-values) when the FDA's "deadline approval" measure is used instead of ours.

Withdrawals: For safety-based withdrawals, we coded from Pharmaprojects. We coded a drug as withdrawn for safety-based reasons if it was permanently withdrawn from the U.S. market or from two or more major foreign markets (such as the E.U., Australia and Canada, for tolcapone and the E.U., Australia and other countries for alatrofloxacin and trovafloxacin). *In every case of a coded withdrawal, our withdrawn drugs were removed by either the U.S. or the E.U., or both*. We did not code alosetron as a withdrawal because it was not a permanent removal from the U.S. market, but we also checked to see whether a recoding of alosetron as a withdrawal produced substantively different results.

In July 2005, we received a paper from Ernst Berndt that had been recently published in *Nature Reviews Drug Discovery*. This paper had an embedded Table entitled "Safety-Based Withdrawals According to CDER" (this is reproduced as Table 3A below). We used this list to check our data to make sure that we had identified all U.S. withdrawals in our sample. Importantly, *this list did not include levomethadyl acetate (Orlaam), even though the FDA's April 2008 posted data states that this drug was withdrawn in 2003*. This list also identified alosetron as a drug that was returned to market, and that was not permanently withdrawn.

Black-Box Warnings: There is no unified database of black-box warnings added to drugs postmarket. The closest is Lasser's article in 2002, which stops coding in 1999. We used this Lasser, which was static, and KUMC. None of the black-box warnings added to drugs after August 1, 2005 were coded. (Some drugs receive multiple black-box warnings over time, and so it is possible that drugs that received an additional black-box warning after August 1, 2005 also received a postmarket boxed warning before August 1, 2005). In addition, **it is possible that some of the drugs that had black-box warnings attached between January and July 2005 were not yet listed in the KUMC database**.

We cannot verify this possibility as we do not have the entire KUMC database as it was posted in August of 2005.

Dosage-Form Discontinuations: We relied on a download from the Drugs@FDA database, which lists specific code for dosage-form discontinuations (because they require an official amendment to the drug's NDA). We do not have the exact date of this download, but it would have occurred before August 2005.

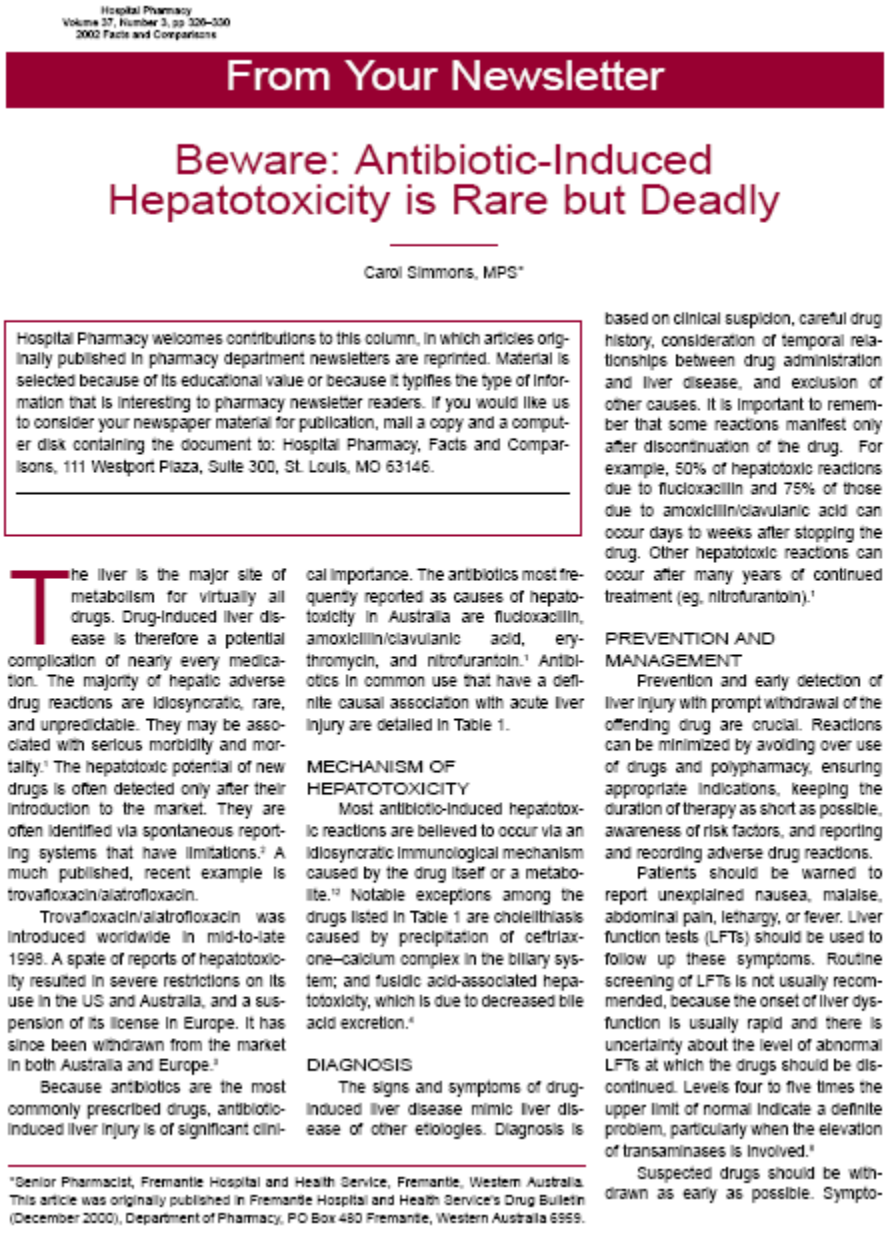
## 1.2 Specific Coding Decisions for Withdrawn Drugs

The list of safety-based withdrawals used in our article is as follows (see Section 3 for approval time data and just-before-deadline classifications for these drugs).

| NDA Number | Generic Name |
|---|---|
| 20760 | Alatrofloxacin Mesylate |
| 20535 | Bromfenac Sodium |
| 20740 | Cerivastatin Sodium |
| 20695 | Grepafloxacin Hydrochloride |
| 20689 | Mibefradil Dihydrochloride |
| 20984 | Rapacuronium bromide |
| 21042 | Rofecoxib |
| 20697 | Tolcapone |
| 20720 | Troglitazone |
| 20759 | Trovafloxacin Mesylate |
| 21341 | Valdecoxib |

The first major difference between our data and the FDA's is that we have coded alatrofloxacin mesylate and trovafloxacin mesylate as safety-based withdrawals. Numerous sources demonstrate that alatrofloxacin and trovafloxacin were withdrawn separately in the European Union, the United Kingdom, and Australia. For instance, an article in the Australian journal *Hospital Pharmacy* in 2002 states clearly that the drugs were withdrawn in Europe and Australia; the first page of the article is embedded in this document in the next page; for a URL see http://www.factsandcomparisons.com/assets/hospitalpharm/mar2002_newsletter.pdf (accessed April 14, 2008). The web site of the Australian National Prescribing Service also states that the drug is withdrawn there (http://www.nps.org.au/site.php?content=/html/news.php&news=/resources/NPS_News/news19) (accessed April 13, 2008). Indeed, while we do not regard it as an authoritative source, it is interesting that Wikipedia lists the drug as withdrawn from the U.S, market (http://en.wikipedia.org/wiki/Alatrofloxacin [accessed April 16, 2008]).

**Figure 1A – Article from Hospital Pharmacy (Australia) stating withdrawal of alatrofloxacin and trovafloxacin in Australia and E.U.**



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2002 Facts and Comparisons

From Your Newsletter

# Beware: Antibiotic-Induced Hepatotoxicity is Rare but Deadly

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Hospital Pharmacy welcomes contributions to this column, in which articles originally published in pharmacy department newsletters are reprinted. Material is selected because of its educational value or because it typifies the type of information that is interesting to pharmacy newsletter readers. If you would like us to consider your newspaper material for publication, mail a copy and a computer disk containing the document to: Hospital Pharmacy, Facts and Comparisons, 111 Westport Plaza, Suite 300, St. Louis, MO 63146.

The liver is the major site of metabolism for virtually all drugs. Drug-induced liver disease is therefore a potential complication of nearly every medication. The majority of hepatic adverse drug reactions are idiosyncratic, rare, and unpredictable. They may be associated with serious morbidity and mortality.[1] The hepatotoxic potential of new drugs is often detected only after their introduction to the market. They are often identified via spontaneous reporting systems that have limitations.[2] A much published, recent example is trovafloxacin/alatrofloxacin.

Trovafloxacin/alatrofloxacin was introduced worldwide in mid-to-late 1998. A spate of reports of hepatotoxicity resulted in severe restrictions on its use in the US and Australia, and a suspension of its license in Europe. It has since been withdrawn from the market in both Australia and Europe.[3]

Because antibiotics are the most commonly prescribed drugs, antibiotic-induced liver injury is of significant clinical importance. The antibiotics most frequently reported as causes of hepatotoxicity in Australia are flucloxacillin, amoxicillin/clavulanic acid, erythromycin, and nitrofurantoin.[1] Antibiotics in common use that have a definite causal association with acute liver injury are detailed in Table 1.

## MECHANISM OF HEPATOTOXICITY

Most antibiotic-induced hepatotoxic reactions are believed to occur via an idiosyncratic immunological mechanism caused by the drug itself or a metabolite.[12] Notable exceptions among the drugs listed in Table 1 are cholelithiasis caused by precipitation of ceftriaxone–calcium complex in the biliary system; and fusidic acid-associated hepatotoxicity, which is due to decreased bile acid excretion.[4]

## DIAGNOSIS

The signs and symptoms of drug-induced liver disease mimic liver disease of other etiologies. Diagnosis is based on clinical suspicion, careful drug history, consideration of temporal relationships between drug administration and liver disease, and exclusion of other causes. It is important to remember that some reactions manifest only after discontinuation of the drug. For example, 50% of hepatotoxic reactions due to flucloxacillin and 75% of those due to amoxicillin/clavulanic acid can occur days to weeks after stopping the drug. Other hepatotoxic reactions can occur after many years of continued treatment (eg, nitrofurantoin).[1]

## PREVENTION AND MANAGEMENT

Prevention and early detection of liver injury with prompt withdrawal of the offending drug are crucial. Reactions can be minimized by avoiding over use of drugs and polypharmacy, ensuring appropriate indications, keeping the duration of therapy as short as possible, awareness of risk factors, and reporting and recording adverse drug reactions.

Patients should be warned to report unexplained nausea, malaise, abdominal pain, lethargy, or fever. Liver function tests (LFTs) should be used to follow up these symptoms. Routine screening of LFTs is not usually recommended, because the onset of liver dysfunction is usually rapid and there is uncertainty about the level of abnormal LFTs at which the drugs should be discontinued. Levels four to five times the upper limit of normal indicate a definite problem, particularly when the elevation of transaminases is involved.[5]

Suspected drugs should be withdrawn as early as possible. Sympto-

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The FDA has alatrofloxacin and trovafloxacin coded as drugs with a black-box warning. Note that there is no debate about whether these drugs are separate NMEs even though they often share the same trade name. They are separate molecules (separate generic names), separate NMEs, separate NMEs as listed on Drugs@FDA, and separate NMEs as

listed in data. (They are also listed as separate NMEs on FDA web post of April 2008; see http://www.fda.gov/oc/pdufa/FDADrugAppSafetyData_files/NMESafetySumm.html [accessed April 16, 2008].)

The other NME in our withdrawn sample that is not in the FDA's sample is Tolcapone, which was withdrawn in the EU, UK, Canada, and Australia. Tolcapone was not withdrawn in the U.S.

The FDA has coded three drugs as withdrawals that are not in our data. The last, tegaserod maleate (Zelnorm) was withdrawn just over a year ago on March 30, 2007, after our paper was already deep in the review process. The second discrepancy is alosetron. We did not code this as a safety-based withdrawal because the drug was withdrawn then reintroduced. Alosetron was, moreover, reintroduced in 2002, 2 years after being withdrawn, and before the end of our data collection. [An article in *Nature Genetics* remarks that it was withdrawn only in the U.S.] We believe this is a plausible and defensible interpretation, and we have checked our results repeatedly (see below).

We did not have Levomethadyl Acetate in our original dataset, in part because it not listed as a withdrawal by FDA. When the removal of levomethadyl acetate was first announced by the FDA in 2003, the drug's removal was announced not as a safety-based withdrawal but as a marketing discontinuation (see Figure 1B, next page). For a similar interpretation of levomethadyl's U.S. removal as a marketing discontinuation induced by the availability of buprenorphine, see Jim Rosack, "Med Check," *Psychiatric News* 38 (19) (October 3, 2003) http://pn.psychiatryonline.org/cgi/content/full/38/19/36 [accessed April 16, 2008]. As we note below, levomethadyl acetate was not listed as a safety-based withdrawal in data provided to Ernst Berndt and co-authors in an article they published in July 2005 in Nature Reviews Drug Discovery. The results of this paper were later presented at an FDA-sponsored public meeting on the re-authorization of PDUFA.

**Figure 1B: FDA Announcement of 2003 Does Not List Levomethadyl as a Safety-Based Withdrawal, but as a Discontinuation**. (from http://www.fda.gov/CDER/drug/shortages/orlaam.htm [accessed April 12, 2008]). [See also Figure 2H below.]

Drug Shortage: Drug to be Discontinued
Letter from Roxane

**August 23, 2003**

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**PRODUCT DISCONTINUATION NOTICE**

**ORLAAM® (Levomethadyl hydrochloride acetate) Oral Solution, 10 mg/mL, CII**

NDC 0054-3649-63

Dear Healthcare Professional:

Roxane Laboratories, Inc. is discontinuing the sale and distribution of ORLAAM® (Levomethadyl hydrochloride acetate) Oral Solution, 10 mg/mL after the current inventory is depleted. We estimate that this will occur early in the first quarter of 2004. Since the introduction of ORLAAM in 1995, Roxane Laboratories has received increasing reports of severe cardiac-related adverse events, including QT interval prolongation (15), Torsades de Pointes (8) and cardiac arrest (6). Other cardiac-related adverse events have also been reported, including arrhythmias, syncope, and angina. These events led to the removal of ORLAAM from the European market in March 2001, and extensive changes (including additional warnings & contraindications) were made to the US package insert in April 2001 (Dear Healthcare Professional letter dated April 11, 2001). Since these changes, the use of ORLAAM has decreased dramatically over the last two years. While there may be a very small number of patients who may benefit from ORLAAM, it is our belief that the risks of continued distribution and use in the face of less toxic treatment alternatives no longer outweigh the overall benefits.

ORLAAM is a synthetic opioid agonist solution indicated for the management of opiate dependence, reserved for the treatment of opiate-addicted patients who fail to show acceptable response to other adequate treatments for opiate addiction. Other first-line treatment options are available for the management of opiate dependence, including methadone and the recently FDA-approved buprenorphine. Methadone hydrochloride is available as an oral solution and a dispersible tablet, both which will continue to be manufactured by Roxane Laboratories and distributed by Cebert Pharmaceuticals. Buprenorphine hydrochloride is available in two sublingual formulations: one containing naloxone hydrochloride (Suboxone®, Reckitt Benckiser Pharmaceuticals) and one without naloxone (Subutex®, Reckitt Benckiser Pharmaceuticals). With these first-line agents available for the treatment of opiate addiction, it is our hope that existing patients can be converted to alternate therapies with minimal disruption to them and the centers that treat them.

Due to the forecasted unavailability shortly after the beginning of 2004, no new patients should be initiated on ORLAAM therapy. For existing ORLAAM patients, it is extremely important for healthcare providers to transfer patients to alternative treatments as soon as possible prior to the product's unavailability. To make sure this transition occurs with minimal disruption to all patients involved, we will reserve the right to limit purchase quantities based upon historical annual volumes. Careful consideration should be given to the appropriate conversion regimens. The information on the next page is from the current package insert for ORLAAM:

Transfer from ORLAAM® to Methadone:

*Patients maintained on ORLAAM may be transferred directly to methadone. Because of the difference between the two compounds' metabolites and their pharmacological half-lives, it is recommended that methadone be started on a daily dose at 80% of the ORLAAM dose being replaced; the initial methadone dose must be given no sooner than 48 hours after the last ORLAAM dose. Subsequent increases or decreases of 5 to 10 mg in the daily methadone dose may be given to control symptoms of withdrawal or, less likely, symptoms of excessive sedation, in accordance with clinical observations.*

For further information about ORLAAM, please contact our Technical Information Department at 1-800-962-8364 or our Customer Service Department at 1-800-520-1631.

Respectfully,

Michael J. Schobelock, PharmD
Associate Director
Medical Affairs Department
Roxane Laboratories, Inc

## 2. General Notes on the Reliability of the FDA's and Nardinelli et al's Postmarket Safety Data for Safety-Based Withdrawals

It is important not to regard either the Drugs@FDA database or the MedWatch system data as authoritative for purposes of drug safety. The database contains some very important omissions. For instance, **Posicor (mibefradil hydrochloride) and Duract [bromfenac sodium) were withdrawn for safety reasons, yet they are not listed on the Drugs@FDA webpage and are absent from the underlying database maintained by FDA**. (As the following six Figures clearly show, searching for these two drugs by generic name, trade name and NDA number fails to return a record with the original NME.) These are two of the most important safety-based withdrawals of the past several decades; their absence from the FDA's own data is troubling.

Below, we attach results of a search of the Drugs@FDA database, using both the U.S. trade names for Duract and Posicor, and separate searches using the respective generic names and the respective NDA numbers. The searches were conducted on April 7, 2008.

**Figure 2A – Duract Not Locatable on Drugs@FDA page using Trade Name search.**

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## Search Results for 'duract'

Your search term did not return any results.

Modify Your Search

- **Spelling or Formatting Problems**
  - If you are not sure of the spelling, try "Browse by Drug Name."
  - Try putting in *part* of the Drug Name or Active Ingredient. You must enter at least three letters or numbers.
  - A drug name containing a combination of letters, punctuation, and spaces has to be formatted exactly as it appears in the database. Examples: H.P. ACTHAR gel or X-TROZINE L.A. Try entering just part of the name, such as "acthar" or "trozine."
- **For Application Number searches, you must enter five digits for NDAs and ANDAs, and six digits for BLAs.**

  More about searching
- **Dietary supplements, most biologic products, animal drugs, and certain drug products are *not* in Drugs@FDA.** More information about the contents of Drugs@FDA

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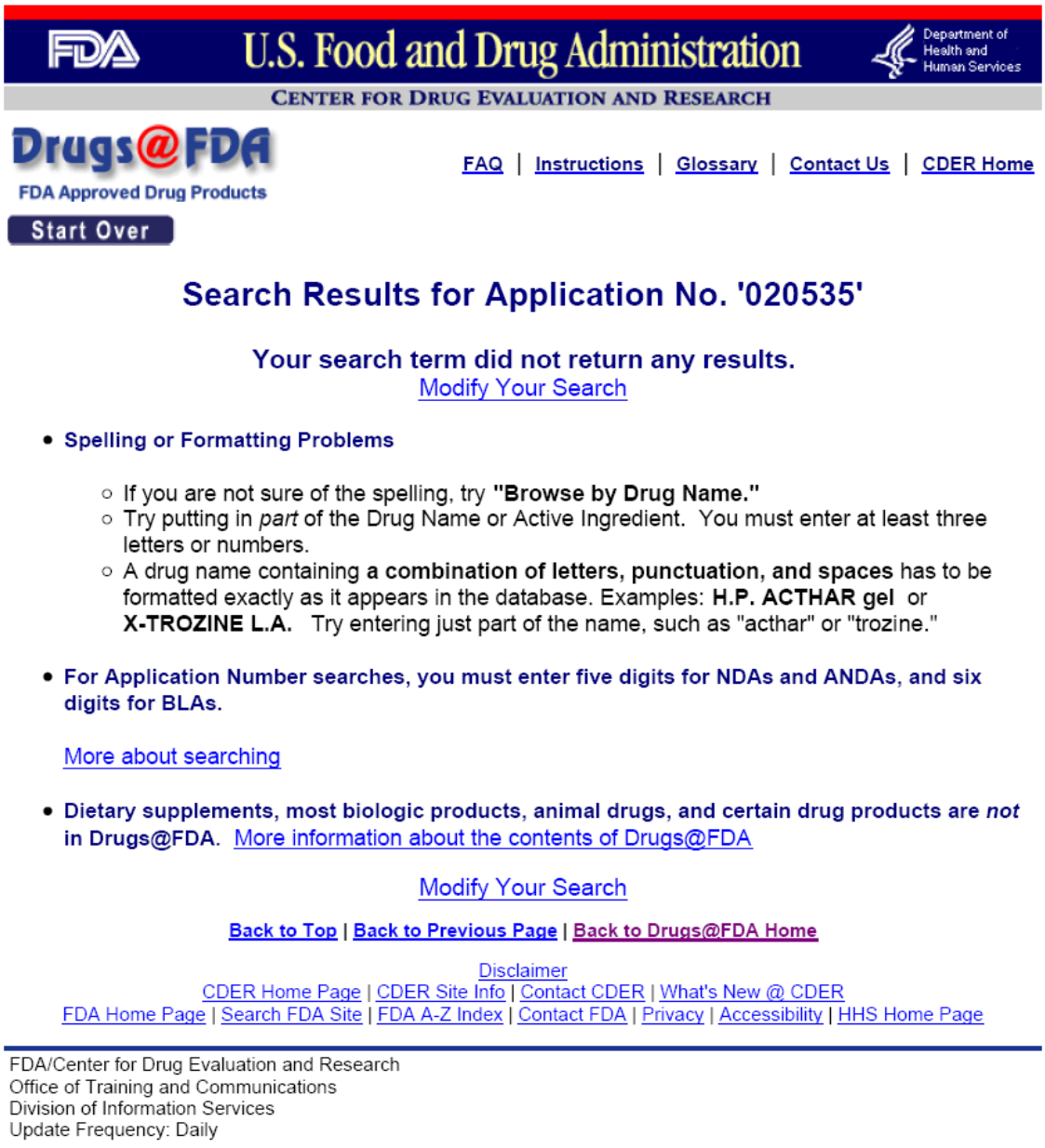
**Figure 2B – Duract Not Locatable on Drugs@FDA page using NDA Number search**



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## Search Results for Application No. '020535'

**Your search term did not return any results.**
Modify Your Search

- **Spelling or Formatting Problems**
  - If you are not sure of the spelling, try **"Browse by Drug Name."**
  - Try putting in *part* of the Drug Name or Active Ingredient. You must enter at least three letters or numbers.
  - A drug name containing **a combination of letters, punctuation, and spaces** has to be formatted exactly as it appears in the database. Examples: **H.P. ACTHAR gel** or **X-TROZINE L.A.** Try entering just part of the name, such as "acthar" or "trozine."
- **For Application Number searches, you must enter five digits for NDAs and ANDAs, and six digits for BLAs.**

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**Figure 2C – Drugs@FDA Does not Have Duract (Bromfenac Sodium) NME, search using generic name [html download of April 7, 2008]. [Note that Duract, NDA # 20689 – the original NME for bromfenac sodium – does not appear but a <u>new formulation</u> of the molecule does appear. We are entirely unable to access the NME for bromfenac sodium at this time.]**

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## Drug Details

| | |
|---|---|
| Drug Name(s) | XIBROM (Brand Name Drug) |
| FDA Application No. | (NDA) 021664 |
| Active Ingredient(s) | BROMFENAC SODIUM |
| Company | ISTA PHARMS |
| Original Approval or Tentative Approval Date | March 24, 2005 |
| Chemical Type | 3 New formulation |
| Review Classification | S Standard review drug |

- There are no TherapeuticÂ Equivalents
- Approval History, Letters, Reviews, and Related Documents
- Label Information

### Products on Application (NDA) #021664

Click on a column header to re-sort the table:

| Drug Name | Active Ingredients | Strength | Dosage Form/Route | Marketing Status | RLD | TE Code |
|---|---|---|---|---|---|---|
| XIBROM | BROMFENAC SODIUM | 0.09% | SOLUTION/DROPS; OPHTHALMIC | Prescription | Yes | None |

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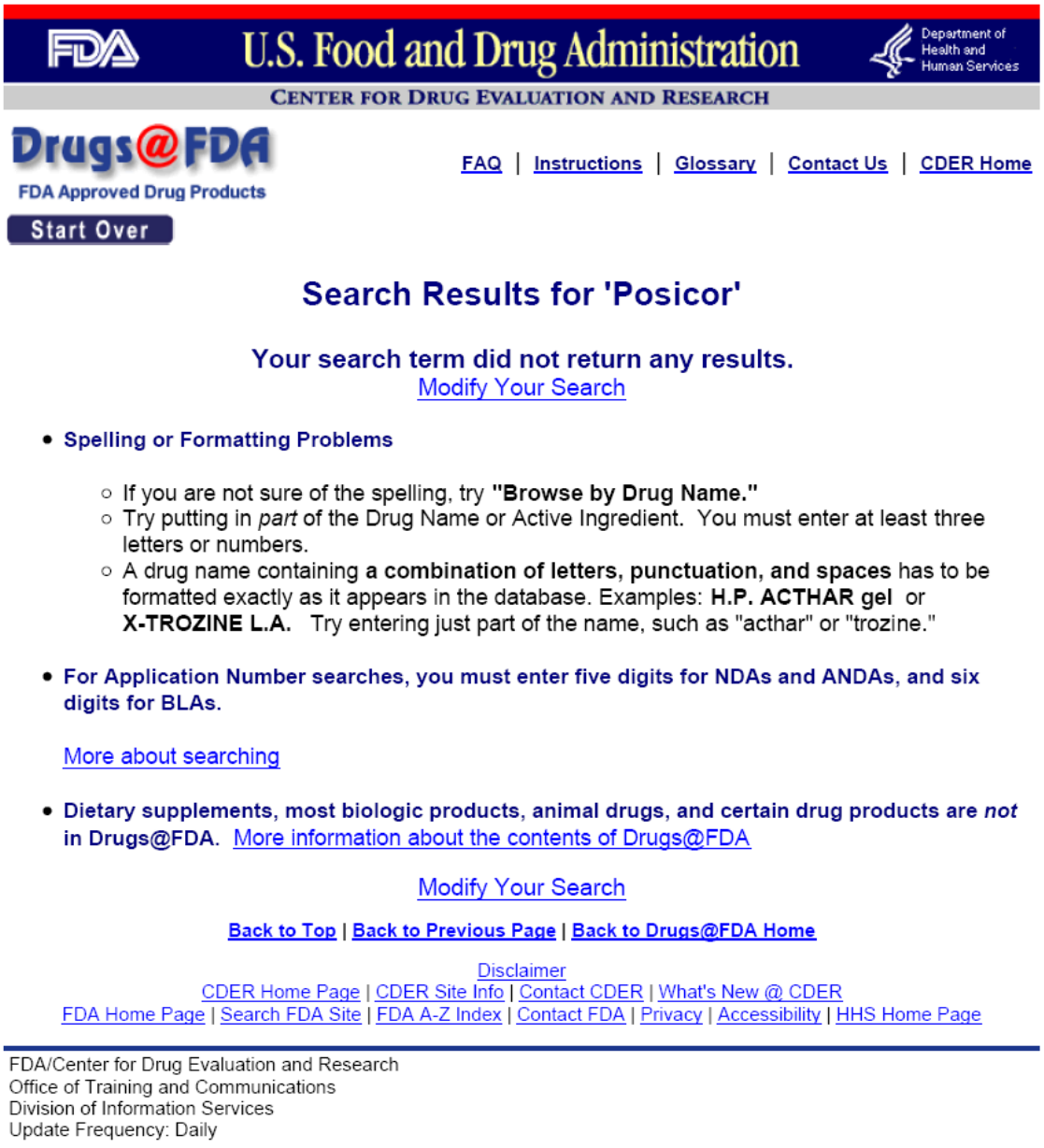
**Figure 2D – Posicor Not Locatable on Drugs@FDA page using Trade Name search.**



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## Search Results for 'Posicor'

**Your search term did not return any results.**

Modify Your Search

- **Spelling or Formatting Problems**
  - If you are not sure of the spelling, try **"Browse by Drug Name."**
  - Try putting in *part* of the Drug Name or Active Ingredient. You must enter at least three letters or numbers.
  - A drug name containing **a combination of letters, punctuation, and spaces** has to be formatted exactly as it appears in the database. Examples: **H.P. ACTHAR gel** or **X-TROZINE L.A.** Try entering just part of the name, such as "acthar" or "trozine."
- **For Application Number searches, you must enter five digits for NDAs and ANDAs, and six digits for BLAs.**

  More about searching
- **Dietary supplements, most biologic products, animal drugs, and certain drug products are *not* in Drugs@FDA.** More information about the contents of Drugs@FDA

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**Figure 2E –Posicor (mibefradil hydrochloride) Not Locatable on Drugs@FDA page using NDA Number search.**

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## Search Results for Application No. '020689'

**Your search term did not return any results.**
Modify Your Search

- **Spelling or Formatting Problems**
  - If you are not sure of the spelling, try **"Browse by Drug Name."**
  - Try putting in *part* of the Drug Name or Active Ingredient. You must enter at least three letters or numbers.
  - A drug name containing **a combination of letters, punctuation, and spaces** has to be formatted exactly as it appears in the database. Examples: **H.P. ACTHAR gel** or **X-TROZINE L.A.** Try entering just part of the name, such as "acthar" or "trozine."
- **For Application Number searches, you must enter five digits for NDAs and ANDAs, and six digits for BLAs.**

  More about searching
- **Dietary supplements, most biologic products, animal drugs, and certain drug products are *not* in Drugs@FDA.** More information about the contents of Drugs@FDA

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**Figure 2F – Drugs@FDA Does Not Have Posicor (mibefradil), generic name search [download of April 7, 2008]**

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## Search Results for 'mibefradil'

**Your search term did not return any results.**

Modify Your Search

- **Spelling or Formatting Problems**
  - If you are not sure of the spelling, try **"Browse by Drug Name."**
  - Try putting in *part* of the Drug Name or Active Ingredient. You must enter at least three letters or numbers.
  - A drug name containing **a combination of letters, punctuation, and spaces** has to be formatted exactly as it appears in the database. Examples: **H.P. ACTHAR gel** or **X-TROZINE L.A.** Try entering just part of the name, such as "acthar" or "trozine."
- **For Application Number searches, you must enter five digits for NDAs and ANDAs, and six digits for BLAs.**

  More about searching
- **Dietary supplements, most biologic products, animal drugs, and certain drug products are *not* in Drugs@FDA.** More information about the contents of Drugs@FDA

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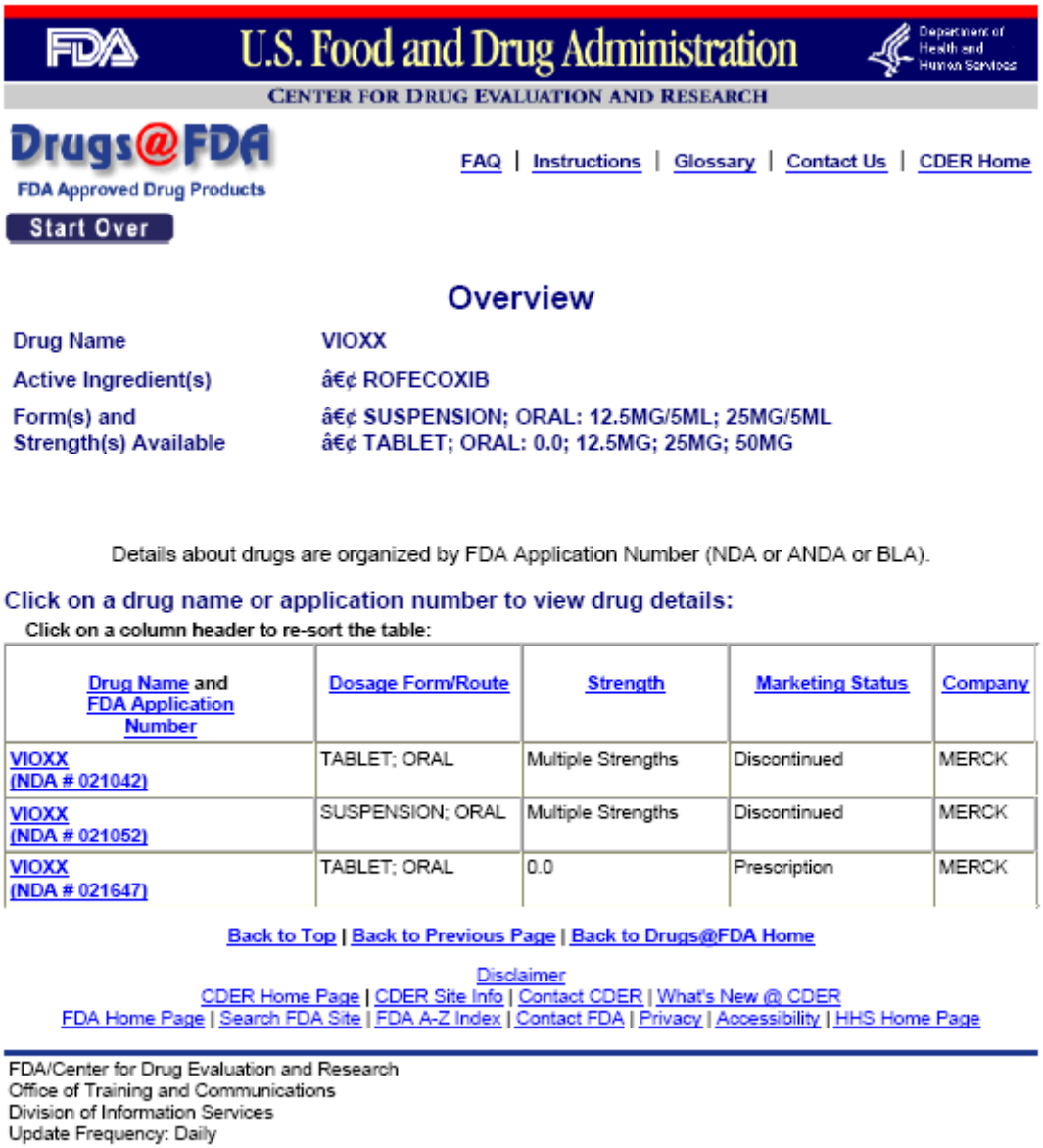
**Figure 2G – Drugs@FDA Does Have Vioxx (rofecoxib), generic name search [download of April 7, 2008]**



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## Overview

| | |
|---|---|
| Drug Name | VIOXX |
| Active Ingredient(s) | â€¢ ROFECOXIB |
| Form(s) and Strength(s) Available | â€¢ SUSPENSION; ORAL: 12.5MG/5ML; 25MG/5ML<br>â€¢ TABLET; ORAL: 0.0; 12.5MG; 25MG; 50MG |

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

Click on a column header to re-sort the table:

| Drug Name and FDA Application Number | Dosage Form/Route | Strength | Marketing Status | Company |
|---|---|---|---|---|
| VIOXX (NDA # 021042) | TABLET; ORAL | Multiple Strengths | Discontinued | MERCK |
| VIOXX (NDA # 021052) | SUSPENSION; ORAL | Multiple Strengths | Discontinued | MERCK |
| VIOXX (NDA # 021647) | TABLET; ORAL | 0.0 | Prescription | MERCK |

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## 2.1 – Significant Differences between April 2008 FDA Data and Other FDA Published and Distributed Data

The FDA's data posted on April 8, 2008 also differ materially from data that FDA published elsewhere, that were provided to other authors, and that were presented at FDA public meetings in November 2005. We note two crucial differences here.

First, the FDA data of April 8, 2008, include Orlaam (Levomethadyl Acetate Hydrochloride), and state that this drug was withdrawn on August 23, 2003. However, in data provided to Ernst Berndt, and reported in a *Nature Reviews Drug Discovery* article in July 2005.[2] Orlaam was not included in NME safety withdrawals "according to CDER" (see Figure on next page).

The Berndt list was based on a document published April 2004. Moreover, as late as November 2005, a presentation based on these data was given at an FDA public meeting on PDUFA re-authorization. [For the Power Point presentation at the docket, see www.fda.gov/ohrms/dockets/dockets/05n0410/05n-0410-ts00006-**Berndt**.ppt (downloaded April 9, 2008).]

For a transcript of this meeting, see http://www.fda.gov/CBER/minutes/pdufa111405t.pdf (downloaded April 9, 2008). Neither "Orlaam" nor "Lotronex" (nor "Levomethadyl acetate" nor "Alosetron Hydrochloride") is mentioned at this meeting. For reference, Vioxx and Bextra are mentioned at this meeting.

Slide 17 of the Berndt presentation lists the source for the FDA's withdrawal data as "Source: "Center for Drug Evaluation and Research 2003 Report to the Nation: Improving Public Health through Human Drugs." U.S. Department of Health and Human Services, Food and Drug Administration, April 23, 2004." See

[2] Ernst R. Berndt, Adrian H. B. Gottschalk, Tomas J. Philipson and Matthew W. Strobeck, "Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates," *Nature Reviews Drug Discovery* 4 (July 2005) 545-554.

www.fda.gov/ohrms/dockets/dockets/05n0410/05n-0410-ts00006-**Berndt**.ppt (downloaded April 9, 2008), slide 17.

Second, as Figure 2H also makes clear, Lotronex (alosetron) was highlighted as a withdrawal that was reintroduced. (See note to Table 3 of Berndt., et al 2005; in Figure 2H, next page). Again, neither Lotronex nor its generic name was mentioned at the November 2005 FDA public meeting.

**2.1 – Significant Differences between April 2008 FDA Data and Other FDA Published and Distributed Data (cont.)**

**Figure 2H. Levomethadyl Acetate (Orlaam) Missing From CDER/FDA Data Provided to Other Authors. [Table 3 from Berndt et al (2005).]**

Table 3 | **NME safety withdrawals according to CDER**

| Drug name | Submission date | Year approved | Year withdrawn |
|---|---|---|---|
| Fenfluramine | 03 Mar 1967 | 1973 | 1997 |
| Azaribine | 17 Dec 1969 | 1975 | 1976 |
| Ticrynafen | 15 Nov 1977 | 1979 | 1980 |
| Zomepirac | 10 Nov 1978 | 1980 | 1983 |
| Benoxaprofen | 23 Jan 1980 | 1982 | 1982 |
| Nomifensine | 16 Mar 1979 | 1984 | 1986 |
| Suprofen | 10 Nov 1978 | 1985 | 1987 |
| Terfenadine | 01 Mar 1983 | 1985 | 1998 |
| Encainide | 13 Jan 1984 | 1986 | 1991 |
| Astemizole | 25 Feb 1985 | 1988 | 1999 |
| Flosequinan | 01 Oct 1990 | 1992 | 1993 |
| Temafloxacin | 30 Nov 1989 | 1992 | 1992 |
| Cisapride | 29 Aug 1991 | 1993 | 2000 |
| Dexfenfluramine* | Unavailable | 1996 | 1997 |
| Bromfenac | 30 Dec 1994 | 1997 | 1998 |
| Cerivastatin | 26 Jul 1996 | 1997 | 2001 |
| Grepafloxin | 08 Nov 1996 | 1997 | 1999 |
| Mibefradil | 11 Mar 1996 | 1997 | 1998 |
| Troglitazone | 01 Aug 1996 | 1997 | 2000 |
| Rapacuronium | 25 Jun 1998 | 1999 | 2001 |
| Rofecoxib‡ | 23 Nov 1998 | 1999 | 2004 |
| Alosetron§ | 30 Jun 1999 | 2000 | 2000 |

*Not considered a new molecular entity (NME). ‡Not in the Center for Drug Research and Evaluation's report. §Returned to the market in 2002 with restrictions. Nine NMEs were withdrawn between 1980 and 1992 and include zomepirac, benoxaprofen, nomifensine, suprofen, terfenadine, eincanide, astemizole, flosequinan and temafloxacin. For the period 1993–2004, CDER reported on nine withdrawals in their report — ten when Vioxx (rofecoxib) is included. However, one of the withdrawals is not considered an NME and a second drug, alosetron, that was withdrawn from market was reintroduced with distribution restrictions. Data adapted from REF. 25.

Notes: (1) Levomethadyl Acetate (Orlaam) not included; (2) Alosetron (Lotronex) coded as reintroduced.

See also Figure 1B above: levomethadyl was not announced as a safety-based withdrawal by the FDA in 2003.

## 3. Data on Safety-Based Withdrawals and Re-Analysis of Data (just-before-deadline classification of Carpenter-Zucker-Avorn)

The following is the list of safety-based withdrawals as analyzed in the NEJM article.

| NDA Number | Generic Name | Submission Date | Approval Date | JB-Deadline Approval |
|---|---|---|---|---|
| 20760 | Alatrofloxacin Mesylate | 12/30/1996 | 12/18/1997 | 1 |
| 20535 | Bromfenac Sodium | 12/30/1994 | 7/15/1997 | 0 |
| 20740 | Cerivastatin Sodium | 6/26/1996 | 6/26/1997 | 1 |
| 20695 | Grepafloxacin Hydrochloride | 11/8/1996 | 11/6/1997 | 1 |
| 20689 | Mibefradil Dihydrochloride | 3/11/1996 | 6/20/1997 | 0 |
| 20984 | Rapacuronium bromide | 6/25/1998 | 8/18/1999 | 0 |
| 21042 | Rofecoxib | 11/23/1998 | 5/20/1999 | 1 |
| 20697 | Tolcapone | 6/3/1996 | 1/29/1998 | 0 |
| 20720 | Troglitazone | 8/1/1996 | 1/29/1997 | 1 |
| 20759 | Trovafloxacin Mesylate | 12/30/1996 | 12/18/1997 | 1 |
| 21341 | Valdecoxib | 1/16/2001 | 11/16/2001 | 1 |

Nardinelli et al claim that only five of the withdrawals in our study qualify as just-before-deadline approvals. As the previous table makes clear, this is incorrect. Alatrofloxacin, cerivastatin sodium, grepafloxacin, rofecoxib, troglitazone, trovafloxacin and valdecoxib were all approved in the final month of their PDUFA deadlines.

### 3A. Safety-Based Withdrawals -- Adding Alosetron to Carpenter/Zucker/Avorn Original Data

We acknowledge that there may be other possible codings of what counts as a safety-based withdrawal, and the FDA clearly uses alternative codes. One possibility emerges in the drug alosetron (Lotronex). Like another popular drug (Wellbutrin), alosetron was withdrawn in the United States but then returned to the market. We considered only permanent withdrawals, and so did not code alosetron as withdrawn in our original analysis.

If we use our original data of 313 drugs and code alosetron as a withdrawal, when the year of submission is controlled for in an exact logistic regression the odds ratio is well above one and is significant with an exact p-value of 0.044. It is only in a simple 2x2 analysis (not used in our study) that the p-value rises above 0.05. We attach the results of this exact logistic regression (as well as random-effects logistic regressions with more control variables) below.

Moreover [see Section 4 below] **if we use the FDA's dataset of 314 NMES and the FDA's deadline approval classification, there is a larger and more statistically significant association between deadline approvals and our measure with alosetron added**.

**3A. Safety-Based Withdrawals -- Adding Alosetron to Carpenter/Zucker/Avorn Original Data (cont.)**

In a simple two-way cross-tabulation using our original 313 data points, addition of alosetron as a withdrawal generates a tabulation in which the exact p-value rises just above 0.05, but this is not how we calculated our results in Figure 2, as this simple approach does not control for year of submission (as in the exact logistic regression) or any of several other important variables that we controlled for (in random-effects logistic regressions; see the on-line Appendix).

```
. tabulate  combowit_addlotronex predead if(subyear > 1992
& ndanum2 ~= 20719 & ndanum2 ~= 20778), exact

combowit_a |        predead
ddlotronex |         0          1 |     Total
-----------+----------------------+----------
         0 |       211         90 |       301
         1 |         5          7 |        12
-----------+----------------------+----------
     Total |       216         97 |       313

           Fisher's exact =                 0.053
   1-sided Fisher's exact =                 0.043
```

However, as the next page shows, the exact p-value falls below 0.05 in an exact logistic regression that controls for submission year. In addition, mixed-effects logistic regressions that add a random effect for the primary indication of the NME, and control for epidemiological characteristics of the primary indication, yields similar results.

## 3A. Safety-Based Withdrawals -- Adding Alosetron to Carpenter/Zucker/Avorn Original Data (cont)

Exact Logistic Regression Results

# Binary Regression

regression (type=logit, model(sbw_addlot = subyrctr predead), estimate(subyrctr predead), method=exact, mle=firth, profile=yes, outtype=odds);

### Basic Information

| | |
|---|---|
| **Data file** | combowit-check-20080329.csv |
| **Model** | sbw_addlot(Response = 1)=%Const+subyrctr+predead |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 313 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

### Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 28.52 | 21 | 0.1259 |
| **Likelihood Ratio** | 338.4 | 3 | 1.394e-009 |

### Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.3601 | NA | Asymptotic | 0.01117 | 11.6 | 0.5643 |
| | | | | Asymptotic(Profile) | 0.01065 | 15.05 | |
| **subyrctr** | PMLE | 0.8559 | NA | Asymptotic | 0.6944 | 1.055 | 0.1449 |
| | | | | Asymptotic(Profile) | 0.6761 | 1.048 | |
| | CMLE | 0.8449 | NA | Exact | 0.6612 | 1.05 | 0.1387 |
| **predead** | PMLE | 4.007 | NA | Asymptotic | 1.253 | 12.81 | 0.01925 |
| | | | | Asymptotic(Profile) | 1.248 | 13.75 | |
| | CMLE | 4.117 | NA | Exact | 1.038 | 17.85 | 0.04333 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

### 3A. Safety-Based Withdrawals -- Adding Alosetron to Carpenter/Zucker/Avorn Original Data (cont)

**NOW ADD LOTRONEX (ALOSETRON) TO THE SAFETY-BASED WITHDRAWALS LIST, USING ORIGINAL 313 NMES**

We first add control for the submission year of the NME to capture time trends, and add 134 random effects for primary indication of NME. We then add covariates for total hospitalizations associated with NME's primary indication in 1997 (= 0 when there are no HCUP hospitalizations associated with ) and average days of hospitalization, per hospitalization (= 0 when there are no HCUP hospitalizations associated with the NME's primary indication).

The estimates for the recoded predeadline measure are highlighted in yellow.

```
Random-effects logistic regression              Number of obs      =       313
Group variable (i): discode                     Number of groups   =       134

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      6.65
Log likelihood  =  -47.52833                    Prob > chi2        =    0.1554

------------------------------------------------------------------------------
      sbwlot |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .8680894    .095934    -1.28   0.201     .6990315    1.078033
pred0410_r~e |   4.029938   2.475958     2.27   0.023     1.208726    13.43597
   hhospdisc |   1.000001   1.59e-06     0.78   0.436     .9999981    1.000004
    hhosleng |   .9854858   .0680306    -0.21   0.832     .8607752    1.128265
-------------+----------------------------------------------------------------
    /lnsig2u |  -2.978378   2.134846                      -7.1626    1.205844
-------------+----------------------------------------------------------------
     sigma_u |   .2255555   .2407632                      .0278395    1.827451
         rho |   .0152287   .0320159                      .0002355     .503749
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.03 Prob >= chibar2 = 0.429
```

.

**3B. Safety-Based Withdrawals -- Adding Levomethadyl Acetate (Orlaam) to Carpenter/Zucker/Avorn Original Data**

Alternatively, one could add Levomethadyl Acetate (Orlaam), which was only discontinued in the U.S., not withdrawn. The effect of adding Levomethadyl Acetate is the same as that of adding Alosetron. In a simple unadjusted two-way cross-tabulation, the exact-p value rises above 0.05.

```
. tabulate   combowit_addorlaam predead if(subyear > 1992 &
ndanum2 ~= 20719 & ndanum2 ~= 20778), exact

combowit_a |        predead
  ddorlaam |         0          1 |     Total
-----------+----------------------+----------
         0 |       211         90 |       301
         1 |         5          7 |        12
-----------+----------------------+----------
     Total |       216         97 |       313

           Fisher's exact =                 0.053
   1-sided Fisher's exact =                 0.043
```

Once again, however, running an exact logistic regression on this data yields an odds-ratio that is above 1.0 with an exact two-tailed probability of less than 0.05. The year of submission is a statistically significant covariate, which points to the importance of controlling for this variable.

**3B. Safety-Based Withdrawals -- Adding Loevomethadyl Acetate to Original Carpenter/Zucker/Avorn Data, then Estimation of Exact Logistic Regression**

# Binary Regression

regression (type=logit, model(sbw_addorl = subyrctr predead), estimate(subyrctr predead), method=exact, mle=firth, profile=yes, outtype=odds);

## Basic Information

| | |
|---|---|
| **Data file** | combowit-check-20080329.csv |
| **Model** | sbw_addorl(Response = 1)=%Const+subyrctr+predead |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 313 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

## Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 25.25 | 21 | 0.2365 |
| **Likelihood Ratio** | 340.9 | 3 | 1.748e-009 |

## Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 1.267 | NA | Asymptotic | 0.03222 | 49.8 | 0.8996 |
| | | | | Asymptotic(Profile) | 0.03277 | 73.19 | |
| **subyrctr** | PMLE | 0.7907 | NA | Asymptotic | 0.6291 | 0.9936 | 0.04395 |
| | | | | Asymptotic(Profile) | 0.607 | 0.9826 | |
| | CMLE | 0.7762 | NA | Exact | 0.5896 | 0.9822 | 0.03306 |
| **predead** | PMLE | 4.514 | NA | Asymptotic | 1.391 | 14.65 | 0.01211 |
| | | | | Asymptotic(Profile) | 1.39 | 15.74 | |
| | CMLE | 4.644 | NA | Exact | 1.154 | 20.51 | 0.02857 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

### 3B. Safety-Based Withdrawals -- Adding Levomethadyl Acetate to Original Carpenter/Zucker/Avorn Data (cont.), estimating Random-Effects Logistic Regression

The estimates for the recoded predeadline measure are highlighted in yellow.

```
Random-effects logistic regression              Number of obs      =       313
Group variable (i): discode                     Number of groups   =       134

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      8.30
Log likelihood  = -46.423539                    Prob > chi2        =    0.0811

------------------------------------------------------------------------------
      sbworl |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .8018767   .0966211    -1.83   0.067      .6332033    1.015482
pred0410_r~e |   4.384225   2.717897     2.38   0.017       1.3008    14.77663
   hhospdisc |   1.000001   1.57e-06     0.75   0.453      .9999981    1.000004
    hhosleng |   .9974191   .0638275    -0.04   0.968      .8798467    1.130703
-------------+----------------------------------------------------------------
    /lnsig2u |  -2.936907   2.711426                     -8.251203     2.37739
-------------+----------------------------------------------------------------
     sigma_u |   .2302814   .3121954                      .0161538    3.282794
         rho |   .0158633   .0423299                      .0000793    .7661221
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.02 Prob >= chibar2 = 0.447
```

### 3C. Re-Examination of Safety-Based Withdrawals: A Coding Focusing only on Permanent U.S. Withdrawals

As an alternative coding, we could focus only on those drugs that were permanently removed from the U.S. market for safety-based reasons. This produces a list of the following 11 withdrawals and a cross-tabulation that is identical to Table 1 in the NEJM article.

The 11 safety-based withdrawals in the original analysis are listed here, with their priority rating, date of submission and of approval, approval time in months, and whether or not the drug was a just-before-deadline approval (7 of 11).

| NDA Number | Generic Name | Date of Submission | Date of Approval | JB-Deadline Approval |
|---|---|---|---|---|
| 20740 | Cerivastatin Sodium | 6/26/1996 | 6/26/1997 | 1 |
| 21341 | Valdecoxib | 1/16/2001 | 11/16/2001 | 1 |
| 20535 | Bromfenac Sodium | 12/30/1994 | 7/15/1997 | 0 |
| 20315 | Levomethadyl acetate | 6/21/1993 | 7/9/1993 | 0 |
| 20689 | Mibefradil Dihydrochloride | 3/11/1996 | 6/20/1997 | 0 |
| 20984 | Rapacuronium bromide | 6/25/1998 | 8/18/1999 | 0 |
| 20695 | Grepafloxacin Hydrochloride | 11/8/1996 | 11/6/1997 | 1 |
| 20720 | Troglitazone | 8/1/1996 | 1/29/1997 | 1 |
| 20759 | Trovafloxacin Mesylate | 12/30/1996 | 12/18/1997 | 1 |
| 20760 | Alatrofloxacin Mesylate | 12/30/1996 | 12/18/1997 | 1 |
| 21042 | Rofecoxib | 11/23/1998 | 5/20/1999 | 1 |

**3C. Re-Examination of Safety-Based Withdrawals – Permanent U.S. Removals (cont.)**

The two-way cross-tabulation for this variable is identical to that for the original article.

```
. tabulate  sbw_usremoval predead if(subyear > 1992 & ndanum2 ~= 20719 & ndanum2 ~=
20778), exact

sbw_usremo |        predead
       val |         0          1 |     Total
-----------+----------------------+----------
         0 |       212         90 |       302
         1 |         4          7 |        11
-----------+----------------------+----------
     Total |       216         97 |       313

           Fisher's exact =                 0.039
   1-sided Fisher's exact =                 0.024
```

And as the next page shows, an exact logistic regression produces an odds ratio that is **larger** than that estimated in the original article, and statistically significant.

## 3C. Re-Examination of Safety-Based Withdrawals (cont.)
## – Exact Logistic Regression with Permanent U.S. Removals

# Binary Regression

regression (type=logit, model(sbw_usremo = subyrctr predead), estimate(subyrctr predead), method=exact, mle=firth, profile=yes, outtype=odds);

### Basic Information

| | |
|---|---|
| **Data file** | combowit-check-20080329.csv |
| **Model** | sbw_usremo(Response = 1)=%Const+subyrctr+predead |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 313 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

### Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 23.09 | 21 | 0.3392 |
| **Likelihood Ratio** | 348.4 | 3 | 1.492e-009 |

### Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 1.134 | NA | Asymptotic | 0.02431 | 52.87 | 0.949 |
| | | | | Asymptotic(Profile) | 0.02461 | 82.07 | |
| **subyrctr** | PMLE | 0.786 | NA | Asymptotic | 0.6188 | 0.9983 | 0.04841 |
| | | | | Asymptotic(Profile) | 0.5941 | 0.9863 | |
| | CMLE | 0.7699 | NA | Exact | 0.5748 | 0.9859 | 0.03665 |
| **predead** | PMLE | 5.601 | NA | Asymptotic | 1.614 | 19.44 | 0.006648 |
| | | | | Asymptotic(Profile) | 1.638 | 21.57 | |
| | CMLE | 5.874 | NA | Exact | 1.356 | 30.14 | 0.015 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

### 3C. Re-Examination of Safety-Based Withdrawals (cont.)
### – Random-Effects Logistic Regression with Permanent U.S. Removals, Additional Control Variables

The estimates for the recoded predeadline measure are highlighted in yellow.

```
Random-effects logistic regression              Number of obs      =       313
Group variable (i): discode                     Number of groups   =       134

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      9.27
Log likelihood  = -42.547429                    Prob > chi2        =    0.0547

------------------------------------------------------------------------------
    sbwusrem |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .8000855   .1013168    -1.76   0.078     .6242329    1.025478
pred0410_r~e |   5.574691    3.69197     2.59   0.009     1.522273    20.41498
   hhospdisc |   1.000001   1.57e-06     0.87   0.385     .9999983    1.000004
    hhosleng |   1.010225   .0638652     0.16   0.872     .8924961    1.143484
-------------+----------------------------------------------------------------
    /lnsig2u |   -2.89283   3.527802                     -9.807195    4.021536
-------------+----------------------------------------------------------------
     sigma_u |   .2354128   .4152449                      .0074198    7.469051
         rho |   .0165663   .0574746                      .0000167    .9443118
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.01 Prob >= chibar2 = 0.464
```

# 4. Re-Analysis of Association between Deadline Approvals and Safety-Based Withdrawals, Using FDA NMEs, FDA Deadline Approval Measure, and Adding pre-2007 Withdrawals as Coded by Nardinelli et al.

We now show that the associations described in our study remain large and statistically significant in analyses of the FDA's data of April 2008, with only slight (and defensible) changes to their measures. For reference, we are able to replicate the FDA cross tabulation using their 314 NMEs, their deadline approval classification, and their measure of safety-based withdrawals, as follows:

```
. tab  sbwfda08  pred01fda, exact

           |       pred01fda
  sbwFDA08 |         0          1 |     Total
-----------+----------------------+----------
         0 |       220         83 |       303
         1 |         6          5 |        11
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.190
   1-sided Fisher's exact =                 0.165
```

### 4.1 Analysis of Original Carpenter-Zucker-Avorn Withdrawal Measure, using FDA NMEs and FDA Deadline Approval Measure

The difference between our analyses and their analyses clearly comes in the coding of safety-based withdrawals. We show here that using our measure, along with the 314 FDA NMEs and the FDA deadline approval measure, *yields larger and stronger results for our hypothesis than were ported in the article*.

To show this, we use Carpenter-Zucker-Avorn SBW measure, with FDA data (notice 314 NMEs) and with FDA pre-deadline approval coding ("pred01fda").

```
. tab  sbwcza pred01fda, exact

           |       pred01fda
    sbwCZA |         0          1 |     Total
-----------+----------------------+----------
         0 |       222         81 |       303
         1 |         4          7 |        11
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.013
   1-sided Fisher's exact =                 0.013
```

Note that when we use the FDA's NMEs and the FDA's deadline approval measure, but keep our withdrawal measure, the exact probability is less than that observed in the original NEJM article (Table 1). Similar strengthening of results is observed in exact logistic regressions, as the next page demonstrates.

## 4.1 Analysis of Original Carpenter-Zucker-Avorn Withdrawal Measure, using FDA NMEs and FDA Deadline Approval Measure (cont.)

An exact logistic regression on the same measure, controlling for year of NME submission, yields an estimated odds ratio and lower 95% confidence interval that are larger than those observed in the original NEJM article.

# Binary Regression

regression (type=logit, model(sbwcza = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

### Basic Information

| | |
|---|---|
| **Data file** | CZAFDAcompare-dump20080410.csv |
| **Model** | sbwCZA(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 10 |
| **Number of groups** | 24 |

### Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 30.39 | 21 | 0.08445 |
| **Likelihood Ratio** | 349.1 | 3 | 1.766e-009 |

### Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.3899 | NA | Asymptotic | 0.0114 | 13.34 | 0.6012 |
| | | | | Asymptotic(Profile) | 0.01096 | 17.94 | |
| **subyrctr** | PMLE | 0.8396 | NA | Asymptotic | 0.6793 | 1.038 | 0.106 |
| | | | | Asymptotic(Profile) | 0.6594 | 1.03 | |
| | CMLE | 0.8275 | NA | Exact | 0.6434 | 1.031 | 0.09745 |
| **pred01fda** | PMLE | 5.615 | NA | Asymptotic | 1.669 | 18.89 | 0.005312 |
| | | | | Asymptotic(Profile) | 1.691 | 20.9 | |
| | CMLE | 5.889 | NA | Exact | 1.406 | 29.1 | 0.01254 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

### 4.1 Analysis of Original Carpenter-Zucker-Avorn Withdrawal Measure, using FDA NMEs and FDA Deadline Approval Measure (cont.)

We can also estimate a random-effects logistic regression on the same data. In addition to the random effects (grouped by primary indication of the NME), the added variables are epidemiological controls for total hospitalizations of NME primary indication, and the average length of hospitalization, per hospitalization.

```
. xtlogit  sbwcza subyrctr  pred01fda  hhospdisc hhosleng, re i(discode) or

Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      9.40
Log likelihood  = -42.677609                    Prob > chi2        =    0.0519

------------------------------------------------------------------------------
      sbwcza |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .8300595   .0979313    -1.58   0.114      .6586939    1.046008
   pred01fda |   6.089567   4.033586     2.73   0.006      1.662534     22.305
   hhospdisc |   1.000001   1.58e-06     0.84   0.399      .9999982    1.000004
    hhosleng |   1.001489   .0672412     0.02   0.982      .8780024    1.142344
-------------+----------------------------------------------------------------
    /lnsig2u |  -2.889474   3.575862                     -9.898034    4.119086
-------------+----------------------------------------------------------------
     sigma_u |   .2358081   .4216085                      .0070904    7.842385
         rho |   .0166211   .0584469                      .0000153    .9492248
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.01 Prob >= chibar2 = 0.466
```

Again, the observed odds ratio estimate is above that reported in the NEJM article (Figure 2).

### 4.2 Adding Alosetron to Carpenter/Zucker/Avorn Withdrawals Measure, Using FDA NMEs and FDA Deadline Approval Measure

As noted previously, the FDA's data also include alosetron (Lotronex). If we add alosetron to our measure, we have 12 withdrawals, and we observe the following results for a two-way cross-tabulation.

```
. tab  sbwlot  pred01fda, exact

           |       pred01fda
    sbwlot |         0          1 |     Total
-----------+----------------------+----------
         0 |       221         81 |       302
         1 |         5          7 |        12
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.042
   1-sided Fisher's exact =                 0.024
```

If we estimate an exact logistic regression on the same data, we retrieve the following estimates.

## 4.2 Adding Alosetron to Carpenter/Zucker/Avorn Withdrawals Measure, Using FDA NMEs and FDA Deadline Approval Measure (cont.)

An exact logistic regression estimated on this measure yields the following results.

# Binary Regression

regression (type=logit, model(sbwlot = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

### Basic Information

| | |
|---|---|
| **Data file** | CZAFDAcompare-dump20080410.csv |
| **Model** | sbwlot(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 10 |
| **Number of groups** | 24 |

### Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 31.11 | 21 | 0.07179 |
| **Likelihood Ratio** | 340.6 | 3 | 1.598e-009 |

### Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.2829 | NA | Asymptotic | 0.01011 | 7.917 | 0.4576 |
| | | | | Asymptotic(Profile) | 0.009569 | 9.873 | |
| **subyrctr** | PMLE | 0.8672 | NA | Asymptotic | 0.7117 | 1.057 | 0.1578 |
| | | | | Asymptotic(Profile) | 0.6953 | 1.051 | |
| | CMLE | 0.8575 | NA | Exact | 0.6817 | 1.053 | 0.1535 |
| **pred01fda** | PMLE | 4.402 | NA | Asymptotic | 1.401 | 13.84 | 0.01119 |
| | | | | Asymptotic(Profile) | 1.395 | 14.81 | |
| | CMLE | 4.522 | NA | Exact | 1.164 | 19.18 | 0.02739 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

### 4.2 Adding Alosetron to Carpenter/Zucker/Avorn Withdrawals Measure, Using FDA NMEs and FDA Deadline Approval Measure (cont.)

A random-effects logistic regression yields similar results. In addition to the random effects (grouped by primary indication of the NME), the added variables are epidemiological controls for total hospitalizations of NME primary indication, and the average length of hospitalization, per hospitalization.

```
. xtlogit  sbwlot subyrctr  pred01fda  hhospdisc hhosleng, re i(discode) or

Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      7.66
Log likelihood  = -47.052943                    Prob > chi2        =    0.1049

------------------------------------------------------------------------------
      sbwlot |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .8603819   .0935033    -1.38   0.166     .6953214    1.064626
   pred01fda |   4.615507   2.854321     2.47   0.013     1.373471    15.51027
   hhospdisc |   1.000001   1.58e-06     0.76   0.448     .9999981    1.000004
    hhosleng |   .9879707   .0674818    -0.18   0.859     .8641797    1.129494
-------------+----------------------------------------------------------------
    /lnsig2u |  -2.955343   2.419151                     -7.696793    1.786107
-------------+----------------------------------------------------------------
     sigma_u |   .2281684   .2759869                      .0213139    2.442577
         rho |   .0155781   .0370986                      .0001381     .644571
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.02 Prob >= chibar2 = 0.440
```

.

### 4.3 Adding Levomethadyl Acetate to the Carpenter/Zucker/Avorn Withdrawals Measure, Using FDA NMEs and FDA Deadline Approval Measure.

The FDA's data also include levomethadyl acetate (Orlaam), but as we noted earlier, this drug was not identified as a safety-based withdrawal by the FDA for up to two years after the market removal. If we add levomethadyl acetate to our measure, we again have 12 withdrawals, and we observe the following results for a two-way cross-tabulation.

```
. tab  sbworl  pred01fda, exact

           |       pred01fda
    sbworl |         0          1 |     Total
-----------+----------------------+----------
         0 |       221         81 |       302
         1 |         5          7 |        12
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.042
   1-sided Fisher's exact =                 0.024
```

### 4.3 Adding Levomethadyl Acetate to the Carpenter/Zucker/Avorn Withdrawals Measure, Using FDA NMEs and FDA Deadline Approval Measure (cont.)

In an exact logistic regression on the same measure, controlling for submission year of the NME, an OR of 4.9 is observed with a p-value of 0.02.

## Binary Regression

regression (type=logit, model(sbworl = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

**Basic Information**

| | |
|---|---|
| **Data file** | CZAFDAcompare-dump20080410.csv |
| **Model** | sbworl(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 10 |
| **Number of groups** | 24 |

**Summary Statistics**

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 28.43 | 21 | 0.1283 |
| **Likelihood Ratio** | 342.9 | 3 | 1.885e-009 |

**Parameter Estimates**

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.8661 | NA | Asymptotic | 0.02645 | 28.36 | 0.9356 |
| | | | | Asymptotic(Profile) | 0.0265 | 39.31 | |
| **subyrctr** | PMLE | 0.8089 | NA | Asymptotic | 0.6535 | 1.001 | 0.05144 |
| | | | | Asymptotic(Profile) | 0.6335 | 0.9918 | |
| | CMLE | 0.7962 | NA | Exact | 0.6177 | 0.9919 | 0.04116 |
| **pred01fda** | PMLE | 4.767 | NA | Asymptotic | 1.504 | 15.11 | 0.007965 |
| | | | | Asymptotic(Profile) | 1.501 | 16.17 | |
| | CMLE | 4.899 | NA | Exact | 1.252 | 20.96 | 0.02024 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

### 4.3 Adding Levomethadyl Acetate to the Carpenter/Zucker/Avorn Withdrawals Measure, Using FDA NMEs and FDA Deadline Approval Measure (cont.)

In a random-effects logistic regression on the same measure, controlling for submission year of the NME, an OR of 5.05 is observed with a p-value of 0.009. In addition to the random effects (grouped by primary indication of the NME), the added variables are epidemiological controls for total hospitalizations of NME primary indication, and the average length of hospitalization, per hospitalization.

```
. xtlogit  sbworl subyrctr  pred01fda  hhospdisc hhosleng, re i(discode) or

Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      9.37
Log likelihood  = -45.896817                    Prob > chi2        =    0.0524

------------------------------------------------------------------------------
      sbworl |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .7968601   .0943533    -1.92   0.055     .6318215    1.005009
   pred01fda |   5.059184   3.158301     2.60   0.009     1.488333    17.19732
   hhospdisc |   1.000001   1.56e-06     0.74   0.462     .9999981    1.000004
    hhosleng |   .9997415   .0634257    -0.00   0.997     .8828474    1.132113
-------------+----------------------------------------------------------------
    /lnsig2u |  -2.887386   3.648302                     -10.03793    4.263154
-------------+----------------------------------------------------------------
     sigma_u |   .2360544   .4305989                      .0066114    8.428148
         rho |   .0166553   .0597514                      .0000133    .9557359
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.01 Prob >= chibar2 = 0.467
```

### 4.4 Adding Alosetron and Levomethadyl Acetate to the Carpenter/Zucker/Avorn Withdrawals Measure, Using FDA NMEs and FDA Deadline Approval Measure

If alosetron and levomethadyl acetate are both added to the withdrawals measure, then it is equivalent to combining our measure of safety-based withdrawals with the FDA's measure, save for the exclusion of Zelnorm, which was withdrawn from the U.S. market in March 2007. This yields 13 withdrawals and the following two-way cross-tabulation.

```
. tab   sbworlot pred01fda, exact

           |       pred01fda
  sbworlot |         0          1 |     Total
-----------+----------------------+----------
         0 |       220         81 |       301
         1 |         6          7 |        13
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.053
   1-sided Fisher's exact =                 0.041
```

Here we observe a p-value from Fisher's exact test of greater than 0.05. But in controlled regressions (including exact logistic regressions with exact distributions), we observe p-values of less than 0.05 once again (see two following pages).

### 4.4 Adding Alosetron and Levomethadyl Acetate to the Carpenter/Zucker/Avorn Withdrawals Measure, Using FDA NMEs and FDA Deadline Approval Measure (cont.)

An exact logistic regression on this same measure (with 13 withdrawals), controlling for year of NME submission, yields an estimated odds ratio of 3.9 with a p-value of 0.04.

## Binary Regression

regression (type=logit, model(sbworlot = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

**Basic Information**

| | |
|---|---|
| **Data file** | CZAFDAcompare-dump20080410.csv |
| **Model** | sbworlot(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 10 |
| **Number of groups** | 24 |

**Summary Statistics**

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 28.97 | 21 | 0.1147 |
| **Likelihood Ratio** | 334.5 | 3 | 1.781e-009 |

**Parameter Estimates**

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.5853 | NA | Asymptotic | 0.02194 | 15.61 | 0.7492 |
| | | | | Asymptotic(Profile) | 0.02155 | 19.98 | |
| **subyrctr** | PMLE | 0.8379 | NA | Asymptotic | 0.6872 | 1.022 | 0.08035 |
| | | | | Asymptotic(Profile) | 0.6705 | 1.014 | |
| | CMLE | 0.8275 | NA | Exact | 0.657 | 1.015 | 0.07148 |
| **pred01fda** | PMLE | 3.855 | NA | Asymptotic | 1.281 | 11.6 | 0.01636 |
| | | | | Asymptotic(Profile) | 1.263 | 12.14 | |
| | CMLE | 3.907 | NA | Exact | 1.055 | 15.04 | 0.04043 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

### 4.4 Adding Alosetron and Levomethadyl Acetate to the Carpenter/Zucker/Avorn Withdrawals Measure, Using FDA NMEs and FDA Deadline Approval Measure (cont.)

In a random-effects logistic regression on the same measure, controlling for submission year of the NME and for epidemiological covariates, an OR of 3.98 is observed with a p-value of 0.02. In addition to the random effects (grouped by primary indication of the NME), the added variables are epidemiological controls for total hospitalizations of NME primary indication, and the average length of hospitalization, per hospitalization.

```
. xtlogit  sbworlot subyrctr  pred01fda  hhospdisc hhosleng, re i(discode) or

Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      7.67
Log likelihood  = -50.159671                    Prob > chi2        =    0.1046

------------------------------------------------------------------------------
    sbworlot |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .8287204   .0900371    -1.73   0.084     .6697742    1.025387
   pred01fda |   3.985446   2.357488     2.34   0.019     1.250174    12.70525
   hhospdisc |   1.000001   1.57e-06     0.65   0.514      .999998    1.000004
    hhosleng |   .9878308   .0638625    -0.19   0.850     .8702681    1.121275
-------------+----------------------------------------------------------------
    /lnsig2u |   -2.95328   2.464286                     -7.783191    1.876631
-------------+----------------------------------------------------------------
     sigma_u |   .2284039   .2814262                      .0204128    2.555673
         rho |   .0156097   .0378664                      .0001266    .6650284
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.02 Prob >= chibar2 = 0.441
```

.

### 4.5 Analysis of Permanent U.S. Removals, including Tegaserod Maleate, with FDA's NMEs and FDA's Deadline Approval Measure

We now return to a different but very intuitive measure that looks at permanent removals from the U.S. market that were partially safety related.

```
. gen  sbwusrem_addzelnorm =  sbwusrem

. browse

. replace  sbwusrem_addzelnorm = 1 if( ndanum_fda == 21200)
(1 real change made)
      {THIS IS RECODING TEGASEROD MALEATE AS A SAFETY-BASED WITHDRAWAL,
EVEN THOUGH IT WAS WITHDRAWN AFTER OUR CODING STOPPED.}
```

This produces the following list, which includes alatrofloxacin mesylate, levomethadyl acetate, and trovafloxacin mesylate – all of which have been permanently removed from the U.S. market – even though these were not officially a safety-based withdrawal in the U.S., they were officially safety-based withdrawals in other countries.

```
. list  ndanum_fda genernam_fda if sbwusrem_addzelnorm == 1

     +-----------------------------------------------+
     | ndanum~a                           genernam_fda |
     |-----------------------------------------------|
  7. |    20760                Alatrofloxacin Mesylate |
 42. |    20535                       Bromfenac Sodium |
 53. |    20740                    Cerivastatin Sodium |
129. |    20695             Grepafloxacin Hydrochloride |
160. |    20315   Levomethadyl Acetate Hydrochloride |
     |-----------------------------------------------|
172. |    20689              Mibefradil Dihydrochloride |
226. |    20984                    Rapacuronium Bromide |
238. |    21042                                Rofecoxib |
265. |    21200                     Tegaserod Maleate |
292. |    20720                           Troglitazone |
     |-----------------------------------------------|
294. |    20759                 Trovafloxacin Mesylate |
299. |    21341                              Valdecoxib |
     +-----------------------------------------------+
```

### 4.5.1 Cross Tabulation with Fisher's Exact Test – Taking data up through December 2007, Combine CZA and FDA Measures for Safety-Based Withdrawals.

A cross-tabulation of the permanent U.S. safety-related removals with the deadline approval measure of the FDA yields the following:

```
. tab  sbwusrem_addzelnorm pred01fda, exact

sbwusrem_a |       pred01fda
 ddzelnorm |         0          1 |     Total
-----------+----------------------+----------
         0 |       221         81 |       302
         1 |         5          7 |        12
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.042
   1-sided Fisher's exact =                 0.024
```

We then write a smaller dataset into a comma-separated file, for use in exact logistic regressions with LogXact software.

```
. outsheet ndanum_fda sbwusrem_addzelnorm subyrctr pred01fda using
c:\fdatemp\sbwusrem-addzelnorm.csv, comma

.
```

### 4.5.2 Exact Logistic Regression – Taking Data up through December 2007, Combine CZA and FDA Measures for Safety-Based Withdrawals.

## Binary Regression

regression (type=logit, model(sbwusrem_a = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, profile=yes, outtype=odds);

**Basic Information**

| | |
|---|---|
| **Data file** | sbwusrem-addzelnorm.csv |
| **Model** | sbwusrem_a(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

**Summary Statistics**

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 27.71 | 21 | 0.1485 |
| **Likelihood Ratio** | 341.4 | 3 | 1.966e-009 |

**Parameter Estimates**

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | MLE | 0.4476 | NA | Asymptotic | 0.01251 | 16.02 | 0.6596 |
| | | | | Asymptotic(Profile) | 0.01324 | 18.89 | |
| **subyrctr** | MLE | 0.8364 | NA | Asymptotic | 0.6741 | 1.038 | 0.1044 |
| | | | | Asymptotic(Profile) | 0.6604 | 1.024 | |
| | CMLE | 0.8377 | NA | Exact | 0.6612 | 1.033 | 0.1033 |
| **pred01fda** | MLE | 4.728 | NA | Asymptotic | 1.412 | 15.83 | 0.01175 |
| | | | | Asymptotic(Profile) | 1.426 | 16.9 | |
| | CMLE | 4.639 | NA | Exact | 1.192 | 19.72 | 0.02485 |

**Analysis Time = 00:00:00**

Notice that the estimated OR is slightly larger than that reported in Figure 2 of the NEJM article, and remains statistically significant (exact P = 0.02).

### 4.5.1 Random-Effects Logistic Regression – Taking data up through December 2007, Combine CZA and FDA Measures for Safety-Based Withdrawals.

Results for deadline approval measure highlighted in yellow.

```
. xtlogit  sbwusrem_addzelnorm subyrctr pred01fda  hhospdisc hhosleng, re i(discode) or

Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      8.22
Log likelihood  = -46.697031                    Prob > chi2        =    0.0839

------------------------------------------------------------------------------
sbwusrem_a~m |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .8399138    .093684    -1.56   0.118     .6749813    1.045148
   pred01fda |    4.75882   2.952028     2.51   0.012     1.410832    16.05178
   hhospdisc |   1.000001   1.56e-06     0.77   0.442     .9999981    1.000004
    hhosleng |   .9990459   .0637837    -0.01   0.988     .8815375    1.132218
-------------+----------------------------------------------------------------
    /lnsig2u |  -2.927233    2.85395                     -8.520872    2.666405
-------------+----------------------------------------------------------------
     sigma_u |   .2313979   .3301989                      .0141161    3.793172
         rho |   .0160151   .0449742                      .0000606    .8139007
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.01 Prob >= chibar2 = 0.452
```

Again, the estimated OR is slightly larger than that reported in Figure 2 of the NEJM article.

# 5. Re-Analysis of Dosage-Form Discontinuations Measure – Random-Effects Logistic Regression

We have re-run our analyses of dosage-form discontinuations with the revised just-before-deadline measure according to Drugs@FDA, and with the FDA's pre-deadline approval measure, and again find estimates that are nearly identical to those of the original paper. Estimated odds ratios are still generally 3 or above (one is at 2.98), and two-tailed exact probability tests produce p-values of $< 0.05$ in both cross-tabulations and exact logistic regressions.

A cross tabulation with Fisher's exact test yields:

```
. tab  discont01_null_fdadata314NMEs pred01fda, exact

discont01_ |
null_fdada |       pred01fda
 ta314NMEs |         0          1 |     Total
-----------+----------------------+----------
         0 |       206         72 |       278
         1 |        20         16 |        36
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.029
   1-sided Fisher's exact =                 0.019
```

An exact logistic regression on the same data, controlling for year of NME submission, yields similar results and is shown on the following page.

## 5.1 Analysis of Dosage-Form Discontinuation Measure, Using FDA 314 NMEs and FDA Deadline Approval Measure (cont.)

# Binary Regression

regression (type=logit, model(discont01_ = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

### Basic Information

| | |
|---|---|
| **Data file** | discont-FDA314NMEs.csv |
| **Model** | discont01 (Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

### Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 28.95 | 21 | 0.1153 |
| **Likelihood Ratio** | 227.7 | 3 | 1.225e-009 |

### Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 3.165 | NA | Asymptotic | 0.3603 | 27.79 | 0.2987 |
| | | | | Asymptotic(Profile) | 0.3737 | 30.02 | |
| **subyrctr** | PMLE | 0.8134 | NA | Asymptotic | 0.7128 | 0.9282 | 0.00217 |
| | | | | Asymptotic(Profile) | 0.7071 | 0.9234 | |
| | CMLE | 0.8092 | NA | Exact | 0.7019 | 0.9231 | 0.001095 |
| **pred01fda** | PMLE | 2.978 | NA | Asymptotic | 1.424 | 6.229 | 0.003744 |
| | | | | Asymptotic(Profile) | 1.419 | 6.243 | |
| | CMLE | 2.977 | NA | Exact | 1.315 | 6.724 | 0.007818 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:01**

### 5.1 Analysis of Dosage-Form Discontinuation Measure, Using FDA 314 NMEs and FDA Deadline Approval Measure (cont.)

A random-effects logistic regression controlling for NME submission year, epidemiological covariates and random-effects groups by NME primary indication yields the following results. Results for the FDA-coded pre-deadline variable appear in yellow.

```
. xtlogit   discont01_null_fdadata314NMEs subyrctr pred01fda  hhospdisc
hhosleng, re i(discode) or

Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =     15.08
Log likelihood  = -102.56459                    Prob > chi2        =    0.0045

------------------------------------------------------------------------------
discont01_~s |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |    .807728   .0581981    -2.96   0.003     .7013498    .9302411
   pred01fda |   3.131616    1.26217     2.83   0.005     1.421344    6.899819
   hhospdisc |   1.000002   1.09e-06     1.56   0.120     .9999996    1.000004
    hhosleng |   .9847929   .0414308    -0.36   0.716     .9068476    1.069438
-------------+----------------------------------------------------------------
    /lnsig2u |  -2.015556    3.03375                     -7.961597    3.930485
-------------+----------------------------------------------------------------
     sigma_u |   .3650291   .5537036                      .0186707    7.136642
         rho |   .0389254   .1134934                      .0001059    .9393254
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.13 Prob >= chibar2 = 0.361
```

## 6. Standard versus Priority Classifications

The priority classification differs for 30 drugs between our data and the same NMEs as noted in Drugs@FDA. The vast majority of these are priority drugs whose reviews took a year or more, often 2-3 years. Therefore, reclassifying them as priority drugs would not affect the measure of whether they were approved just before the deadline; these reviews went well past both the standard and the priority deadlines.

Most of the original data used in our analysis came from a request made to the FDA under the Freedom of Information Act in 2000. We cannot tell whether the discrepancy in standard versus priority codes was a function of the data sent to us by the FDA's FOIA office, or whether it came from later from our own research team (this team was led by Dr. Carpenter, who assumes full responsibility for any errors in coding). For approved NMEs submitted from 2000 to 2003, we relied on approval letters from the CDER website (http://www.fda.gov/cder/foi/nda/index.htm) (latest access April 15, 2008).

We now present a list of the differences between the priority coding of the FDA and the priority coding of the Carpenter-Zucker-Avorn data, followed by a full list of the drugs coded as priority in our original dataset, and a full list of the drugs coded as priority in the FDA's dataset of April 2008.

## 6.1 List of Drugs Whose Priority Classifications Differ between Carpenter/Zucker/Avorn Data and FDA Data of April 2008.

Drugs highlighted in yellow are NMEs coded as standard by CZA and coded as priority in FDA Data of April 2008.

```
. list  ndanum2 ndanum genernam apptimex  priority priority_recoded if( priority ~=
priority_recoded)
```

| | ndanum2 | ndanum | genernam | apptimex | priority | priori~d |
|---|---|---|---|---|---|---|
| 6. | 20315 | 20315 | Levomethadyl acetate | .59 | 0 | 1 |
| 7. | 20326 | 20326 | Trimetrexate glucuronate | 10.49 | 0 | 1 |
| 11. | 20356 | 20356 | Nisoldipine | 22.09 | 1 | 0 |
| 13. | 20363 | 20363 | Famciclovir | 11.97 | 1 | 0 |
| 30. | 20444 | 20444 | Epoprostenol | 18.71 | 0 | 1 |
| 33. | 20451 | 20451 | Porfimer | 20.48 | 0 | 1 |
| 34. | 20459 | 20459 | Nalmefene | 11.61 | 1 | 0 |
| 38. | 20482 | 20482 | Acarbose | 12 | 1 | 0 |
| 43. | 20498 | 20498 | Bicalutamide | 12.66 | 1 | 0 |
| 57. | 20564 | 20564 | Lamivudine | 4.37 | 0 | 1 |
| 68. | 20599 | 20599 | Riluzole | 5.46 | 0 | 1 |
| 95. | 20687 | 20687 | Mifepristone | 55.3 | 0 | 1 |
| 98. | 20690 | 20690 | donepezil hydrochloride | 7.92 | 0 | 1 |
| 106. | 20715 | 20715 | Triptorelin Pamoate | 6.066667 | 1 | 0 |
| 194. | 21060 | 21060 | Ziconotide | 60.9 | 0 | 1 |
| 207. | 21106 | 21106 | Pegvisomant | 27.43333 | 0 | 1 |
| 208. | 21107 | 21107 | Alosetron HC1 | 7.5 | 0 | 1 |
| 209. | 21119 | 21119 | Verteporfin | 8.066667 | 0 | 1 |
| 220. | 21196 | 21196 | Sodium Oxybate | 21.83333 | 0 | 1 |
| 222. | 21200 | 21200 | Tegaserod Maleate | 29.8 | 0 | 1 |
| 226. | 21223 | 21223 | Zoledronic Acid | 20.26667 | 0 | 1 |
| 227. | 21226 | 21226 | Lopinavir;Ritonavir | 3.566667 | 0 | 1 |
| 229. | 21232 | 21232 | Nitisinone | 25.1 | 0 | 1 |
| 232. | 21257 | 21257 | Travoprost | 8.433333 | 0 | 1 |
| 233. | 21264 | 21264 | Apomorphine Hydrochloride | 15.86667 | 0 | 1 |
| 235. | 21272 | 21272 | Treprostinil Sodium | 19.4 | 0 | 1 |
| 242. | 21320 | 21320 | Abarelix | 35.96667 | 0 | 1 |
| 249. | 21345 | 21345 | Fondaparinux Sodium | 9.833333 | 0 | 1 |
| 264. | 21431 | 21431 | Acamprosate Calcium | 31.5 | 0 | 1 |
| 268. | 21446 | 21446 | Pregabalin | 14.23333 | 0 | 1 |
| 271. | 21462 | 21462 | Pemetrexed Disodium | 4.266667 | 0 | 1 |
| 279. | 21506 | 21506 | Micafungin Sodium | 35.06667 | 0 | 1 |
| 286. | 21572 | 21572 | Daptomycin | 8.9 | 0 | 1 |
| 292. | 21640 | 21640 | Ovine Hyaluronidase | 9.166667 | 0 | 1 |
| 294. | 21665 | 21665 | Hyaluronidase | 16.93333 | 0 | 1 |
| 296. | 21670 | 21670 | Trypan Blue | 13.96667 | 0 | 1 |
| 297. | 21673 | 21673 | Clofarabine | 9.133333 | 0 | 1 |
| 301. | 21743 | 21743 | Erlotinib Hydrochloride | 3.733333 | 0 | 1 |
| 302. | 21749 | 21749 | Pentetate Calcium Trisodium | 4.4 | 0 | 1 |
| 303. | 21751 | 21751 | Pentetate Zinc Trisodium | 4.266667 | 0 | 1 |
| 312. | 50678 | 50678 | Dirithromycin | 25.68 | 1 | 0 |
| 321. | 50794 | 50794 | Azacitidine | 4.833333 | 0 | 1 |

## 6.1 List of Drugs Whose Priority Classifications Differ between Carpenter/Zucker/Avorn Data and FDA Data of April 2008 (cont.)

There would appear to be 35 drugs that we coded as standard but which the FDA codes as priority NMES, and 7 drugs which we coded as priority but that the FDA codes as standard NMES.

```
. count if( priority == 0 &  priority_recoded == 1)
   35

. count if( priority == 1 &  priority_recoded == 0)
    7
```

So the total difference is 28 drugs, which if added to our 102 priority NMEs in the original data set makes 130.

In addition, the FDA data has five NMEs that are not in our data set, two of which – hyaluronidase (NDA # 21716) and Fludeoxyglucoase F 18 (NDA # 20306) – are coded by the FDA as priority NMEs. Adding this to the 130 priority NMEs in our revised data brings the total to 132, which is the FDA's count according to the Nardinelli, et al. letter.

## 6.2. LIST OF DRUGS THAT CZA CODED STANDARD THAT FDA CODES AS PRIORITY, AS OF APRIL 2008

The majority of the discrepancies are drugs that we coded as priority that FDA coded as standard. In the next section, we show that most of these drugs were approved in well over one year of review time, and many others were approved well before the two-month before deadline window. Hence very few of our pre-deadline classifications were affected by the discrepancy.

Drugs with 14 months or greater approval time are highlighted in yellow.

```
. list  ndanum2 ndanum genernam apptimex  priority priority_recoded if( priority ==  0 &
priority_recoded == 1)
```

| | ndanum2 | ndanum | genernam | apptimex | priority | priori~d |
|---|---|---|---|---|---|---|
| 6. | 20315 | 20315 | Levomethadyl acetate | .59 | 0 | 1 |
| 7. | 20326 | 20326 | Trimetrexate glucuronate | 10.49 | 0 | 1 |
| 30. | 20444 | 20444 | Epoprostenol | 18.71 | 0 | 1 |
| 33. | 20451 | 20451 | Porfimer | 20.48 | 0 | 1 |
| 57. | 20564 | 20564 | Lamivudine | 4.37 | 0 | 1 |
| 68. | 20599 | 20599 | Riluzole | 5.46 | 0 | 1 |
| 95. | 20687 | 20687 | Mifepristone | 55.3 | 0 | 1 |
| 98. | 20690 | 20690 | donepezil hydrochloride | 7.92 | 0 | 1 |
| 194. | 21060 | 21060 | Ziconotide | 60.9 | 0 | 1 |
| 207. | 21106 | 21106 | Pegvisomant | 27.43333 | 0 | 1 |
| 208. | 21107 | 21107 | Alosetron HC1 | 7.5 | 0 | 1 |
| 209. | 21119 | 21119 | Verteporfin | 8.066667 | 0 | 1 |
| 220. | 21196 | 21196 | Sodium Oxybate | 21.83333 | 0 | 1 |
| 222. | 21200 | 21200 | Tegaserod Maleate | 29.8 | 0 | 1 |
| 226. | 21223 | 21223 | Zoledronic Acid | 20.26667 | 0 | 1 |
| 227. | 21226 | 21226 | Lopinavir;Ritonavir | 3.566667 | 0 | 1 |
| 229. | 21232 | 21232 | Nitisinone | 25.1 | 0 | 1 |
| 232. | 21257 | 21257 | Travoprost | 8.433333 | 0 | 1 |
| 233. | 21264 | 21264 | Apomorphine Hydrochloride | 15.86667 | 0 | 1 |
| 235. | 21272 | 21272 | Treprostinil Sodium | 19.4 | 0 | 1 |
| 242. | 21320 | 21320 | Abarelix | 35.96667 | 0 | 1 |
| 249. | 21345 | 21345 | Fondaparinux Sodium | 9.833333 | 0 | 1 |
| 264. | 21431 | 21431 | Acamprosate Calcium | 31.5 | 0 | 1 |
| 268. | 21446 | 21446 | Pregabalin | 14.23333 | 0 | 1 |
| 271. | 21462 | 21462 | Pemetrexed Disodium | 4.266667 | 0 | 1 |
| 279. | 21506 | 21506 | Micafungin Sodium | 35.06667 | 0 | 1 |
| 286. | 21572 | 21572 | Daptomycin | 8.9 | 0 | 1 |
| 292. | 21640 | 21640 | Ovine Hyaluronidase | 9.166667 | 0 | 1 |
| 294. | 21665 | 21665 | Hyaluronidase | 16.93333 | 0 | 1 |
| 296. | 21670 | 21670 | Trypan Blue | 13.96667 | 0 | 1 |
| 297. | 21673 | 21673 | Clofarabine | 9.133333 | 0 | 1 |
| 301. | 21743 | 21743 | Erlotinib Hydrochloride | 3.733333 | 0 | 1 |
| 302. | 21749 | 21749 | Pentetate Calcium Trisodium | 4.4 | 0 | 1 |
| 303. | 21751 | 21751 | Pentetate Zinc Trisodium | 4.266667 | 0 | 1 |
| 321. | 50794 | 50794 | Azacitidine | 4.833333 | 0 | 1 |

## 6.2. LIST OF DRUGS THAT CZA CODED STANDARD THAT FDA CODES AS PRIORITY, AS OF APRIL 2008

Comparing the drugs that we coded as standard but which the FDA codes as priority, shows that there is a material difference in average approval time between the drugs with discrepancies and the sample of drugs coded as priority by the FDA. In particular, the average approval time for the total sample of priority NMES as coded in the FDA's April 2008 data is 11.33 months, whereas the discrepancy drugs average 16.5 months of review time. Again, Dr. Carpenter and his research team assume responsibility for any errors – which seem to have come from our coding of FDA approval letters on the FDA web site – but the lengthier review of these drugs should be noted.

```
. sum apptimex if( priority == 0 &  priority_recoded == 1)

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
    apptimex |        35    16.50533    14.19526        .59       60.9

. sum  apptime_fda if(priority_fda01 == 1)

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
 apptime_fda |       132    11.33333    9.658439         .6       60.1
```

Note that fully 17 of these FDA's priority drugs that we coded as standard NMEs had approval times of 14 months or greater.

# 7. Timing of Approvals

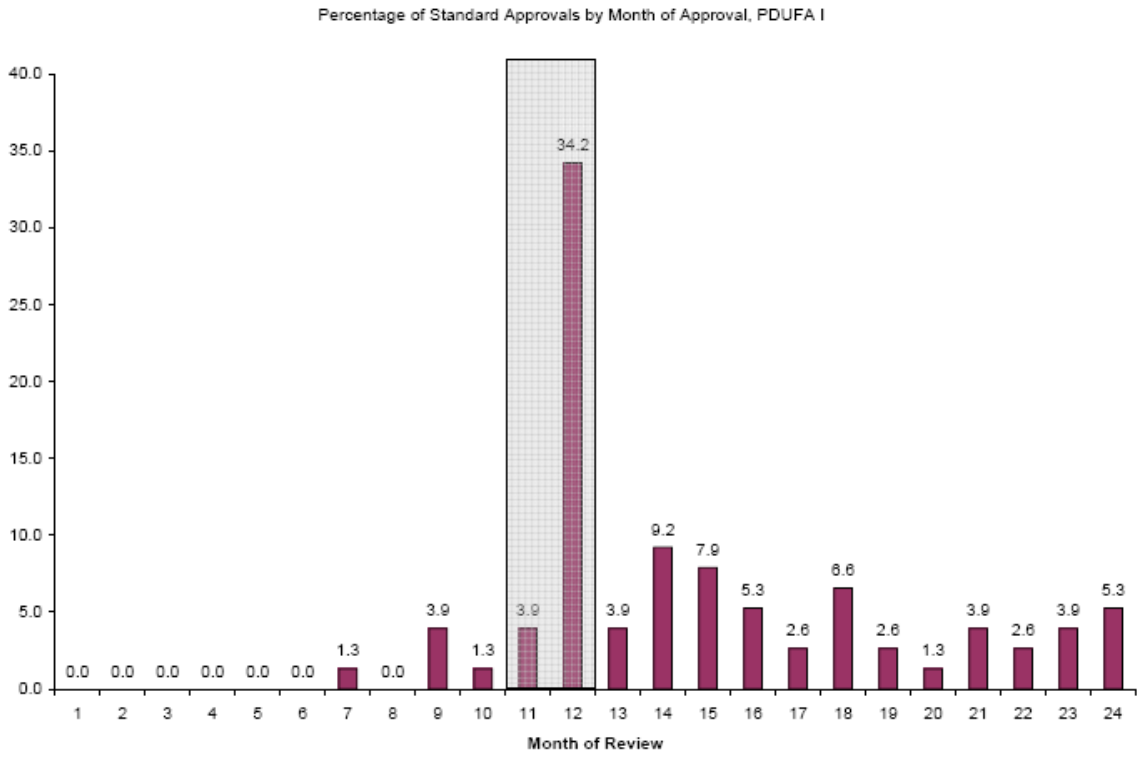
Nardinelli et al. also argue that our approval time data are faulty, pointing in particular to 25 standard NMEs under PDUFA II and after that are approved before the tenth month in our data, whereas they observe only five such NMEs in their data. This difference is simply a matter of rounding. Our original coding was based on dividing the number of days of approval by 30 (in separate data that was sent to us by former FDA official Ed Hass, a similar measure with similar denominator was used). This produced a number of drugs that had met the review deadlines but had numerical review times that appeared to put them past the deadlines. For instance, L-Glutamine (Nutrestore; NDA # 21667) was submitted on August 8, 2003 and approved on June 10, 2004, which generates a review time of 10.23 months – so we rounded down to produce the patterns Figure 1. This had the effect of rendering NMEs that went into the tenth month of review being coded as ninth-month approvals, which accounts for the difference.

**We note that, to the extent that the FDA's rounding is preferred, *our argument about the concentration (or "piling") of approval decisions near the deadline approvals is even stronger*.** If for the 10-month deadline period (standard NMEs submitted under PDUFA II and afterwards) there are more tenth-month approvals and fewer ninth-month approvals, *then a greater proportion of NMES are being approved immediately before the operative deadline*. What is more, since the differences are being driven by distinctions between ninth and tenth month approvals, none of these discrepancies affects our coding of just-before-deadline approvals.

## 7.1. Timing of Approvals (cont.)

**COUNT OF APPROVAL TIMES, ROUNDING TO NEAREST INTEGER INSTEAD OF ROUNDING DOWN**

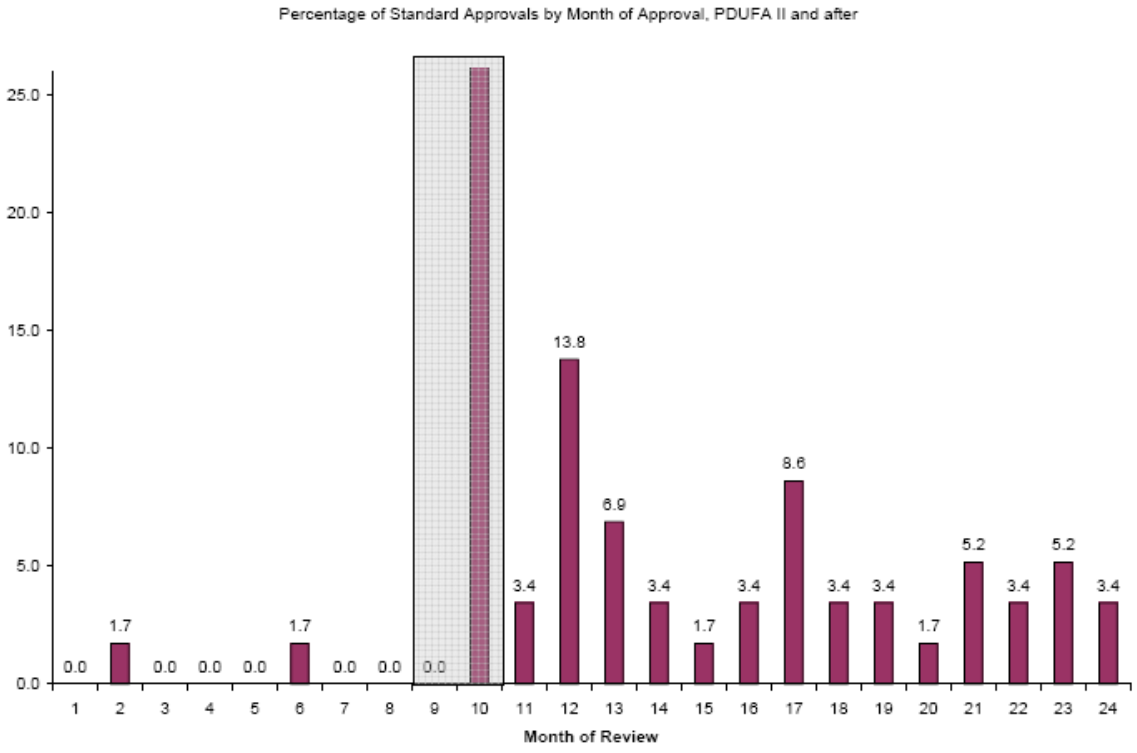
First do standard NMEs under PDUFA I



## 7.2. Timing of Approvals (cont.)

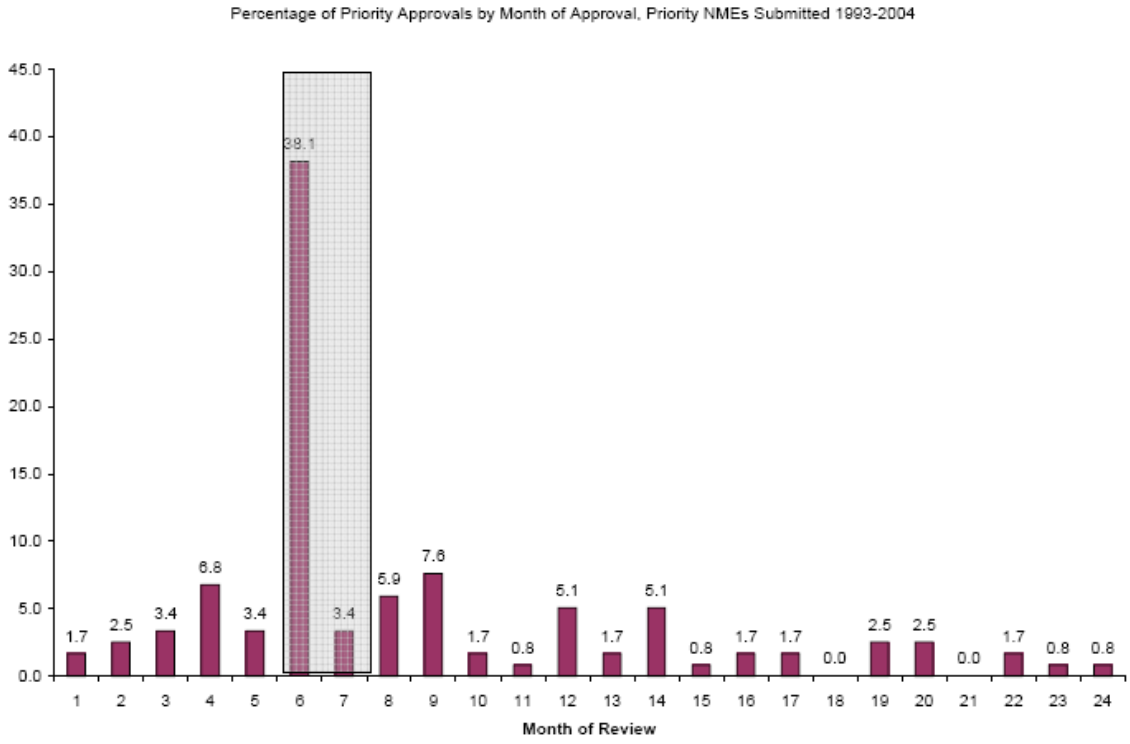
**RE-TABULATION USING DIFFERENT ROUNDING RULE (cont.)**

Next do standard NMEs under PDUFA II and after. This produces just 2 NMEs approved before the 10th month.



## 7.1. Timing of Approvals (cont.)

Now re-tabulate priority NMEs using rounding to nearest integer.



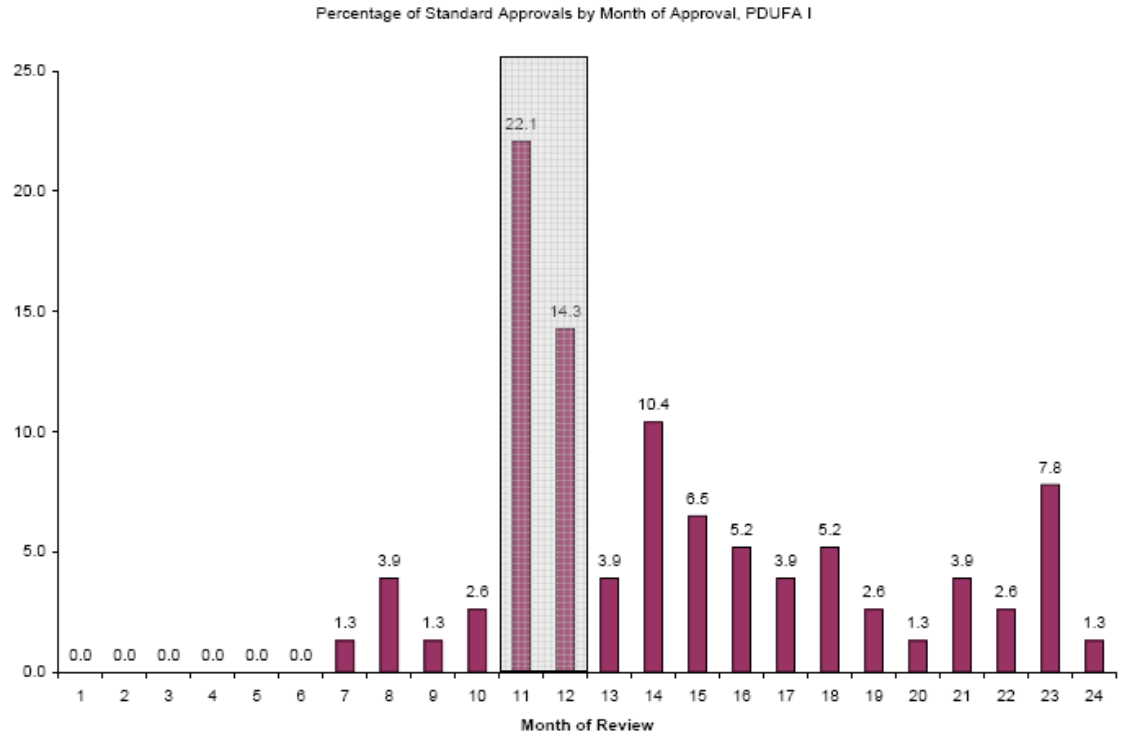
### 7.2. Timing of Approvals (Using Floor Function)

**RE-TABULATION OF APPROVAL TIMES BY MONTH, USING "FLOOR" FUNCTION.**

We then tried another rounding function, which appears to produce numbers closer to the FDA for standard NMEs since PDUFA II (see below). Again, using this rounding function does not change our coding of pre-deadline measures and does not change our substantive results.

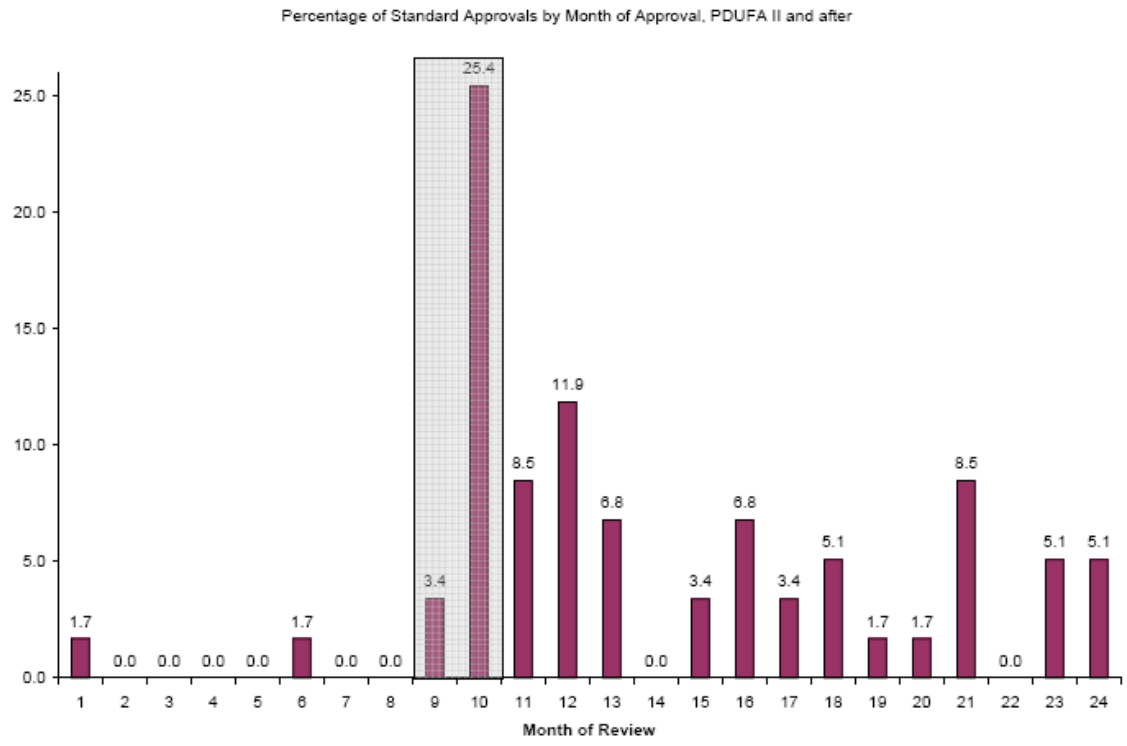
```
In STATA SE9, floor(x) returns the integer n such that n < x < n+1.
floor(x) returns x(not ".") if x is missing, meaning floor(.a) = .a.

. gen apptime_floor = floor(apptimex)
```

First do standard NMEs under PDUFA I



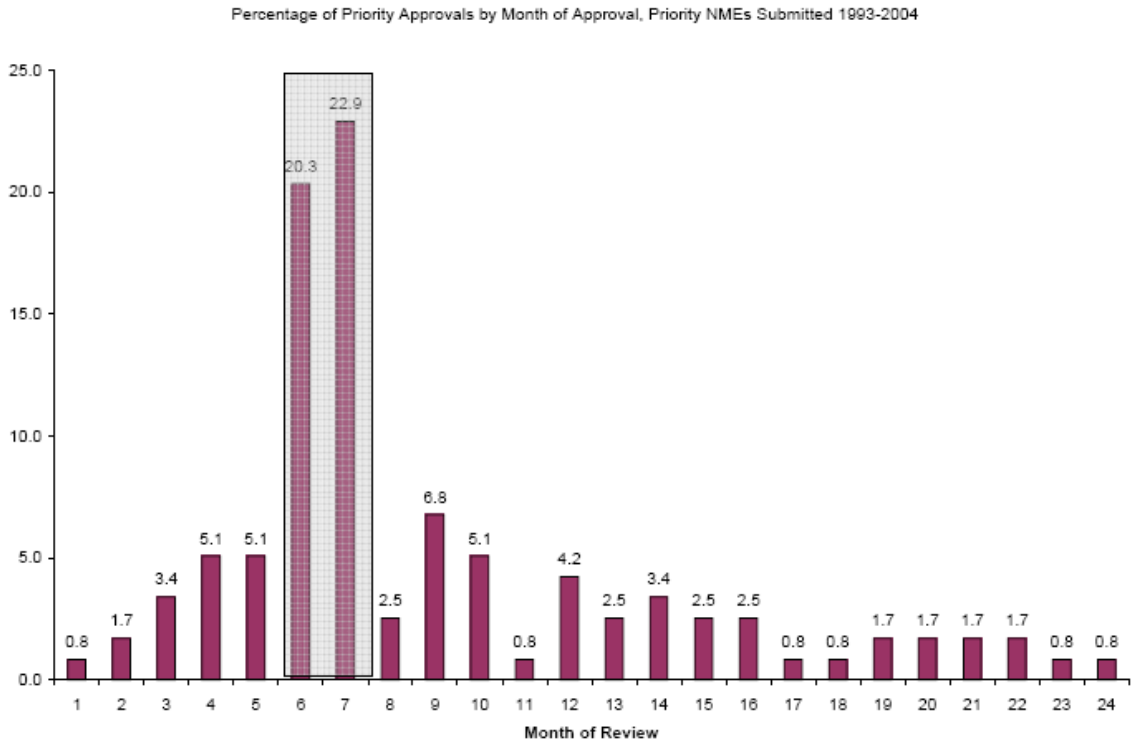
### 7.2. Timing of Approvals (Using Floor Function) (cont.)

Now do standard NMEs under PDUFA II and after, for first 24 months of review cycle. This produces 4 drugs, which is very close to the 5 drugs described in the Nardinelli et al. letter.



## 7.2. Timing of Approvals (Using Floor Function) (cont.)

Now tabulate priority NMEs for first 24 months of review cycle.



# Memorandum to *NEJM* Editors on Differences between Carpenter/Zucker/Avorn data and FDA data on Black-Box Warnings, and Re-Analysis of Data (cont.)

## 8. Coding Black-Box Warnings[3]

We completed our coding in the summer of 2005; the first version of this paper was submitted to the *New England Journal of Medicine* in January 2006.

Black-Box Warnings: There is no unified database of black-box warnings added to drugs postmarket. The closest is Lasser's paper of 2002, which stops coding in 1999. We used this Lasser article [*JAMA* [2002; 287(17) May 1:2215-20], which was static, and the KUMC database, a comprehensive list of black-box warnings added to drugs that is regularly updated (http://www.formularyproductions.com/master/showpage.php?dir=blackbox&whichpage=9 (most recent download May 17, 2008). Postmarket black box warnings listed on the KUMC were coded until July 2005, when Mr. Zucker stopped working on the project; nowork was completed on or after August 1, 2005. (Some drugs receive multiple black-box warnings over time, and so it is possible that drugs that received an additional black-box warning after August 1, 2005 also received a postmarket boxed warning before August 1, 2005). In addition it is possible that some of the drugs that had black-box warnings attached between January and July 2005 were not yet listed in the KUMC database. We cannot verify this possibility as we do not have the entire KUMC database as it was posted in August of 2005.

[3] For a review of our coding rules in general, see Section 1.1 of the document.

# 9. Differences between the April 2008 Nardinelli et al data and the Carpenter, Zucker and Avorn (CZA) data.

## 9.1 Catalog of Black-Box Warning (BBW) Differences

The following is the list of NMEs with a postmarket black-box warning as coded by Carpenter, Zucker and Avorn.

```
. list  ndanum_fda  genernam_fda if(bbwcza == 1)

     +-----------------------------------------+
     | ndanum~a                    genernam_fda |
     |-----------------------------------------|
  3. |    21341                      Valdecoxib |
 42. |    21492                     Oxaliplatin |
104. |    20430               Danaparoid Sodium |
106. |    21345             Fondaparinux Sodium |
112. |    21500                   Emtricitabine |
     |-----------------------------------------|
120. |    21356   Tenofovir Disoproxil Fumarate |
124. |    21814                     Tipranavir |
137. |    20759          Trovafloxacin Mesylate |
177. |    21427        Duloxetine Hydrochloride |
221. |    20697                       Tolcapone |
     |-----------------------------------------|
232. |    20720                    Troglitazone |
300. |    21797                       Entecavir |
301. |    21449              Adefovir Dipivoxil |
311. |    21618                      Tinidazole |
     +-----------------------------------------+
```

## 9.1 Catalog of Black-Box Warning (BBW) Differences (cont.)

The following is the complete list of NMEs with postmarket BBWs as coded by Nardinelli et al in their April 2008 web-posted data.

```
. list  ndanum_fda  genernam_fda bbwdate_fda if( bbwfda08 == 1)

     +-----------------------------------------------------+
     | ndanum~a                    genernam_fda   bbwdate~a |
     |-----------------------------------------------------|
  2. |    20998                       Celecoxib   29-Jul-05 |
  3. |    21341                     Valdecoxib   24-Nov-04 |
  4. |    20938                      Meloxicam   11-Aug-05 |
 14. |    20535              Bromfenac Sodium   31-Mar-98 |
 33. |    20896                  Capecitabine    7-Sep-01 |
     |-----------------------------------------------------|
 54. |    20169                     Nilutamide   29-Sep-00 |
104. |    20430            Danaparoid Sodium   30-Jan-98 |
108. |    20564                     Lamivudine   15-Dec-97 |
114. |    20628                     Saquinavir   14-Nov-00 |
134. |    21144                  Telithromycin   12-Feb-07 |
     |-----------------------------------------------------|
137. |    20759       Trovafloxacin Mesylate    9-Jun-99 |
138. |    20760     Alatrofloxacin Mesylate    9-Jun-99 |
175. |    20822     Citalopram Hydrobromide   18-Feb-05 |
176. |    20415                   Mirtazapine   12-Jan-05 |
177. |    21427     Duloxetine Hydrochloride   18-Feb-05 |
     |-----------------------------------------------------|
183. |    20592                    Olanzapine   16-Feb-06 |
184. |    21436                  Aripiprazole   16-Feb-06 |
185. |    20639          Quetiapine Fumarate   20-Sep-06 |
186. |    20825    Ziprasidone Hydrochloride   17-Aug-05 |
189. |    21302                   Pimecrolimus   19-Jan-06 |
     |-----------------------------------------------------|
221. |    20697                     Tolcapone   16-Nov-98 |
228. |    21073   Pioglitazone Hydrochloride   14-Aug-07 |
232. |    20720                   Troglitazone   15-Dec-97 |
236. |    21071       Rosiglitazone Maleate   14-Aug-07 |
244. |    21411    Atomoxetine Hydrochloride    8-Nov-05 |
     |-----------------------------------------------------|
260. |    20937              Gadoversetamide    4-Sep-07 |
266. |    21064 Perflutren Lipid Microsphere   10-Oct-07 |
273. |    20815     Raloxifene Hydrochloride   13-Sep-07 |
284. |    21107      Alosetron Hydrochloride    7-Jun-02 |
     +-----------------------------------------------------+
```

Of these 29 NMEs, 13 (highlighted in yellow) had their warnings attached since the beginning of August 2005, while four more (in green), and 17 have had their black-box warnings added since

January 2005, in the wake of the Vioxx withdrawal. .Thus, 58% of the postmarket black-box warnings listed by Nardinelli et al were added since the withdrawal of Vioxx, and 45 percent were added after August 1, 2005, when our coding stopped. These calculations assume that all of the FDA's NMEs represent methodologically sound coding of post-market BBWs.

The pattern of adding black-box warnings changed appreciably since the withdrawal of rofecoxib (Vioxx) in September 2004. This consideration did not drive our decision to terminate coding in at the end of July 2005; this is simply when our data collection stopped. However, the shift that occurs during the period September 2004 to January 2005 is noticeable and dramatic. Nearly six in ten of the FDA's BBWs occur in the last one-fifth of the FDA's time window.[4] Put differently, a highly disproportionate share of the FDA's coded BBWs are added from 2005 through 2007. No such discontinuity is evident for other periods of time, especially as demonstrated by Lasser and collagues (*JAMA* 2002). *The high prevalence of molecular-class relabelings in recent years may mean that post-Vioxx BBWs reflect an aspect of FDA's postmarket warnings policies that are different from the dimensions captured by pre-Vioxx BBWs*.

At least one significant difference between class BBW relabelings and more specific BBW relabelings is the specificity of the evidence concerned. Class relabelings occur with indirect evidence from other molecules that rely upon similar mechanisms; they are not based upon direct evidence of studies of the molecule itself. Such patterns are observed for the BBWs added to "atypical antipsychotic" drugs in recent years (apiprazole, olanzipine, quetiapine, ziprasidone).

Hence the more recent BBW data may not be comparable to the BBW data of the sort that Lasser and others collected. Further research may be necessary to examine how post-Vioxx black-box warning decisions differ from those before the rofecoxib withdrawal. To assess what happens when we exclude those NMEs whose black-box warnings are based upon indirect clinical

[4] Note that since many of the 314 NMEs in the FDA's April 2008 data were not approved until well after 1993, it is not true that 58 percent of these NMEs received a black-box warning in the last three years of their market life. Still, there is a stark and rather odd discontinuity in the FDA's black-box warning data, as we document below.

evidence and upon therapeutic class and molecular mechanism similarities to other NMEs, see Section 15 below.

### 9.2 Erroneous Coding in the FDA's Data of April 2008

The FDA's April 2008 data do not include at least five NMEs where a black-box warning has been added or significantly modified. These five are

- **Tenofovir** (Viread)
- **Adefovir** (Hepsera)
- **Entecavir** (Baraclude)
- **Tiprinavir** (Aptivus)
- **Emtricitabine** (Emtriva)

We have conducted year-by-year searches of these drugs in the *Physicians' Desk Reference* since their FDA approval. While we are not certain that we have captured all of the changes to the BBWs for these drugs,[5] we are confident that we have identified at least one significant labeling boxed warning change in each of them, and are confident that the FDA has thus erred in their April 2008 coding.

There are also cases where we believe that the FDA has coded a drug as receiving a black box warning, when in fact no warning was added or it is not clear that significant new safety information was conveyed by the labeling change. The clearest case of an error comes in the drug **saquinavir** (**Invirase**). While this drug did receive a new black-box warning in February 2008 (see Roche "Dear Doctor Letter" of February 2008, available at http://www.rocheusa.com/products/invirase/DM11.1_Invirase_Dear_Doctor_Letter.pdf (accessed May 12, 2008)]), *a February 2002 publication by the National Institutes of Health and the AHRQ states clearly that no Black Box Warning was evident for saquinavir at that time* (see

[5] Both the Lasser 2002 article in *JAMA* and a communication by physicians Charles Bennett and Oliver Sartor [*Annals of Internal Medicine* 139 (6) (September 16, 2003) 529] identify possible discrepancies between information in the PDR and other sources. It is clear, however, that significant safety information in boxed warnings was added to the labels in at least one instance for each of these five drugs.

Figure 9A, page after next). *This is more than a year after the date for which the FDA's April 2008 data has the warning added*.

This omission is odd, given that two FDA officials (Heidi Jolson and Jeffrey Murray) appear to have served as participants in the creation of this report. (See Figure 9B, below, page after Figure 9A.)

In other cases, the FDA codes drugs that as having postmarket BBWs where there were not significant changes to the label or where the changes were directed to very small patient populations relative to the target population. The first of these cases is **nilutamide (Nilandron)** and **capecitabine (Xeloda)**, both of them oncologic drugs that are used concomitantly with other therapies. In a communication to the *Annals of Internal Medicine*, Drs. Charles Bennett and Oliver Sartor note that small-scale changes in evidence spurred the labeling modifications for nilutamide, and that different sources code these changes quite variably. ["Pneumonitis with Anti-Androgens," *Annals of Internal Medicine* 139 (6) (September 16, 2003) 529]. Dr. Bennett is one of the nation's most respected authorities on postmarket risks of oncologic drugs.

The second of these cases is and **capecitabine (Xeloda)**. Here the labeling change drew attention to interactions with warfarin in a small number of patients. [Laurel M. Janney and Nancee V. Waterbury, "Capecitabine-Warfarin Interaction," *The Annals of Pharmacotherapy* 39 (9) 1546-1551.]

Both of these drugs – nilutamide (Nilandron) and capecitabine (Xeloda) – are oncologic drugs that are used concomitantly with other therapies; as Bennett has noted, postmarket surveillance and coding of safety problems for oncologic therapies is highly problematic ["The Research on Adverse Drug Events and Reports (RADAR) Project," *JAMA*.2005; 293: 2131-2140].

**Figure 9A: NIH Publication of February 2002 Lists Saquinavir as Not Having BBW.**

| | |
|---|---|
| Nevirapine (Viramune™) | • **Severe, life-threatening hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure.** Patients should be advised to seek medical evaluation immediately should signs and symptoms of hepatitis occur.<br>• **Severe, life-threatening, and even fatal skin reactions,** including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction have occurred with nevirapine treatment<br>• Patients should be monitored intensively during the first 12 weeks of nevirapine therapy to detect potentially life-threatening hepatotoxicity or skin reactions.<br>• A 14-day lead-in period with nevirapine 200mg daily must be strictly followed.<br>• **Nevirapine should not be restarted after severe hepatic, skin, or hypersensitivity reactions** |
| Ritonavir (Norvir™) | • Co-administration of ritonavir with certain medications may result in potentially serious and/or life-threatening adverse events due to effects of ritonavir on hepatic metabolism of certain drugs |
| Saquinavir (Fortovase™, Invirase™) | None |
| Stavudine (Zerit™) | • **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases,** have been reported with the use of antiretroviral nucleoside analogues alone or in combination<br>• **Fatal lactic acidosis has been reported in pregnant women who received a combination of stavudine and didanosine** along with other antiretroviral combinations<br>  ○ Stavudine and didanosine combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks<br>• **Fatal and non-fatal pancreatitis** have occurred when stavudine was part of a combination regimen with didanosine with or without hydroxyurea |

http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat2.table.10535 (accessed May 4, 2008).

**Figure 9B: Two FDA Officials Were Participants in the February 2002 NIH/AHRQ Study that Listed Saquinavir as not having a BBW.**

**Participants from the Department of Health and Human Services:**

| | |
|---|---|
| Victoria Cargill | National Institutes of Health |
| Oren Cohen | National Institutes of Health |
| Mark Dybul | National Institutes of Health |
| T. Randolph Graydon | Centers for Medicare and Medicaid Services |
| Heidi Jolson | Food and Drug Administration |
| Jonathan Kaplan | Centers for Disease Control and Prevention |
| Abe Macher | Health Resources and Services Administration |
| Henry Masur | National Institutes of Health |
| Lynne Mofenson | National Institutes of Health |
| Jeffrey Murray | Food and Drug Administration |
| Joseph O'Neill | Health Resources and Services Administration |
| Alice Pau | National Institutes of Health |
| Lucille C. Perez | Substance Abuse and Mental Health Services Administration |

http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat2.chapter.10256 (accessed May 4, 2008).

### 9.3 Erroneous Codings in the Carpenter Data

Thorough re-evaluation of all our coding has revealed some instances of errors in coding of the Black-Box Warning (BBW) data. First, some drugs that received postmarket black-box warnings well before August 2005 were not coded as such: citalopram (Celexa), lamivudine (Epivir), bromfenac (Duract), alatrofloxacin (Trovan) and alosetron (Lotronex).[6] In two of these cases – alatrofloxacin and bromfenac– we had correctly coded these drugs as withdrawn from the market, but failed to detect the BBW added before the withdrawal. Dr. Carpenter assumes sole responsibility for these two errors.

Another drug – celecoxib (Celebrex) – appears to have had its BBW added on July 29, 2005. This occurred while Mr. Zucker completed his work during the middle of the summer and was omitted. It is quite possible, although we cannot say for sure, that the KUMC web database had not yet updated its list by July 31, 2005. Again, Dr. Carpenter assumes sole responsibility for this error.

We coded three drugs as having postmarket BBWs added when less than significant safety information was communicated in the labeling changes: oxaliplatin (Eloxatin), fondaparinux (Arixtra) and tinidazole (Tindamax). In all three cases the label's black box warning did change but we did not distinguish adequately between formatting changes and information-based changes. Dr. Carpenter assumes sole responsibility for these errors.

[6] Alosetron did not have a black-box warning added before its 2000 withdrawal, but did have a black-box warning when it was reintroduced in 2002, which we failed to detect. In hindsight, we should have coded alosetron as having had a black-box warning added.

## 10. Additional General Notes on the Reliability of the FDA's Postmarket Safety Data, esp as concerns Black Box Warnings

More broadly, we believe that the FDA's data of April 2008 are methodologically flawed and empirically inconsistent with numerous sources, including the FDA's own publications.[7]

(a) It is important not to regard either the Drugs@FDA database or the MedWatch system data as authoritative for purposes of drug safety. The database contains some very important omissions. For instance, **Posicor (mibefradil hydrochloride) and Duract [bromfenac sodium) were withdrawn for safety reasons, yet they are not listed on the Drugs@FDA webpage and are absent from the underlying database maintained by FDA**. (As Figures 2A through 2F above clearly show, searching for these two drugs by generic name, trade name and NDA number fails to return a record with the original NME.) These are two of the most important safety-based withdrawals of the past several decades; their absence from the FDA's own data is troubling.

Regarding Black Box Warnings in particular, not every addition to an existing black-box warning conveys important new safety information.

The FDA letter to the Editor cites "FDA data," but we know of no single, accessible database where such data are kept. Indeed, the data posted to the FDA website on April 7, 2008 (http://www.fda.gov/oc/pdufa/FDADrugAppSafetyData_files/NMESafetySumm.html), are the first such publication of FDA data by the agency that combine approval time information with safety-related postmarket regulatory events.

Moreover, the information posted by Narindelli et al is not an authoritative database. As footnote 5 of the FDA letter states, "The FDA data is based on major safety labeling changes posted on

[7] We refer to the FDA's "data of April 2008" because this data differs so appreciably from other data on the FDA website, other data that the FDA has published, and other data that the FDA has provided to other authors and which has been presented at FDA-sponsored conferences. While Nardinelli et al refer to "FDA data," it is important to point out that there is no unified, consistent "FDA data" on approvals and postmarket safety problems.

Medwatch and Drugs@FDA." There is no other methodology noted or acknowledged to compile these data. How for instance is a "major" safety labeling change defined? Does the "and" in the sentence mean that the safety labeling change must be posted on both Medwatch and Drugs@FDA in order to qualify?

For these and related reasons, we used independent sources – principally the article of Lasser (*JAMA* [2002; 287(17) May 1:2215-20]) – to code post-market safety events. We also used an independent source, a list maintained by the Kansas University Medical Center (http://www.formularyproductions.com/master/showpage.php?dir=blackbox&whichpage=9 [most recent access May 17, 2008]). These sources existed years before the FDA's data were assembled, they are publicly accessible in single data form, and in both cases (especially the Lasser article) a clear methodology is used.

Nardinelli et al do not acknowledge previous research methods in defining their new classification of black-box warnings. In 2006 FDA Nardinelli and colleagues circulated a paper under the National Bureau of Economic Research (NBER) Working Paper Series that analyzed NMEs and black-box warnings. [We do not know of its current publication status, but cannot find evidence of its publication. We used an April 7, 2008 download from the nber.org website, but cannot find this paper on the FDA website.] Among the many glaring inaccuracies in the paper, **the Lasser article (JAMA 2002) was not even cited**. Since we suspect that much of the data that FDA is using was also used in this paper, this omission underscores the fundamental methodological weaknesses of the FDA's black-box warning data.

## 10. Quality and Reliability of FDA Postmarket Safety Data (cont.)

### Figure 10A – Title Page of Begosh, et al Working paper

NBER WORKING PAPER SERIES

BLACK BOX WARNINGS AND DRUG SAFETY:
EXAMINING THE DETERMINANTS AND TIMING OF FDA WARNING LABELS

Allan Begosh
John Goldsmith
Ed Hass
Randall W. Lutter
Clark Nardinelli
John A. Vernon

Working Paper 12803
http://www.nber.org/papers/w12803

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
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December 2006

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**10. Quality and Reliability of FDA Postmarket Safety Data (cont.)**

**Figure 10B – Page 21 ("References") of Begosh et al Working Paper, with Eight Total References. Lasser and Other Medical Literature Not Cited.**

**REFERENCES**


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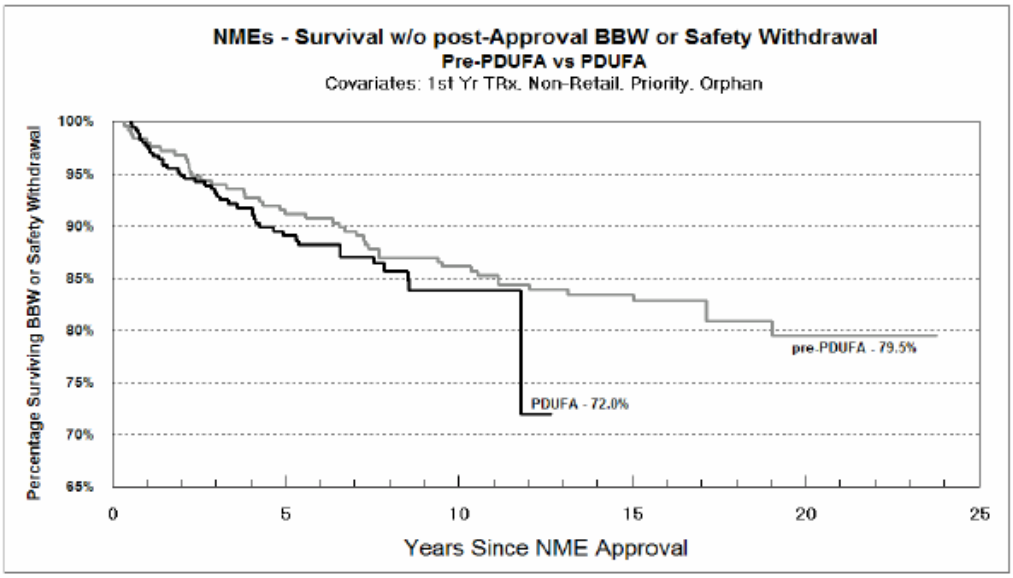
**10. Quality and Reliability of FDA Postmarket Safety Data (cont.)**

There are other worrisome aspects to this paper. There appears to be a large, discontinuous change in FDA black-box warnings, comprising 12 percent of the data or more, added at exactly the same time (see Figure 2 of the Begosh et al paper, reproduced below). The simultaneous occurrence of such a large fraction of BBWs or withdrawals should raise concerns about the quality of the data.

**Figure 2 of Begosh et al, working paper (p. 14, download of April 7, 2008).**

**Figure 2: Survival of NMEs by PDUFA Status with Drug-Specific Covariates**




This simultaneous recoding does not appear in our black-box warning data (and no such discontinuity appears in the data presented by Lasser and colleagues in 2002). We nonetheless reproduce it here to note that it is highly improbable that a rigorously-coded boxed warning measure would yield such a discontinuity. Such a discontinuity would require that 12 percent of the NMEs in the post-PDUFA sample (288 drugs, or either 34 or 35 drugs) would have to have received black-box warnings *at the exact same year + month interval* after having been approved. If for instance the discontinuity appears at 11 years and 10 months, for instance, it would have to be the case that at least 34 drugs received a black-box warning exactly 11 years and 10 months after having been coded.

**10. Quality and Reliability of FDA Postmarket Safety Data (cont.)**

**(e) FDA Postmarket Safety Data May Substantially Overcount Black-Box Warnings, Compared to Published Sources. [An Example, from Comparison of the FDA's data with Lasser from 1981 to 1992]**

In their 2006 paper, for the "pre-PDUFA period" 1981 to 1992, FDA counts 21% of 228 drugs, or 47 NMEs, as having had a black-box warning added by the end of their sample period (pp. 11-12).[8]

For approved NMEs submitted in the same period (1981 to 1992), Lasser and colleagues count just 28 (see Table 1, Lasser 2002).[9] This is a difference of 68 percent. Some of the difference could be the more recent data of the FDA, but this seems unlikely to count for all of the difference.

These issues raise important doubts about the quality of the black-box warnings presented by Nardinelli et al as "FDA data."

[8] "Among the pre-PDUFA NMEs, 79 percent survived to the end of the data sample period without new BBWs" (Begosh, et al., 11).

[9] If one focuses on the approval year as opposed to the submission year, it is possible to retrieve an estimate of 30 drugs so coded from Lasser, Table 1, Yet drugs must be coded as to submission date if an accurate coding of pre-PDUFA versus post-PDUFA drugs is to be achieved.

# 11. Reanalysis with Corrected CZA Measure of Black Box Warnings (BBWs), and Analyses Combining Corrected CZA Measure with Nardinelli et al Measure.

### 11.1.1 Combined Measure with Corrections for Carpenter-Zucker-Avorn (CZA) errors.

We first generated combined measure as of August 2005, but corrected for three NMEs that represent CZA error (fondaparinux sodium, tinidazole, oxaliplatin).

```
. gen  CZAFDAbbw_august2005_corrected =  CZAFDAcombobbw_august2005

. replace  CZAFDAbbw_august2005_corrected = 0 if(ndanum_fda == 21345)
(1 real change made) {THIS IS FONDAPARINUX SODIUM (ARIXTRA)}

. replace  CZAFDAbbw_august2005_corrected = 0 if(ndanum_fda == 21618)
(1 real change made) {THIS IS TINIDAZOLE (TINDAMAX)}

. replace  CZAFDAbbw_august2005_corrected = 0 if(ndanum_fda == 21492)
(1 real change made) {THIS IS OXALIPLATIN (ELOXATIN)}
```

A cross-tabulation of this measure upon the FDA's deadline approval measure, using the FDA's 314 NMEs, yields the following:

```
. tab  CZAFDAbbw_august2005_corrected pred01fda, exact

CZAFDAbbw_ |
august2005 |       pred01fda
_corrected |         0          1 |     Total
-----------+----------------------+----------
         0 |       217         76 |       293
         1 |         9         12 |        21
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.004
   1-sided Fisher's exact =                 0.004
```

To generate a shorter name for this variable, to be used in LogXact8 (which has max 9 characters in variable names), we used the following code:

```
. gen  combcorr1 =  CZAFDAbbw_august2005_corrected
```

This variable is used as the dependent variable in the exact logistic regressions on the following page.

### 11.1.2 Exact Logistic Regression on Combined CZA-FDA Measure, dropping Erroneous CZA Positive Codings, stop coding August 2005

## Binary Regression

regression (type=logit, model(combcorr1 = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

**Basic Information**

| | |
|---|---|
| **Data file** | combocorrectbbws20080513.csv |
| **Model** | combcorr1(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

**Summary Statistics**

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 26.23 | 21 | 0.1977 |
| **Likelihood Ratio** | 289.5 | 3 | 1.244e-009 |

**Parameter Estimates**

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.05751 | NA | Asymptotic | 0.004505 | 0.7342 | 0.02797 |
| | | | | Asymptotic(Profile) | 0.004188 | 0.7388 | |
| **subyrctr** | PMLE | 0.9855 | NA | Asymptotic | 0.8545 | 1.136 | 0.8403 |
| | | | | Asymptotic(Profile) | 0.85 | 1.136 | |
| | CMLE | 0.9832 | NA | Exact | 0.8447 | 1.139 | 0.8561 |
| **pred01fda** | PMLE | 3.802 | NA | Asymptotic | 1.551 | 9.319 | 0.003502 |
| | | | | Asymptotic(Profile) | 1.555 | 9.594 | |
| | CMLE | 3.851 | NA | Exact | 1.4 | 11 | 0.007451 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

This OR of 3.8 is substantial. It is 0.6 units below the OR we originally reported (see Figure 2), but the lower CI on the OR is also 0.2 units above the lower CI reported in the paper (1.2) and the associated exact p-value is lower (= 0.007).

### 11.1.3 Random Effects Logistic Regression on Combined CZA-FDA Measure, dropping Erroneous CZA Positive Codings, stop coding August 2005

Results for FDA Deadline Approval Measure highlighted in yellow.

```
. xtlogit  CZAFDAbbw_august2005_corrected subyrctr pred01fda  hhospdisc hhosleng, re
i(discode) or

Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      9.24
Log likelihood  = -68.889417                    Prob > chi2        =    0.0555

------------------------------------------------------------------------------
CZAFDAbbw_~d |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .9430763   .0865306    -0.64   0.523     .7878546    1.128879
   pred01fda |   5.729092   3.407662     2.93   0.003      1.78563    18.38147
   hhospdisc |   1.000001   2.09e-06     0.37   0.709     .9999967    1.000005
    hhosleng |   1.051545   .0643333     0.82   0.411     .9327208    1.185508
-------------+----------------------------------------------------------------
    /lnsig2u |    .848002   .4883908                     -.1092263     1.80523
-------------+----------------------------------------------------------------
     sigma_u |   1.528063   .3731459                      .9468514    2.466044
         rho |   .4151184   .1185789                      .2141526    .6489399
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     5.55 Prob >= chibar2 = 0.009
```

.

This OR is larger than that reported in the paper (5.7 vs 4.4), and the lower limit of the CI is higher.

### 11.2.1 Combined Measure with Corrections, Drop Entecavir and Tiprinavir from Measure.

We then generated a more conservative combined measure, dropping 2 more NMEs that are clearly postmarket BBWs but for which *Physicians' Desk Reference* has labeling revision after our data collection stopped in August 2005. Put differently, we recoded Entecavir and Tiprinavir as not having had BBWs added postmarket, even though BBWs have been added.

```
. gen  CZAFDAbbw_august2005_corrected2 =   CZAFDAbbw_august2005_corrected

. replace  CZAFDAbbw_august2005_corrected2 = 0 if(ndanum_fda == 21797)
(1 real change made) {THIS IS ENTECAVIR}

. replace  CZAFDAbbw_august2005_corrected2 = 0 if(ndanum_fda == 21814)
(1 real change made) {THIS IS TIPRINAVIR}
```

```
. tab  CZAFDAbbw_august2005_corrected2 pred01fda, exact

CZAFDAbbw_ |
august2005 |
_corrected |       pred01fda
         2 |         0          1 |     Total
-----------+----------------------+----------
         0 |       217         78 |       295
         1 |         9         10 |        19
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.031
   1-sided Fisher's exact =                 0.017
```

To generate a shorter name for this variable, to be used in LogXact8 (which has max 9 characters in variable names), we used the following code:

```
. gen bbw0805_corr2 =  CZAFDAbbw_august2005_corrected2
```

This variable is used as the dependent variable in the exact logistic regressions on the following page.

### 11. 2. 2. Exact Logistic Regression on Combined Measure with Corrections, omitting Entecavir and Tiprinavir from Measure, Using FDA's NMEs and FDA's Deadline Approval Measure

## Binary Regression

regression (type=logit, model(bbw0805_co = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

**Basic Information**

| | |
|---|---|
| **Data file** | BBWchecks-20080528.csv |
| **Model** | bbw0805_co(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

**Summary Statistics**

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 26.33 | 21 | 0.1943 |
| **Likelihood Ratio** | 298.4 | 3 | 1.581e-009 |

**Parameter Estimates**

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.179 | NA | Asymptotic | 0.01242 | 2.58 | 0.2063 |
| | | | | Asymptotic(Profile) | 0.01187 | 2.754 | |
| **subyrctr** | PMLE | 0.922 | NA | Asymptotic | 0.7901 | 1.076 | 0.3021 |
| | | | | Asymptotic(Profile) | 0.7825 | 1.073 | |
| | CMLE | 0.9175 | NA | Exact | 0.7753 | 1.075 | 0.3052 |
| **pred01fda** | PMLE | 3.383 | NA | Asymptotic | 1.333 | 8.588 | 0.01034 |
| | | | | Asymptotic(Profile) | 1.322 | 8.791 | |
| | CMLE | 3.406 | NA | Exact | 1.169 | 10.11 | 0.02308 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

The OR is still above 3 and is still statistically significant using an exact distribution. However, it is 1 unit lower than reported in the paper, and the lower bound of the CI is 0.05 units lower.

### 11. 2. 3. Random-Effects Logistic Regression on Combined Measure with Corrections, Drop Entecavir and Tiprinavir from Measure, Using FDA's NMEs and FDA's Deadline Approval Measure

Results for FDA Deadline Approval Measure highlighted in yellow.

```
. xtlogit  bbw0805_corr2 subyrctr pred01fda  hhospdisc hhosleng, re i(discode) or


Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      8.17
Log likelihood  = -66.108957                    Prob > chi2        =    0.0857

------------------------------------------------------------------------------
bbw0805_co~2 |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .8884057   .0830225    -1.27   0.205      .739717    1.066982
   pred01fda |   4.525702   2.597366     2.63   0.009     1.469498    13.93808
   hhospdisc |   1.000001   1.86e-06     0.41   0.680     .9999971    1.000004
    hhosleng |   1.049108   .0559989     0.90   0.369      .944898     1.16481
-------------+----------------------------------------------------------------
    /lnsig2u |   .3723609   .5647479                     -.7345247    1.479247
-------------+----------------------------------------------------------------
     sigma_u |    1.20464   .3401589                      .6926279    2.095146
         rho |    .306085   .1199508                      .1272637    .5716041
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     2.56 Prob >= chibar2 = 0.055

.
```

This OR of 4.53 is very close to (though slightly larger than) that reported in Figure 2 of the paper and the lower bound of the CI is also slightly larger than that reported in Figure 2 of the paper.

# 12. Results for Combined "Withdrawal or Black-Box Warning" Measure

**12.1.1.** Generate Combined SBW and BBW Measures, Using Corrected BBW Measures as Above.

```
. gen  sbworbbw_fda0805andCZA_correct1 =  0

. replace  sbworbbw_fda0805andCZA_correct1 = 1 if( sbwfdas05 == 1)
(10 real changes made)

. replace  sbworbbw_fda0805andCZA_correct1 = 1 if(  sbwcza == 1)
(3 real changes made)

. replace  sbworbbw_fda0805andCZA_correct1 = 1 if(
CZAFDAbbw_august2005_corrected == 1)
(14 real changes made)
```

This produces the following list of drugs that had either a safety-based withdrawal or a postmarket black-box warning.

```
. list ndanum_fda  genernam_fda pred01fda if(sbworbbw_fda0805andCZA_correct1 == 1)
     +-------------------------------------------------------------+
     | ndanum~a                          genernam_fda   pred01~a |
     |-------------------------------------------------------------|
  6. |    21449                   Adefovir Dipivoxil          1 |
  7. |    20760              Alatrofloxacin Mesylate          1 |
 13. |    21107              Alosetron Hydrochloride          0 |
 42. |    20535                     Bromfenac Sodium          0 |
 47. |    20896                         Capecitabine          1 |
     |-------------------------------------------------------------|
 52. |    20998                            Celecoxib          1 |
 53. |    20740                  Cerivastatin Sodium          1 |
 59. |    20822              Citalopram Hydrobromide          0 |
 66. |    20430                    Danaparoid Sodium          0 |
 82. |    21427             Duloxetine Hydrochloride          0 |
     |-------------------------------------------------------------|
 87. |    21500                          Emtricitabine          1 |
 90. |    21797                              Entecavir          1 |
129. |    20695          Grepafloxacin Hydrochloride          1 |
152. |    20564                            Lamivudine          1 |
160. |    20315   Levomethadyl Acetate Hydrochloride          0 |
     |-------------------------------------------------------------|
172. |    20689           Mibefradil Dihydrochloride          0 |
177. |    20415                           Mirtazapine          0 |
188. |    20169                            Nilutamide          0 |
226. |    20984                 Rapacuronium Bromide          0 |
238. |    21042                              Rofecoxib          1 |
     |-------------------------------------------------------------|
245. |    20628                            Saquinavir          0 |
269. |    21356        Tenofovir Disoproxil Fumarate          1 |
278. |    21814                            Tipranavir          1 |
281. |    20697                             Tolcapone          0 |
292. |    20720                          Troglitazone          1 |
     |-------------------------------------------------------------|
294. |    20759              Trovafloxacin Mesylate          1 |
299. |    21341                            Valdecoxib          1 |
     +-------------------------------------------------------------+
```

**12.1.2.** Cross-Tabulation with Fisher's Exact Test – Combined SBW and BBW Measures, Using Corrected BBW Measures, Using FDA's NMEs and FDA's Deadline Approval Measure

```
. tab  sbworbbw_fda0805andCZA_correct1 pred01fda, exact

sbworbbw_f |
da0805andC |
ZA_correct |       pred01fda
         1 |         0          1 |     Total
-----------+----------------------+----------
         0 |       214         73 |       287
         1 |        12         15 |        27
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.003
   1-sided Fisher's exact =                 0.002
```

To generate a shorter name for this variable, to be used in LogXact8 (which has max 9 characters in variable names), we used the following code:

```
. gen  combcom1 =   sbworbbw_fda0805andCZA_correct1
```

This variable is used as the dependent variable in the exact logistic regressions on the following page.

### 12.1.3. Exact Logistic Regression – Combined SBW and BBW Measures, Using Corrected BBW Measures, Using FDA's NMEs and FDA's Deadline Approval Measure

## Binary Regression

regression (type=logit, model(combcom1 = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

**Basic Information**

| | |
|---|---|
| **Data file** | combocorrectSBWorBBW-20080513.csv |
| **Model** | combcom1(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

**Summary Statistics**

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 26.22 | 21 | 0.1982 |
| **Likelihood Ratio** | 262 | 3 | 1.093e-009 |

**Parameter Estimates**

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.1681 | NA | Asymptotic | 0.01688 | 1.675 | 0.1284 |
| | | | | Asymptotic(Profile) | 0.0164 | 1.707 | |
| **subyrctr** | PMLE | 0.941 | NA | Asymptotic | 0.8251 | 1.073 | 0.365 |
| | | | | Asymptotic(Profile) | 0.8208 | 1.071 | |
| | CMLE | 0.9384 | NA | Exact | 0.8161 | 1.073 | 0.3692 |
| **pred01fda** | PMLE | 3.898 | NA | Asymptotic | 1.737 | 8.747 | 0.0009725 |
| | | | | Asymptotic(Profile) | 1.743 | 8.908 | |
| | CMLE | 3.932 | NA | Exact | 1.602 | 9.883 | 0.002076 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

This OR of 3.9 is slightly lower than that reported in Figure 2 of the paper; the lower bound of the CI is slightly higher than reported in Figure 2 of the paper (that is, the result is more statistically significant than the result originally reported).

### 12.1.4. Random-Effects Logistic Regression – Combined SBW and BBW Measures, Using Corrected BBW Measures, Using FDA's NMEs and FDA's Deadline Approval Measure

Results for FDA Deadline Approval Measure in yellow.

```
. xtlogit  sbworbbw_fda0805andCZA_correct1 subyrctr pred01fda   hhospdisc hhosleng, re
i(discode) or


Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =     11.33
Log likelihood  = -83.820375                    Prob > chi2        =    0.0231

------------------------------------------------------------------------------
sbworbbw_f~1 |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .9112509   .0737148    -1.15   0.251      .777644    1.067813
   pred01fda |   5.101227   2.574711     3.23   0.001     1.896937    13.71818
   hhospdisc |   1.000001   1.63e-06     0.85   0.394     .9999982    1.000005
    hhosleng |    1.01765   .0567741     0.31   0.754     .9122423    1.135236
-------------+----------------------------------------------------------------
    /lnsig2u |   .4489665   .4762334                     -.4844338    1.382367
-------------+----------------------------------------------------------------
     sigma_u |   1.251676   .2980449                      .7848859    1.996076
         rho |    .322593   .1040697                      .1577213     .547734
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     4.03 Prob >= chibar2 = 0.022
```

.

This OR of 5.1 is slightly higher than that reported in Figure 2 of the paper; the lower bound of the CI is slightly higher than reported in Figure 2 of the paper (that is, the result is more statistically significant than the result originally reported).

**12.2.1** Generate Combined SBW and BBW Measures, Using Corrected BBW Measures, omitting Entecavir and Tiprinavir from Measure, Using FDA's NMEs and FDA's Deadline Approval Measure

```
. gen sbworbbw_fda0805andCZA_correct2 =  0

. replace sbworbbw_fda0805andCZA_correct2 = 1 if(sbwfdas05 == 1)
(10 real changes made)

. replace sbworbbw_fda0805andCZA_correct2 = 1 if(sbwcza == 1)
(3 real changes made)

. replace  sbworbbw_fda0805andCZA_correct2 = 1
if(CZAFDAbbw_august2005_corrected2 == 1)
(12 real changes made)

. list ndanum_fda  genernam_fda pred01fda if(sbworbbw_fda0805andCZA_correct2
== 1)
```

| | ndanum~a | genernam_fda | pred01~a | pred01~A |
|---|---|---|---|---|
| 6. | 21449 | Adefovir Dipivoxil | 1 | 1 |
| 7. | 20760 | Alatrofloxacin Mesylate | 1 | 1 |
| 13. | 21107 | Alosetron Hydrochloride | 0 | 0 |
| 42. | 20535 | Bromfenac Sodium | 0 | 0 |
| 47. | 20896 | Capecitabine | 1 | 1 |
| 52. | 20998 | Celecoxib | 1 | 1 |
| 53. | 20740 | Cerivastatin Sodium | 1 | 1 |
| 59. | 20822 | Citalopram Hydrobromide | 0 | 0 |
| 66. | 20430 | Danaparoid Sodium | 0 | 0 |
| 82. | 21427 | Duloxetine Hydrochloride | 0 | 0 |
| 87. | 21500 | Emtricitabine | 1 | 1 |
| 129. | 20695 | Grepafloxacin Hydrochloride | 1 | 1 |
| 152. | 20564 | Lamivudine | 1 | 1 |
| 160. | 20315 | Levomethadyl Acetate Hydrochloride | 0 | 0 |
| 172. | 20689 | Mibefradil Dihydrochloride | 0 | 0 |
| 177. | 20415 | Mirtazapine | 0 | 0 |
| 188. | 20169 | Nilutamide | 0 | 0 |
| 226. | 20984 | Rapacuronium Bromide | 0 | 0 |
| 238. | 21042 | Rofecoxib | 1 | 1 |
| 245. | 20628 | Saquinavir | 0 | 0 |
| 269. | 21356 | Tenofovir Disoproxil Fumarate | 1 | 1 |
| 281. | 20697 | Tolcapone | 0 | 0 |
| 292. | 20720 | Troglitazone | 1 | 1 |
| 294. | 20759 | Trovafloxacin Mesylate | 1 | 1 |
| 299. | 21341 | Valdecoxib | 1 | 1 |

**12.2.2.** Cross-Tabulation with Fisher's Exact Test – Combined SBW and BBW Measures, Using Corrected BBW Measures, Drop Entecavir and Tiprinavir from Measure, Using FDA's NMEs and FDA's Deadline Approval Measure

```
. tab sbworbbw_fda0805andCZA_correct2 pred01fda, exact

sbworbbw_f |
da0805andC |
ZA_correct |       pred01fda
         2 |         0          1 |     Total
-----------+----------------------+----------
         0 |       214         75 |       289
         1 |        12         13 |        25
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.009
   1-sided Fisher's exact =                 0.007
```

To generate a shorter name for this variable, to be used in LogXact8 (which has max 9 characters in variable names), we used the following code:

```
. gen WOW0805_corr2 =   sbworbbw_fda0805andCZA_correct2
```

This variable is used as the dependent variable in the exact logistic regressions on the following page.

**12.2.3.** Exact Logistic Regression – Combined SBW and BBW Measures, Using Corrected BBW Measures, Drop Entecavir and Tiprinavir from Measure, Using FDA's NMEs and FDA's Deadline Approval Measure

# Binary Regression

regression (type=logit, model(wow0805_co = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

## Basic Information

| | |
|---|---|
| **Data file** | BBWchecks-20080528.csv |
| **Model** | WOW0805_co(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

## Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 26.43 | 21 | 0.1906 |
| **Likelihood Ratio** | 270.8 | 3 | 1.396e-009 |

## Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| **Model Term** | **Type** | **Odds Ratio** | **SE(Odds)** | **Type** | **Lower** | **Upper** | **P-Value** |
| **%Const** | PMLE | 0.4475 | NA | Asymptotic | 0.04026 | 4.974 | 0.5129 |
| | | | | Asymptotic(Profile) | 0.04 | 5.289 | |
| **subyrctr** | PMLE | 0.8876 | NA | Asymptotic | 0.7704 | 1.023 | 0.0988 |
| | | | | Asymptotic(Profile) | 0.7641 | 1.019 | |
| | CMLE | 0.8834 | NA | Exact | 0.7581 | 1.02 | 0.0929 |
| **pred01fda** | PMLE | 3.559 | NA | Asymptotic | 1.543 | 8.207 | 0.002899 |
| | | | | Asymptotic(Profile) | 1.54 | 8.33 | |
| | CMLE | 3.579 | NA | Exact | 1.401 | 9.266 | 0.006492 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

This OR of 3.6 is 0.8 units lower than that reported in Figure 2 of the paper; the lower bound of the CI is nearly identical with the one reported in Figure 2 of the paper.

**12.2.4.** Random Effects Logistic Regression – Combined SBW and BBW Measures, Using Corrected BBW Measures, Drop Entecavir and Tiprinavir from Measure, Using FDA's NMEs and FDA's Deadline Approval Measure

```
. xtlogit  WOW0805_corr2 subyrctr pred01fda  hhospdisc hhosleng, re i(discode) or

Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =     10.84
Log likelihood  = -80.770639                    Prob > chi2        =    0.0284

------------------------------------------------------------------------------
WOW0805_co~2 |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .8662177   .0710962    -1.75   0.080     .7375022    1.017398
   pred01fda |   4.204735   2.040519     2.96   0.003     1.624271    10.88476
   hhospdisc |   1.000001   1.46e-06     0.87   0.387     .9999984    1.000004
    hhosleng |   1.018908    .049659     0.38   0.701     .9260825    1.121039
-------------+----------------------------------------------------------------
    /lnsig2u |  -.1489429   .5819359                     -1.289516    .9916306
-------------+----------------------------------------------------------------
     sigma_u |    .928234   .2700864                      .5247894    1.641836
         rho |   .2075445   .0957109                      .0772463    .4503598
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     1.57 Prob >= chibar2 = 0.105
```

.

This OR of 4.2 is slightly lower than that reported in Figure 2 of the paper; the lower bound of the CI is slightly above that reported in Figure 2 of the paper.

## 12.3 Combined Measure Accepting All of FDA's Positive Coding Decisions and Coding Through December 2007

We then took data through December 2007, combined CZA and FDA Measures for both SBWs and BBWs, and dropped erroneous BBW codings from Carpenter-Zucker-Avorn (fondaparinux sodium, oxaliplatin, tinidazole).

```
. gen CZAFDAcomboSBWorBBW_dec2007 = 0

. replace CZAFDAcomboSBWorBBW_dec2007 = 1 if(sbwcza == 1)
(11 real changes made) {This adds the 11 NMEs with SBWs from the original
paper.}

. replace CZAFDAcomboSBWorBBW_dec2007 = 1 if(sbwfda08 == 1)
(3 real changes made) {This adds the 3 NMEs coded as SBWs by FDA that are not
in the CZA list - Zelnorm, Orlaam, and alosetron.}

. replace CZAFDAcomboSBWorBBW_dec2007 = 1 if(bbwfda08 == 1)
(22 real changes made) {This adds the 22 NMEs that FDA has as BBWS that are
not already coded as SBWs.}

. replace CZAFDAcomboSBWorBBW_dec2007 = 1 if(bbwcza == 1)
(8 real changes made) {This adds the NMEs that CZA originally coded as BBWs
that were not already coded as SBWS and which the FDA had not coded as BBWs.}

. replace CZAFDAcomboSBWorBBW_dec2007 = 0 if(ndanum_fda == 21345)
(1 real change made) {THIS DROPS FONDAPARINUX SODIUM}

. replace CZAFDAcomboSBWorBBW_dec2007 = 0 if(ndanum_fda == 21618)
(1 real change made) {THIS DROPS TINIDAZOLE}

. replace CZAFDAcomboSBWorBBW_dec2007 = 0 if(ndanum_fda == 21492)
(1 real change made) {THIS DROPS OXALIPLATIN}



. list ndanum_fda genernam_fda pred01fda if(CZAFDAcomboSBWorBBW_dec2007 == 1)

     +-----------------------------------------------------------+
     | ndanum~a                          genernam_fda   pred01~a |
     |-----------------------------------------------------------|
  6. |    21449                   Adefovir Dipivoxil          1 |
  7. |    20760              Alatrofloxacin Mesylate          1 |
 13. |    21107              Alosetron Hydrochloride          0 |
 23. |    21436                           Aripiprazole          0 |
 27. |    21411            Atomoxetine Hydrochloride          0 |
     |-----------------------------------------------------------|
 42. |    20535                       Bromfenac Sodium          0 |
 47. |    20896                           Capecitabine          1 |
 52. |    20998                              Celecoxib          1 |
 53. |    20740                  Cerivastatin Sodium          1 |
 59. |    20822              Citalopram Hydrobromide          0 |
```

| | | | |
|---|---|---|---|
| 66. | 20430 | Danaparoid Sodium | 0 |
| 82. | 21427 | Duloxetine Hydrochloride | 0 |
| 87. | 21500 | Emtricitabine | 1 |
| 90. | 21797 | Entecavir | 1 |
| 119. | 20937 | Gadoversetamide | 0 |
| 129. | 20695 | Grepafloxacin Hydrochloride | 1 |
| 152. | 20564 | Lamivudine | 1 |
| 160. | 20315 | Levomethadyl Acetate Hydrochloride | 0 |
| 167. | 20938 | Meloxicam | 0 |
| 172. | 20689 | Mibefradil Dihydrochloride | 0 |
| 177. | 20415 | Mirtazapine | 0 |
| 188. | 20169 | Nilutamide | 0 |
| 193. | 20592 | Olanzapine | 0 |
| 213. | 21064 | Perflutren Lipid Microsphere | 0 |
| 214. | 21302 | Pimecrolimus | 0 |
| 215. | 21073 | Pioglitazone Hydrochloride | 1 |
| 222. | 20639 | Quetiapine Fumarate | 0 |
| 224. | 20815 | Raloxifene Hydrochloride | 1 |
| 226. | 20984 | Rapacuronium Bromide | 0 |
| 238. | 21042 | Rofecoxib | 1 |
| 241. | 21071 | Rosiglitazone Maleate | 1 |
| 245. | 20628 | Saquinavir | 0 |
| 265. | 21200 | Tegaserod Maleate | 0 |
| 266. | 21144 | Telithromycin | 0 |
| 269. | 21356 | Tenofovir Disoproxil Fumarate | 1 |
| 278. | 21814 | Tipranavir | 1 |
| 281. | 20697 | Tolcapone | 0 |
| 292. | 20720 | Troglitazone | 1 |
| 294. | 20759 | Trovafloxacin Mesylate | 1 |
| 299. | 21341 | Valdecoxib | 1 |
| 311. | 20825 | Ziprasidone Hydrochloride | 0 |

.

Adopting this measure accepts virtually all the assumptions made in the FDA's April 2008 argument. All of the FDA's April 2008 coding decisions are used, the coding is not stopped in August 2005 but runs through December 2007 (long after analysis had stopped for the original paper), and only eight additional drugs (adefovir pipivoxil, alatrofloxacin, emtricitabine, entecavir, tenofovir disoproxil, tipranavir, tolcapone, and trovafloxacin) are coded as having had postmarket regulatory events.

Even with all of these assumptions made, there is a statistically significant difference between just-before-deadline approvals and all other drugs in the postmarket regulatory problems they experience.

**12.3.1 Cross Tabulation with Fisher's Exact Test** – Taking data up through December 2007, Combine CZA and FDA Measures for both SBWs and BBWs, and dropping CZA's erroneous BBW codings (fondaparinux sodium, oxaliplatin, tinidazole).

```
. tab  CZAFDAcomboSBWorBBW_dec2007 pred01fda, exact

CZAFDAcomb |
oSBWorBBW_ |       pred01fda
   dec2007 |         0          1 |     Total
-----------+----------------------+----------
         0 |       203         70 |       273
         1 |        23         18 |        41
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.024
   1-sided Fisher's exact =                 0.015
```

To generate a shorter name for this variable, to be used in LogXact8 (which has max 9 characters in variable names), we used the following code:

```
. gen SBWBBWd07 =  CZAFDAcomboSBWorBBW_dec2007
```

This variable is used as the dependent variable in the exact logistic regressions on the following page.

**12.3.2 Exact Logistic Regression – Taking data up through December 2007**, Combine CZA and FDA Measures for both SBWs and BBWs, and dropping CZA's erroneous BBW codings (fondaparinux, oxaliplatin, tinidazole).

## Binary Regression

regression (type=logit, model(sbwbbwd07 = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

### Basic Information

| | |
|---|---|
| **Data file** | combocorrectSBWorBBW-dec2007-20080513.csv |
| **Model** | SBWBBWd07(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

### Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 26.22 | 21 | 0.1982 |
| **Likelihood Ratio** | 197.4 | 3 | 9.234e-010 |

### Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.1371 | NA | Asymptotic | 0.02025 | 0.928 | 0.0417 |
| | | | | Asymptotic(Profile) | 0.01978 | 0.92 | |
| **subyrctr** | PMLE | 0.9908 | NA | Asymptotic | 0.8897 | 1.103 | 0.8657 |
| | | | | Asymptotic(Profile) | 0.8881 | 1.102 | |
| | CMLE | 0.9897 | NA | Exact | 0.8854 | 1.104 | 0.8777 |
| **pred01fda** | PMLE | 2.295 | NA | Asymptotic | 1.162 | 4.533 | 0.01673 |
| | | | | Asymptotic(Profile) | 1.155 | 4.52 | |
| | CMLE | 2.287 | NA | Exact | 1.079 | 4.798 | 0.02995 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:03**

Even using this measure, *which again as constructed accepts all of the coding decisions in the FDA's April 2008 argument*, there is a statistically significant difference between deadline approvals and other NMEs. The OR is smaller than reported in the paper (2.3 versus 4.4), but it is statistically significant with an exact p-value of 0.03. However, it is not clear that all of the assumptions made by Nardinelli et al should be accepted, for reasons stated above.

**12.3.3 Random-Effects Logistic Regression – Taking data up through December 2007**, Combine CZA and FDA Measures for both SBWs and BBWs, and dropping CZA's erroneous BBW codings (fondaparinux sodium, oxaliplatin, tinidazole).

Results for FDA Deadline Approval Measure highlighted in yellow.

```
. xtlogit  CZAFDAcomboSBWorBBW_dec2007 subyrctr pred01fda  hhospdisc hhosleng, re
i(discode) or

Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      8.00
Log likelihood  = -111.61559                    Prob > chi2        =    0.0916

------------------------------------------------------------------------------
CZ~W_dec2007 |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .9654842    .069295    -0.49   0.625     .8387886    1.111317
   pred01fda |   3.425254   1.649158     2.56   0.011     1.333106    8.800779
   hhospdisc |   1.000002   1.77e-06     1.08   0.280     .9999984    1.000005
    hhosleng |   1.030768   .0606853     0.51   0.607     .9184329    1.156843
-------------+----------------------------------------------------------------
    /lnsig2u |   1.143569   .4641163                      .2339177     2.05322
-------------+----------------------------------------------------------------
     sigma_u |   1.771425   .4110737                      1.124073    2.791587
         rho |   .4881826   .1159643                      .2774933    .7031561
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =    10.92 Prob >= chibar2 = 0.000
```

Again using a combined measure *which accepts all of the positive coding decisions in the FDA's April 2008 argument*, there is a statistically significant difference between deadline approvals and other NMEs. The OR is one unit less than reported in the paper (3.4 versus 4.4), but is large ( > 3) and is statistically significant with a p-value of 0.01.

# 13. Re-Analysis of Association between Deadline Approvals and Black-Box Warnings, Using FDA NMEs, FDA Deadline Approval Measure, and Nardinelli et al Black-Box Warning Measures

In this section we examine what happens to the analysis when we rely entirely on the FDA's BBW codings but stop coding earlier. We use the 314 NMEs posted in the FDA's April 2008 data, combined with the FDA's "deadline approval" measure, and re-examine the pattern of postmarket black-box warnings. For the sake of hypothesis and demonstration, we do not correct here for clear FDA errors identified in Section 9 (above). For reference purposes, here is the replicated cross-tabulation result from the FDA's communication.

```
. tab  bbwfda08  pred01fda, exact

           |       pred01fda
  bbwFDA08 |         0          1 |     Total
-----------+----------------------+----------
         0 |       207         78 |       285
         1 |        19         10 |        29
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.395
   1-sided Fisher's exact =                 0.270
```

We now discuss the variable results of statistical analysis when coding of these warnings is stopped in August 2005 (when we stopped coding) or after Vioxx (when it appears that the FDA began to change its policy for issuing black-box warnings).

### 13.2 Using the FDA's BBW Measure, Stopping Coding in August 2005

The following is the list of NMEs with a post-market BBW as coded by the FDA, if coding is stopped in August 2005. Notice that we have not recoded saquinavir (see Section 9.2 above).

```
. list  ndanum_fda  genernam_fda  bbwdate_fda if( bbwfdas05 == 1)

     +-------------------------------------------------+
     | ndanum~a               genernam_fda   bbwdate~a |
     |-------------------------------------------------|
  2. |    20998                  Celecoxib   29-Jul-05 |
  3. |    21341                 Valdecoxib   24-Nov-04 |
 14. |    20535           Bromfenac Sodium   31-Mar-98 |
 33. |    20896               Capecitabine    7-Sep-01 |
 54. |    20169                 Nilutamide   29-Sep-00 |
     |-------------------------------------------------|
104. |    20430          Danaparoid Sodium   30-Jan-98 |
108. |    20564                 Lamivudine   15-Dec-97 |
114. |    20628                 Saquinavir   14-Nov-00 |
137. |    20759     Trovafloxacin Mesylate    9-Jun-99 |
138. |    20760    Alatrofloxacin Mesylate    9-Jun-99 |
     |-------------------------------------------------|
175. |    20822    Citalopram Hydrobromide   18-Feb-05 |
176. |    20415                Mirtazapine   12-Jan-05 |
177. |    21427   Duloxetine Hydrochloride   18-Feb-05 |
221. |    20697                  Tolcapone   16-Nov-98 |
232. |    20720               Troglitazone   15-Dec-97 |
     |-------------------------------------------------|
284. |    21107    Alosetron Hydrochloride    7-Jun-02 |
     +-------------------------------------------------+
```

.

### 13.2 Using the FDA's BBW Measure, Stopping Coding in August 2005 (cont.)

If we then assume that the FDA's coding is correct (and we have already argued that it is not reliable; see Sections 9 and 10), and we analyze the warnings data as stopped in August 2005, we get the following two-way tabulation.

```
. tab  bbwfdas05 pred01fda, exact
           |       pred01fda
 bbwFDAs05 |         0          1 |     Total
-----------+----------------------+----------
         0 |       217         81 |       298
         1 |         9          7 |        16
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.160
   1-sided Fisher's exact =                 0.126
```

This two-way tabulation yields an exact p-value of 0.16, though the exact p-value is less than half that of the original FDA calculation (0.395). An exact logistic regression yields an odds ratio of 2.6 with a p-value of 0.14. However, a random-effects logistic regression analysis yields an odds-ratio of 3.4 with a p-value of less than 0.05.

## 13.2 Exact Logistic Regression Analysis of Nardinelli BBW Measure, stopping Coding in August 2005

# Binary Regression

regression (type=logit, model(bbwfdas05 = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

### Basic Information

| | |
|---|---|
| **Data file** | bbwdump20080412.csv |
| **Model** | bbwfdas05(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

### Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 21.16 | 21 | 0.4492 |
| **Likelihood Ratio** | 314.6 | 3 | 1.619e-009 |

### Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.7845 | NA | Asymptotic | 0.03945 | 15.6 | 0.8736 |
| | | | | Asymptotic(Profile) | 0.03923 | 18.79 | |
| **subyrctr** | PMLE | 0.843 | NA | Asymptotic | 0.7037 | 1.01 | 0.06369 |
| | | | | Asymptotic(Profile) | 0.6906 | 1.003 | |
| | CMLE | 0.8347 | NA | Exact | 0.6798 | 1.004 | 0.05556 |
| **pred01fda** | PMLE | 2.577 | NA | Asymptotic | 0.9367 | 7.092 | 0.06675 |
| | | | | Asymptotic(Profile) | 0.9049 | 7.15 | |
| | CMLE | 2.552 | NA | Exact | 0.7593 | 8.268 | 0.1396 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

### 13.2 Using the Nardinelli et al BBW Measure, Stopping Coding in August 2005 (cont.)

A random-effects logistic regression that controls for submission year and epidemiological covariates yields an odds ratio of 3.4 which is statistically significant at the 0.05 level. The estimates for the FDA's deadline approval measure are highlighted in yellow.

```
Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      7.39
Log likelihood  = -58.174155                    Prob > chi2        =    0.1165

------------------------------------------------------------------------------
   bbwfdas05 |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .7977957   .0888142    -2.03   0.042     .6414047    .9923188
   pred01fda |   3.394705   2.093189     1.98   0.047     1.013789    11.36727
   hhospdisc |   1.000001   1.91e-06     0.45   0.656     .9999971    1.000005
    hhosleng |   1.041778   .0577726     0.74   0.460     .9344825    1.161393
-------------+----------------------------------------------------------------
    /lnsig2u |   .4309571   .5054874                     -.5597799    1.421694
-------------+----------------------------------------------------------------
     sigma_u |   1.240455   .3135173                      .7558669    2.035715
         rho |   .3186701   .1097511                      .1479681    .5574567
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     3.03 Prob >= chibar2 = 0.041
```

Hence in a controlled statistical analysis, there is a large and statistically differentiable relationship *even if we rely entirely on the problematic data posted by Nardinelli et al.*

### 13.3 Using the Nardinelli et al BBW Measure, Stopping Coding after Vioxx withdrawal (cont.)

If we now use the FDA's BBW measure but stop coding in January 2005 (equivalently, after the Vioxx withdrawal), we get the following list.

```
. list  ndanum_fda genernam_fda  bbwdate_fda if( bbwfdaw05 == 1)

     +-----------------------------------------------+
     | ndanum~a              genernam_fda   bbwdate~a |
     |-----------------------------------------------|
  3. |    21341                Valdecoxib   24-Nov-04 |
 14. |    20535          Bromfenac Sodium   31-Mar-98 |
 33. |    20896              Capecitabine    7-Sep-01 |
 54. |    20169                Nilutamide   29-Sep-00 |
104. |    20430         Danaparoid Sodium   30-Jan-98 |
     |-----------------------------------------------|
108. |    20564                Lamivudine   15-Dec-97 |
114. |    20628                Saquinavir   14-Nov-00 |
137. |    20759    Trovafloxacin Mesylate    9-Jun-99 |
138. |    20760   Alatrofloxacin Mesylate    9-Jun-99 |
221. |    20697                 Tolcapone   16-Nov-98 |
     |-----------------------------------------------|
232. |    20720              Troglitazone   15-Dec-97 |
284. |    21107   Alosetron Hydrochloride    7-Jun-02 |
     +-----------------------------------------------+
```

### 13.3 Using the Nardinelli et al BBW Measure, Stopping Coding After Vioxx Withdrawal (cont.)

```
. tab  bbwfdaw05 pred01fda, exact

           |       pred01fda
 bbwFDAw05 |         0          1 |     Total
-----------+----------------------+----------
         0 |       220         82 |       302
         1 |         6          6 |        12
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.103
   1-sided Fisher's exact =                 0.085
```

This crude two-way cross-tabulation yields an exact p-value of greater than 0.10. An exact logistic regression with one control for submission year yields a *p*-value of 0.08. The more adequately controlled analysis is presented below.

## 13.3 Using the Nardinelli et al BBW Measure, Stopping Coding After Vioxx Withdrawal (cont.)

# Binary Regression

regression (type=logit, model(bbwfdaw05 = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

### Basic Information

| | |
|---|---|
| **Data file** | bbwdump20080412.csv |
| **Model** | bbwfdaw05(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

### Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 22.35 | 21 | 0.3797 |
| **Likelihood Ratio** | 341.4 | 3 | 1.98e-009 |

### Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 1.526 | NA | Asymptotic | 0.04373 | 53.24 | 0.8156 |
| | | | | Asymptotic(Profile) | 0.04459 | 77.33 | |
| **subyrctr** | PMLE | 0.789 | NA | Asymptotic | 0.6331 | 0.9834 | 0.03496 |
| | | | | Asymptotic(Profile) | 0.6118 | 0.973 | |
| | CMLE | 0.7753 | NA | Exact | 0.5954 | 0.9725 | 0.0253 |
| **pred01fda** | PMLE | 3.513 | NA | Asymptotic | 1.121 | 11.01 | 0.03112 |
| | | | | Asymptotic(Profile) | 1.089 | 11.44 | |
| | CMLE | 3.528 | NA | Exact | 0.8824 | 14.21 | 0.0775 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

### 13.3 Using the Nardinelli et al BBW Measure, Stopping Coding after Vioxx withdrawal (cont.)

Yet again, analysis of the data in a random-effects logistic regression with controls for submission year and epidemiological covariates generates a p-value of less than 0.05. The estimates for the FDA's deadline approval measure are highlighted in yellow.

```
Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      8.38
Log likelihood  = -46.283691                    Prob > chi2        =    0.0786

------------------------------------------------------------------------------
   bbwfdaw05 |          OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .7729781   .0953021    -2.09   0.037     .6070448    .9842686
   pred01fda |   3.784404   2.353177     2.14   0.032     1.118697    12.80214
   hhospdisc |   1.000001   1.65e-06     0.44   0.659     .9999975    1.000004
    hhosleng |   1.046485   .0468186     1.02   0.310       .95863    1.142391
-------------+----------------------------------------------------------------
    /lnsig2u |  -3.034237   1.577145                     -6.125384    .0569094
-------------+----------------------------------------------------------------
     sigma_u |    .219343   .1729678                      .0467616    1.028863
         rho |   .0144133   .0224042                      .0006642    .2434351
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.07 Prob >= chibar2 = 0.398
```

**Hence in a controlled statistical analysis, there is a large (OR > 3) and statistically differentiable relationship *even if we rely entirely on the FDA's posted data.*** This relationship is associated with a p = 0.08 estimate in an exact logistic regression and with a p = 0.03 estimate in a random-effects logistic regression. These p-values are far below those of the FDA analysis, and *these analyses abandon our data entirely and assume that the FDA data are correct*.

### 13.4 Use of a Combined BBW Measure, with coding stopped August 1, 2005.

If we create a combined measure, coded 1 if the NME was coded *either* by Carpenter, Zucker and Avorn or as coded by Nardinelli et al as having a black-box warning added, but again stop coding at August 2005, we get the following.

```
. gen CZAFDAcombobbw_august2005 = 0

. replace  CZAFDAcombobbw_august2005 = 1 if( bbwcza == 1)
(14 real changes made)

. replace  CZAFDAcombobbw_august2005 = 1 if(  bbwfdas05 == 1)
(10 real changes made)
```

This recoding produces the following list of BBWs.

```
. list  ndanum_fda  genernam_fda if(  CZAFDAcombobbw_august2005 == 1)

     +-----------------------------------------+
     | ndanum~a                    genernam_fda |
     |-----------------------------------------|
  2. |    20998                       Celecoxib |
  3. |    21341                      Valdecoxib |
 14. |    20535                Bromfenac Sodium |
 33. |    20896                    Capecitabine |
 42. |    21492                     Oxaliplatin |
     |-----------------------------------------|
 54. |    20169                      Nilutamide |
104. |    20430               Danaparoid Sodium |
106. |    21345             Fondaparinux Sodium |
108. |    20564                      Lamivudine |
112. |    21500                    Emtricitabine |
     |-----------------------------------------|
114. |    20628                      Saquinavir |
120. |    21356   Tenofovir Disoproxil Fumarate |
124. |    21814                      Tipranavir |
137. |    20759          Trovafloxacin Mesylate |
138. |    20760         Alatrofloxacin Mesylate |
     |-----------------------------------------|
175. |    20822         Citalopram Hydrobromide |
176. |    20415                     Mirtazapine |
177. |    21427        Duloxetine Hydrochloride |
221. |    20697                       Tolcapone |
232. |    20720                    Troglitazone |
     |-----------------------------------------|
284. |    21107         Alosetron Hydrochloride |
300. |    21797                       Entecavir |
301. |    21449              Adefovir Dipivoxil |
311. |    21618                      Tinidazole |
     +-----------------------------------------+
```

.

### 13.4 Using a Combined Measure, with coding stopped August 1, 2005 (cont.)

If we then analyze this combined measure statistically, using the FDA's pre-deadline approval measure, we get the following results. A two-way cross tabulation with Fisher's exact test produces the following.

```
. tab  CZAFDAcombobbw_august2005 pred01fda, exact

CZAFDAcomb |
obbw_augus |       pred01fda
     t2005 |         0          1 |     Total
-----------+----------------------+----------
         0 |       215         75 |       290
         1 |        11         13 |        24
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.007
   1-sided Fisher's exact =                 0.005
```

## 13.4 Using a Combined Measure, with coding stopped August 1, 2005 (cont.)

An exact logistic regression yields the following.

# Binary Regression

regression (type=logit, model(bbwcombo08 = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

### Basic Information

| | |
|---|---|
| **Data file** | bbwdump20080412.csv |
| **Model** | bbwcombo08(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

### Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 25.25 | 21 | 0.2366 |
| **Likelihood Ratio** | 274 | 3 | 1.425e-009 |

### Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.02426 | NA | Asymptotic | 0.002139 | 0.2752 | 0.002688 |
| | | | | Asymptotic(Profile) | 0.001956 | 0.2669 | |
| **subyrctr** | PMLE | 1.047 | NA | Asymptotic | 0.9169 | 1.195 | 0.4976 |
| | | | | Asymptotic(Profile) | 0.9147 | 1.197 | |
| | CMLE | 1.046 | NA | Exact | 0.911 | 1.201 | 0.5304 |
| **pred01fda** | PMLE | 3.162 | NA | Asymptotic | 1.362 | 7.34 | 0.007376 |
| | | | | Asymptotic(Profile) | 1.359 | 7.467 | |
| | CMLE | 3.182 | NA | Exact | 1.234 | 8.346 | 0.01499 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

### 13.4 Using a Combined Measure, with coding stopped August 1, 2005 (cont.)

A random-effects logistic regression with controls for epidemiological covariates produces the following. The estimates for the FDA's deadline approval measure are highlighted in yellow.

```
Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      9.01
Log likelihood  = -76.257824                    Prob > chi2        =    0.0609

------------------------------------------------------------------------------
CZAFDAc~2005 |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   1.033437   .0869026     0.39   0.696      .8764064    1.218603
   pred01fda |   4.488479   2.493757     2.70   0.007      1.510705    13.33579
   hhospdisc |   1.000001   2.03e-06     0.38   0.704      .9999968    1.000005
    hhosleng |   1.061063    .061535     1.02   0.307       .947059    1.188791
-------------+----------------------------------------------------------------
    /lnsig2u |   .8414595   .4808614                     -.1010114    1.783931
-------------+----------------------------------------------------------------
     sigma_u |   1.523073   .3661934                      .9507485     2.43992
         rho |   .4135309     .11662                      .2155383    .6440722
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     5.96 Prob >= chibar2 = 0.007
```

Hence combining the FDA's codes of before August 2005 with the Carpenter-Zucker-Avorn codes of before August 2005 yields estimated odds ratios of greater than three (3), and in all three tests the *p*-value is below 0.05 for a two-tailed test, and in both regressions the estimated odds ratio is above three (3).

# 14. Re-Analysis of Association between Deadline Approvals and Combined Withdrawal-or-Warning Measure, Using FDA NMEs, FDA Deadline Approval Measure, and FDA Warning Measures

In this section we proceed as we did in Section 7, but focus on the combined "withdrawal or warnings" measure that we used in our paper. Again, for the sake of hypothesis and demonstration, we do not correct here for clear FDA errors identified in Section 9 (above) or in Section 2 (above). If we then proceed according to Carpenter, Zucker and Avorn 2008, and we create a combined withdrawal or black-box warning measure, and <u>if we rely entirely on the FDA's data</u> and stop coding in August 2005, we get the following list of postmarket safety events for NMEs.

```
. list  ndanum_fda genernam_fda sbwdate_fda bbwdate_fda if( sbworbbw_fda0805 == 1)

     +-------------------------------------------------------------------------+
     | ndanum~a                          genernam_fda   sbwdate~a   bbwdate~a |
     |-------------------------------------------------------------------------|
  1. |    21042                             Rofecoxib   30-Sep-04             |
  2. |    20998                             Celecoxib                29-Jul-05 |
  3. |    21341                            Valdecoxib    6-Apr-05   24-Nov-04 |
 14. |    20535                      Bromfenac Sodium   22-Jun-98   31-Mar-98 |
 33. |    20896                          Capecitabine                7-Sep-01 |
     |-------------------------------------------------------------------------|
 54. |    20169                             Nilutamide                29-Sep-00 |
 84. |    20740                  Cerivastatin Sodium    8-Aug-01             |
 95. |    20689           Mibefradil Dihydrochloride    8-Jun-98             |
104. |    20430                    Danaparoid Sodium                30-Jan-98 |
108. |    20564                             Lamivudine                15-Dec-97 |
     |-------------------------------------------------------------------------|
114. |    20628                             Saquinavir                14-Nov-00 |
137. |    20759               Trovafloxacin Mesylate                 9-Jun-99 |
138. |    20760              Alatrofloxacin Mesylate                 9-Jun-99 |
139. |    20695          Grepafloxacin Hydrochloride   27-Oct-99             |
175. |    20822              Citalopram Hydrobromide                18-Feb-05 |
     |-------------------------------------------------------------------------|
176. |    20415                           Mirtazapine                12-Jan-05 |
177. |    21427             Duloxetine Hydrochloride                18-Feb-05 |
182. |    20315   Levomethadyl Acetate Hydrochloride   23-Aug-03             |
206. |    20984                  Rapacuronium Bromide   27-Mar-01             |
221. |    20697                             Tolcapone                16-Nov-98 |
     |-------------------------------------------------------------------------|
232. |    20720                           Troglitazone   22-Mar-00   15-Dec-97 |
284. |    21107             Alosetron Hydrochloride   28-Nov-00    7-Jun-02 |
     +-------------------------------------------------------------------------+
```

### 14.1 Combined Withdrawal and Black-Box Warning Measure, Using FDA Data Only, August 2005 Stop Coding (cont.)

A two-way cross-tabulation yields a *p*-value of 0.08, but an exact logistic regression on the same data (controlling for submission year) yields a *p*-value of 0.04.

```
. tab sbworbbw_fda0805  pred01fda, exact

sbworbbw_f |       pred01fda
    da0805 |         0          1 |     Total
-----------+----------------------+----------
         0 |       214         78 |       292
         1 |        12         10 |        22
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.082
   1-sided Fisher's exact =                 0.054
```

An exact logistic regression yields the following results.

## Binary Regression

regression (type=logit, model(sbworbbw_f = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, profile=yes, outtype=odds);

**Basic Information**

| | |
|---|---|
| **Data file** | bbwdump20080412-2.csv |
| **Model** | sbworbbw_f(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

**Summary Statistics**

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 22.5 | 21 | 0.3714 |
| **Likelihood Ratio** | 285.7 | 3 | 1.657e-009 |

**Parameter Estimates**

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | MLE | 1.676 | NA | Asymptotic | 0.1088 | 25.82 | 0.7114 |
| | | | | Asymptotic(Profile) | 0.1154 | 28.71 | |
| **subyrctr** | MLE | 0.8155 | NA | Asymptotic | 0.6901 | 0.9638 | 0.0167 |
| | | | | Asymptotic(Profile) | 0.6819 | 0.9552 | |
| | CMLE | 0.8169 | NA | Exact | 0.6829 | 0.961 | 0.01288 |
| **pred01fda** | MLE | 2.922 | NA | Asymptotic | 1.174 | 7.269 | 0.02113 |
| | | | | Asymptotic(Profile) | 1.156 | 7.309 | |
| | CMLE | 2.891 | NA | Exact | 1.039 | 7.941 | 0.04139 |

**Analysis Time = 00:00:00**

### 14.1 Combined Withdrawal and Black-Box Warning Measure, Using FDA Data Only, August 2005 Stop Coding (cont.)

A random-effects logistic regression of the same data on submission year and epidemiological covariates yields a *p*-value of 0.02. The estimates for the FDA's deadline approval measure are highlighted in yellow.

```
Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =     10.31
Log likelihood  = -72.948822                    Prob > chi2        =    0.0356

------------------------------------------------------------------------------
sbworbb~0805 |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .7822211   .0782345    -2.46   0.014     .6429777    .9516191
   pred01fda |   3.660941   2.000369     2.37   0.018     1.254553    10.68308
   hhospdisc |   1.000001   1.63e-06     0.90   0.368     .9999983    1.000005
    hhosleng |   1.009056   .0569524     0.16   0.873     .9033836    1.127089
-------------+----------------------------------------------------------------
    /lnsig2u |   .3745936   .5488167                     -.7010674    1.450255
-------------+----------------------------------------------------------------
     sigma_u |   1.205985   .3309324                      .7043121    2.064994
         rho |   .3065594   .1166679                      .1310263    .5644906
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     2.77 Prob >= chibar2 = 0.048
```

**In summary: *If we rely entirely upon the FDA's data* and we stop coding when Carpenter, Zucker and Avorn stop coding, we still find large (ORs > 2.8) and statistically significant relationships between pre-deadline approvals and post-market safety problems.**

## 14.2 Combined Withdrawal and Black-Box Warning Measure, Using FDA Data Only, Stop Coding After Vioxx Withdrawal

If we then proceed as according to Carpenter, Zucker and Avorn 2008, and we create a combined withdrawal or black-box warning measure, and if we rely entirely on the FDA's data and stop coding in after the Vioxx withdrawal, we get the following list of postmarket safety events for NMEs.

```
. list  ndanum_fda genernam_fda sbwdate_fda bbwdate_fda if( sbworbbw_fda0805 == 1)

     +-------------------------------------------------------------------------+
     | ndanum~a                          genernam_fda   sbwdate~a   bbwdate~a |
     |-------------------------------------------------------------------------|
  1. |    21042                             Rofecoxib   30-Sep-04             |
  2. |    20998                             Celecoxib                29-Jul-05 |
  3. |    21341                            Valdecoxib    6-Apr-05   24-Nov-04 |
 14. |    20535                      Bromfenac Sodium   22-Jun-98   31-Mar-98 |
 33. |    20896                          Capecitabine                7-Sep-01 |
     |-------------------------------------------------------------------------|
 54. |    20169                            Nilutamide                29-Sep-00 |
 84. |    20740                  Cerivastatin Sodium    8-Aug-01             |
 95. |    20689          Mibefradil Dihydrochloride    8-Jun-98             |
104. |    20430                    Danaparoid Sodium                30-Jan-98 |
108. |    20564                            Lamivudine                15-Dec-97 |
     |-------------------------------------------------------------------------|
114. |    20628                            Saquinavir                14-Nov-00 |
137. |    20759             Trovafloxacin Mesylate                    9-Jun-99 |
138. |    20760            Alatrofloxacin Mesylate                    9-Jun-99 |
139. |    20695         Grepafloxacin Hydrochloride   27-Oct-99             |
175. |    20822            Citalopram Hydrobromide                18-Feb-05 |
     |-------------------------------------------------------------------------|
176. |    20415                           Mirtazapine                12-Jan-05 |
177. |    21427           Duloxetine Hydrochloride                   18-Feb-05 |
182. |    20315  Levomethadyl Acetate Hydrochloride   23-Aug-03             |
206. |    20984                Rapacuronium Bromide   27-Mar-01             |
221. |    20697                            Tolcapone                16-Nov-98 |
     |-------------------------------------------------------------------------|
232. |    20720                          Troglitazone   22-Mar-00   15-Dec-97 |
284. |    21107            Alosetron Hydrochloride   28-Nov-00    7-Jun-02 |
     +-------------------------------------------------------------------------+
```

### 14.2 Combined Withdrawal and Black-Box Warning Measure, Using FDA Data Only, post-Vioxx Stop Coding (cont.)

A two-way cross-tabulation yields a *p*-value of 0.054, but an exact logistic regression on the same data (controlling for submission year) yields a *p*-value of 0.04.

```
. tab sbworbbw_fda0105 pred01fda, exact

sbworbbw_f |       pred01fda
    da0105 |         0          1 |     Total
-----------+----------------------+----------
         0 |       217         79 |       296
         1 |         9          9 |        18
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.054
   1-sided Fisher's exact =                 0.035
```

An exact logistic regression yields the following results, with an estimated odds ratio of 3.68 and an exact p-value of 0.02.

## Binary Regression

regression (type=logit, model(comb0105 = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

**Basic Information**

| | |
|---|---|
| **Data file** | SBWorBBWdump4-20080412.csv |
| **Model** | comb0105(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

**Summary Statistics**

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 23.52 | 21 | 0.317 |
| **Likelihood Ratio** | 309.6 | 3 | 1.553e-009 |

**Parameter Estimates**

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| %Const | PMLE | 2.544 | NA | Asymptotic | 0.1257 | 51.5 | 0.5429 |
| | | | | Asymptotic(Profile) | 0.1318 | 64.69 | |
| subyrctr | PMLE | 0.7829 | NA | Asymptotic | 0.6496 | 0.9434 | 0.01012 |
| | | | | Asymptotic(Profile) | 0.6358 | 0.9347 | |
| | CMLE | 0.7734 | NA | Exact | 0.6246 | 0.9338 | 0.005584 |
| pred01fda | PMLE | 3.663 | NA | Asymptotic | 1.387 | 9.676 | 0.00879 |
| | | | | Asymptotic(Profile) | 1.373 | 9.881 | |
| | CMLE | 3.68 | NA | Exact | 1.197 | 11.43 | 0.02143 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

**14.2 Combined Withdrawal and Black-Box Warning Measure, Using FDA Data Only, post-Vioxx Stop Coding (cont.)**

A random-effects logistic regression of the same data on submission year and epidemiological covariates yields a *p*-value of 0.01. The estimates for the FDA's deadline approval measure are highlighted in yellow.

```
Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =     11.71
Log likelihood  = -62.426216                    Prob > chi2        =    0.0196

------------------------------------------------------------------------------
sbworbb~0105 |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .7727803   .0783442    -2.54   0.011     .6335217    .9426503
   pred01fda |   3.803343   1.962027     2.59   0.010     1.383748    10.45379
   hhospdisc |   1.000001   1.33e-06     0.87   0.384     .9999985    1.000004
    hhosleng |   1.012535   .0473796     0.27   0.790      .923804    1.109789
-------------+----------------------------------------------------------------
    /lnsig2u |  -3.113168   1.109992                     -5.288712   -.9376236
-------------+----------------------------------------------------------------
     sigma_u |   .2108551   .1170238                      .0710511    .6257453
         rho |    .013334   .0146033                      .0015321    .1063602
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.16 Prob >= chibar2 = 0.346

.
```

**Again, *if we rely entirely upon the FDA's data* and we merely stop coding boxed warnings and withdrawals after the withdrawal of Vioxx, we observe large (ORs > 3.6) and statistically significant relationships between pre-deadline approvals and post-market safety problems.**

# 15. Notes on Reanalysis of BBWs without NMEs Changed through Indirect Class Relabeling

At least one significant difference between class BBW relabelings and more specific BBW relabelings is the specificity of the evidence concerned. Class relabelings occur with indirect evidence from other molecules that rely upon similar mechanisms; they are not based upon direct evidence of studies of the molecule itself. Such patterns have been observed for the BBWs added to "atypical antipsychotic" drugs in recent years (aripiprazole, olanzapine).

First we generate a new variable that excludes indirect class relabelings, as follows:

```
. gen BBWcombo_excludeclassrelabel =  CZAFDAcombobbw_dec2007

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 20998)
(1 real change made) {THIS IS CELECOXIB}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 20937)
(1 real change made) {THIS IS GADOVERSETAMIDE}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 20639)
(1 real change made) {THIS IS QUETIAPINE FUMARATE}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 20592)
(1 real change made) {THIS IS OLANZAPINE}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 21436)
(1 real change made) {THIS IS ARIPIPRAZOLE}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 20825)
(1 real change made) {THIS IS ZIPRASIDONE}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 20938)
(1 real change made) {THIS IS MELOXICAM}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 20822)
(1 real change made) {THIS IS CITALOPRAM}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 21427)
(1 real change made) {THIS IS DULOXETINE}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 20415)
(1 real change made) {THIS IS MIRTAZAPINE}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 21449)
(1 real change made) {THIS IS ADEFOVIR DIPIVOXIL}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 21500)
(1 real change made) {THIS IS EMTRICITABINE}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 21618)
(1 real change made) {THIS IS TINIDAZOLE, CZA Positive Coding Error}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 21492)
(1 real change made) {THIS IS ELOXATIN, CZA Positive Coding Error}

. replace  BBWcombo_excludeclassrelabel = 0 if( ndanum_fda == 21345)
(1 real change made) {This is Fondaparinux Sodium, CZA Positive Coding Error}
```

**15.1.2. Revised List of BBWs after Exclusion of Indirect Therapeutic Class Relabeling**.
[Notice Saquinavir Included; see Section 15.2 and Section 16 for analyses where it is not coded as BBW.]

```
. list  ndanum_fda genernam_fda pred01fda if( BBWcombo_excludeclassrelabel == 1)
```

| | ndanum~a | genernam_fda | pred01~a |
|---|---|---|---|
| 7. | 20760 | Alatrofloxacin Mesylate | 1 |
| 13. | 21107 | Alosetron Hydrochloride | 0 |
| 27. | 21411 | Atomoxetine Hydrochloride | 0 |
| 42. | 20535 | Bromfenac Sodium | 0 |
| 47. | 20896 | Capecitabine | 1 |
| 66. | 20430 | Danaparoid Sodium | 0 |
| 90. | 21797 | Entecavir | 1 |
| 152. | 20564 | Lamivudine | 1 |
| 188. | 20169 | Nilutamide | 0 |
| 213. | 21064 | Perflutren Lipid Microsphere | 0 |
| 214. | 21302 | Pimecrolimus | 0 |
| 215. | 21073 | Pioglitazone Hydrochloride | 1 |
| 224. | 20815 | Raloxifene Hydrochloride | 1 |
| 241. | 21071 | Rosiglitazone Maleate | 1 |
| 245. | 20628 | Saquinavir | 0 |
| 266. | 21144 | Telithromycin | 0 |
| 269. | 21356 | Tenofovir Disoproxil Fumarate | 1 |
| 278. | 21814 | Tipranavir | 1 |
| 281. | 20697 | Tolcapone | 0 |
| 292. | 20720 | Troglitazone | 1 |
| 294. | 20759 | Trovafloxacin Mesylate | 1 |
| 299. | 21341 | Valdecoxib | 1 |

```
.
```

### 15.1.3. List of NMEs Recoded on the Basis of Indirect Class Relabeling

To see the time distribution of the drugs that were recoded, we reprint the exclusions along with generic name and the date of BBW. Notice that 10 (**34 percent**) of the 29 NMEs that Nardinelli et al coded in April 2008 as having black-box warnings added were based partially or wholly on indirect class relabeling, and notice that two others (which the FDA missed) also qualify.

```
. list  ndanum_fda genernam_fda pred01fda  bbwdate_fda if(
BBWcombo_excludeclassrelabel == 0 &  CZAFDAcombobbw_dec2007 == 1)
```

| | ndanum~a | genernam_fda | pred01~a | bbwdate~a |
|---|---|---|---|---|
| 6. | 21449 | Adefovir Dipivoxil | 1 | |
| 23. | 21436 | Aripiprazole | 0 | 16-Feb-06 |
| 52. | 20998 | Celecoxib | 1 | 29-Jul-05 |
| 59. | 20822 | Citalopram Hydrobromide | 0 | 18-Feb-05 |
| 82. | 21427 | Duloxetine Hydrochloride | 0 | 18-Feb-05 |
| 87. | 21500 | Emtricitabine | 1 | |
| 119. | 20937 | Gadoversetamide | 0 | 4-Sep-07 |
| 167. | 20938 | Meloxicam | 0 | 11-Aug-05 |
| 177. | 20415 | Mirtazapine | 0 | 12-Jan-05 |
| 193. | 20592 | Olanzapine | 0 | 16-Feb-06 |
| 222. | 20639 | Quetiapine Fumarate | 0 | 20-Sep-06 |
| 311. | 20825 | Ziprasidone Hydrochloride | 0 | 17-Aug-05 |

.

### 15.2.1. Cross-Tabulation of BBW Measure without Indirect Therapeutic Class Relabelings, corrected CZA Measure, with Fisher's Exact Test

```
. tab  BBWcombo_excludeclassrelabel pred01fda, exact

BBWcombo_e |
xcludeclas |       pred01fda
  srelabel |         0          1 |     Total
-----------+----------------------+----------
         0 |       216         76 |       292
         1 |        10         12 |        22
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.007
   1-sided Fisher's exact =                 0.006
```

To generate a shorter name for this variable, to be used in LogXact8 (which has max 9 characters in variable names), we used the following code:

```
. gen  BBWnoclass =  BBWcombo_excludeclassrelabel
```

This variable is used as the dependent variable in the exact logistic regressions on the following page.

### 15.2.2. Exact Logistic Regression Analysis of BBW Measure without Indirect Therapeutic Class Relabelings, corrected CZA Measure, with Fisher's Exact Test

# Binary Regression

regression (type=logit, model(bbwnoclass = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

## Basic Information

| | |
|---|---|
| **Data file** | comboBBWnoclass.csv |
| **Model** | BBWnoclass(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

## Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 26.1 | 21 | 0.2027 |
| **Likelihood Ratio** | 283.2 | 3 | 1.291e-009 |

## Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.05982 | NA | Asymptotic | 0.00495 | 0.723 | 0.02675 |
| | | | | Asymptotic(Profile) | 0.004619 | 0.7256 | |
| **subyrctr** | PMLE | 0.9891 | NA | Asymptotic | 0.8603 | 1.137 | 0.8778 |
| | | | | Asymptotic(Profile) | 0.8561 | 1.137 | |
| | CMLE | 0.987 | NA | Exact | 0.8511 | 1.14 | 0.8933 |
| **pred01fda** | PMLE | 3.409 | NA | Asymptotic | 1.422 | 8.175 | 0.005985 |
| | | | | Asymptotic(Profile) | 1.419 | 8.354 | |
| | CMLE | 3.437 | NA | Exact | 1.279 | 9.45 | 0.01272 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

### 15.2.3. Random-Effects Logistic Regression Analysis of BBW Measure without Indirect Therapeutic Class Relabelings, corrected CZA Measure, with Fisher's Exact Test

Results for FDA deadline approval measure highlighted in yellow.

```
. xtlogit BBWcombo_excludeclassrelabel subyrctr pred01fda  hhospdisc hhosleng, re
i(discode) or


Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      8.03
Log likelihood  = -75.602148                    Prob > chi2        =    0.0904

------------------------------------------------------------------------------
BBWcombo_e~l |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .9872738   .0734065    -0.17   0.863      .8533917     1.14216
   pred01fda |   3.538954   1.638027     2.73   0.006      1.428535     8.767157
   hhospdisc |   .9999999   1.66e-06    -0.06   0.950      .9999966     1.000003
    hhosleng |   1.035291    .041364     0.87   0.385      .9573117     1.119621
-------------+----------------------------------------------------------------
    /lnsig2u |  -2.848745   4.281551                     -11.24043     5.542939
-------------+----------------------------------------------------------------
     sigma_u |   .2406594   .5151977                      .0036239    15.98211
         rho |   .0173001   .0727897                      3.99e-06    .9872839
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.01 Prob >= chibar2 = 0.458
```

.

Hence if we use a corrected measure and exclude only class relabelings that are based on indirect evidence, we observe ORs above 3.4 in exact logistic and random-effects logistic regressions, with p-values less than 0.02.

### 15.3.1. Now use the same measure excluding therapeutic class relabelings, but drop Saquinavir from count, as FDA Coding Error

```
. gen  BBWcombonoclassbbw_dropsaquin =  BBWcombo_excludeclassrelabel

. replace  BBWcombonoclassbbw_dropsaquin = 0 if(ndanum_fda == 20628)
(1 real change made)
```

```
. tab   BBWcombonoclassbbw_dropsaquin pred01fda, exact

BBWcombono |
classbbw_d |       pred01fda
 ropsaquin |         0          1 |     Total
-----------+----------------------+----------
         0 |       217         76 |       293
         1 |         9         12 |        21
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.004
   1-sided Fisher's exact =                 0.004
```

To generate a shorter name for this variable, to be used in LogXact8 (which has max 9 characters in variable names), we used the following code:

```
gen BBWnocnos =  BBWcombonoclassbbw_dropsaquin
```

This variable is used as the dependent variable in the exact logistic regressions on the following page.

### 15.3.2. Exact Logistic Regression of BBW Measure without Indirect Therapeutic Class Relabelings, corrected CZA Measure, drop Saquinavir

# Binary Regression

regression (type=logit, model(bbwnocnos = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

## Basic Information

| | |
|---|---|
| **Data file** | comboBBWnoclass.csv |
| **Model** | BBWnocnos(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

## Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 28.78 | 21 | 0.1193 |
| **Likelihood Ratio** | 289.5 | 3 | 1.226e-009 |

## Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.04356 | NA | Asymptotic | 0.003401 | 0.558 | 0.01602 |
| | | | | Asymptotic(Profile) | 0.003133 | 0.5559 | |
| **subyrctr** | PMLE | 1.001 | NA | Asymptotic | 0.869 | 1.154 | 0.985 |
| | | | | Asymptotic(Profile) | 0.865 | 1.154 | |
| | CMLE | 0.9995 | NA | Exact | 0.8599 | 1.157 | 1 |
| **pred01fda** | PMLE | 3.727 | NA | Asymptotic | 1.522 | 9.13 | 0.004 |
| | | | | Asymptotic(Profile) | 1.524 | 9.397 | |
| | CMLE | 3.775 | NA | Exact | 1.372 | 10.77 | 0.008435 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

### 15.3.3. Random-Effects Logistic Regression of BBW Measure without Indirect Therapeutic Class Relabelings, corrected CZA Measure, drop Saquinavir from BBW list

Results for FDA deadline approval measure highlighted in yellow.

```
. xtlogit  BBWcombonoclassbbw_dropsaquin subyrctr pred01fda  hhospdisc hhosleng, re i(discode) or

Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      8.71
Log likelihood  = -72.663012                    Prob > chi2        =    0.0687

------------------------------------------------------------------------------
BBWcombono~n |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .9996823   .0751741    -0.00   0.997     .8626872    1.158432
   pred01fda |   3.878498   1.838523     2.86   0.004     1.531683    9.821057
   hhospdisc |   .9999999   1.73e-06    -0.09   0.932     .9999965    1.000003
    hhosleng |   1.028765   .0439154     0.66   0.506     .9461948    1.118541
-------------+----------------------------------------------------------------
    /lnsig2u |  -2.936272   2.717393                     -8.262265    2.389721
-------------+----------------------------------------------------------------
     sigma_u |   .2303545   .3129819                      .0160647    3.303098
         rho |   .0158733   .0424492                      .0000784    .7683244
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.01 Prob >= chibar2 = 0.466
```

.

Hence if we use a corrected measure and exclude only class relabelings that are based on indirect evidence, and recode saquinavir as not having had a BBW, we observe ORs above 3.7 in exact logistic and random-effects logistic regressions, with p-values less than 0.01.

# Section 16: Notes on Reanalysis of BBWs, Drop Saquinavir (FDA Coding Error)

First begin with the combined black-box warning measure that stops coding in August 2005, then recode only saquinavir.

```
. replace  CZAFDAbbw0805_corrdropsaquin = 0 if(ndanum_fda == 20628)
(1 real change made)  {THIS IS SAQUINAVIR}

. save "F:\fdadata\FDAData-314NMEs-20080509.dta", replace
file F:\fdadata\FDAData-314NMEs-20080509.dta saved

. save "c:\fdatemp\FDAData-314NMEs-20080509.dta", replace
file c:\fdatemp\FDAData-314NMEs-20080509.dta saved
```

### 16.1.1. Cross-Tabulation of Revised BBW Measure with Stopped Coding in August 2005, Using FDA's NMES and FDA's Deadline Approval Measure, with Fisher's Exact Test

```
. tab  CZAFDAbbw0805_corrdropsaquin pred01fda, exact

CZAFDAbbw0 |
805_corrdr |       pred01fda
  opsaquin |         0          1 |     Total
-----------+----------------------+----------
         0 |       218         76 |       294
         1 |         8         12 |        20
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.003
   1-sided Fisher's exact =                 0.002
```

### 16.1.2 Exact Logistic Regression Analysis of Revised BBW Measure with Stopped Coding in August 2005, Using FDA's NMES and FDA's Deadline Approval Measure

# Binary Regression

regression (type=logit, model(bbw0805 = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

## Basic Information

| | |
|---|---|
| **Data file** | analysesdroppingsaquinavir20080509.csv |
| **Model** | bbw0805(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

## Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 25.87 | 21 | 0.2116 |
| **Likelihood Ratio** | 295.9 | 3 | 1.249e-009 |

## Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.04114 | NA | Asymptotic | 0.003026 | 0.5593 | 0.01656 |
| | | | | Asymptotic(Profile) | 0.002774 | 0.5583 | |
| **subyrctr** | PMLE | 0.9981 | NA | Asymptotic | 0.8634 | 1.154 | 0.9791 |
| | | | | Asymptotic(Profile) | 0.859 | 1.154 | |
| | CMLE | 0.9961 | NA | Exact | 0.8536 | 1.157 | 0.9958 |
| **pred01fda** | PMLE | 4.201 | NA | Asymptotic | 1.671 | 10.56 | 0.002282 |
| | | | | Asymptotic(Profile) | 1.683 | 10.97 | |
| | CMLE | 4.28 | NA | Exact | 1.513 | 12.79 | 0.004698 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

### 16.1.3 Random-Effects Logistic Regression Analysis of Revised BBW Measure with Stopped Coding in August 2005, Using FDA's NMES and FDA's Deadline Approval Measure

Now we use the same corrected BBW variable with coding stopped in August 2005, and analyze the association between this variable and just-before-deadline approvals, using the Nardinelli et al "deadline approval" measure. Results for Deadline Approval Variable highlighted in yellow.

```
. xtlogit  CZAFDAbbw0805_corrdropsaquin subyrctr pred01fda  hhospdisc hhosleng, re
i(discode) or

Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =     10.35
Log likelihood  = -66.294539                    Prob > chi2        =    0.0349

------------------------------------------------------------------------------
CZAFDAbbw0~n |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .9638772   .0894364    -0.40   0.692     .8036007    1.156121
   pred01fda |   6.973425   4.342355     3.12   0.002     2.057797    23.63141
   hhospdisc |   1.000001   2.11e-06     0.39   0.698     .9999967    1.000005
    hhosleng |   1.050633   .0661873     0.78   0.433     .9285977    1.188707
-------------+----------------------------------------------------------------
    /lnsig2u |   .8583714   .4872433                     -.0966078    1.813351
-------------+----------------------------------------------------------------
     sigma_u |   1.536006   .3742044                      .9528442    2.476077
         rho |   .4176383   .1185056                      .2162838    .6507877
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     4.83 Prob >= chibar2 = 0.014
```

### 16.2 Analysis of Combined CZA and FDA Measure Extending until December 2007. Drop Saquinavir.

Now we use the same corrected BBW variable with coding stopped in August 2005, and analyze the association between this variable and just-before-deadline approvals, using the Nardinelli et al "deadline approval" measure. We also recode saquinavir as not having had a BBW (see Section 9).

```
. gen  CZAFDAcombobbw1207_dropsaquin =  CZAFDAcombobbw_dec2007

. replace   CZAFDAcombobbw1207_dropsaquin = 0 if(ndanum_fda == 20628)
(1 real change made)
```

A cross-tabulation with Fisher's exact test yields the following.

```
. tab   CZAFDAcombobbw1207_dropsaquin pred01fda, exact

CZAFDAcomb |
obbw1207_d |       pred01fda
 ropsaquin |         0          1 |     Total
-----------+----------------------+----------
         0 |       206         72 |       278
         1 |        20         16 |        36
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.029
   1-sided Fisher's exact =                 0.019
```

### 16.2.2 Exact Logistic Regression Analysis of Combined CZA and FDA Measure Extending until December 2007. Drop Saquinavir.

Now we use the same corrected BBW variable with coding stopped in August 2005, and analyze the association between this variable and just-before-deadline approvals, using the Nardinelli et al "deadline approval" measure. We also recode saquinavir as not having had a BBW (see Section 9).

## Binary Regression

regression (type=logit, model(bbw1207 = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

**Basic Information**

| | |
|---|---|
| **Data file** | analysesdroppingsaquinavir20080509.csv |
| **Model** | bbw1207(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

**Summary Statistics**

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 20.12 | 21 | 0.5134 |
| **Likelihood Ratio** | 218 | 3 | 1.084e-009 |

**Parameter Estimates**

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.03096 | NA | Asymptotic | 0.00399 | 0.2402 | 0.000886 |
| | | | | Asymptotic(Profile) | 0.003772 | 0.2321 | |
| **subyrctr** | PMLE | 1.069 | NA | Asymptotic | 0.956 | 1.195 | 0.2418 |
| | | | | Asymptotic(Profile) | 0.9554 | 1.196 | |
| | CMLE | 1.069 | NA | Exact | 0.9531 | 1.199 | 0.2578 |
| **pred01fda** | PMLE | 2.112 | NA | Asymptotic | 1.033 | 4.32 | 0.04054 |
| | | | | Asymptotic(Profile) | 1.023 | 4.305 | |
| | CMLE | 2.102 | NA | Exact | 0.9474 | 4.597 | 0.06903 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:02**

### 16.2.3 Random-Effects Logistic Regression Analysis of Combined CZA and FDA Measure Extending until December 2007. Drop Saquinavir.

Now we use the same corrected BBW variable with coding stopped in August 2005, and analyze the association between this variable and just-before-deadline approvals, using the Nardinelli et al "deadline approval" measure. We also recode saquinavir as not having had a BBW (see Section 9). Results for Deadline Approval Variable highlighted in yellow.

```
. xtlogit  CZAFDAcombobbw1207_dropsaquin subyrctr pred01fda  hhospdisc hhosleng, re
i(discode) or

Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      9.53
Log likelihood  = -99.940022                    Prob > chi2        =    0.0492

------------------------------------------------------------------------------
CZAFDAcomb~n |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   1.072593   .0797693     0.94   0.346     .9271087    1.240907
   pred01fda |   3.671742   1.902987     2.51   0.012     1.329573    10.13986
   hhospdisc |   1.000001   1.95e-06     0.68   0.498     .9999975    1.000005
    hhosleng |   1.072317   .0626088     1.20   0.232     .9563666    1.202325
-------------+----------------------------------------------------------------
    /lnsig2u |   1.200583   .4364999                      .3450585    2.056107
-------------+----------------------------------------------------------------
     sigma_u |    1.82265   .3977932                     1.188307    2.795618
         rho |   .5024338   .1091224                      .300317    .7037583
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =    12.44 Prob >= chibar2 = 0.000
```

.

### 16.3 Analysis of Combined Withdrawal or Black-Box Warnings Measure, Stop Coding in August 2005, Drop Saquinavir

We now take the combined "Withdrawals or Warnings" Measure and exclude saquinavir from the BBW count.

```
. gen sbworbbwFDACZA0805_dropsaquin = CZAFDAbbw_august2005_corrected

. replace   sbworbbwFDACZA0805_dropsaquin = 0 if(ndanum_fda == 20628)
(1 real change made)
```

### 16.3.1. Cross-Tabulation of Combined Withdrawal or Black-Box Warnings Measure, Stop Coding in August 2005, Drop Saquinavir; Fisher's Exact Test.

```
. tab sbworbbwFDACZA0805_dropsaquin pred01fda, exact

sbworbbwFD |
ACZA0805_d |       pred01fda
 ropsaquin |         0          1 |     Total
-----------+----------------------+----------
         0 |       218         76 |       294
         1 |         8         12 |        20
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.003
   1-sided Fisher's exact =                 0.002
```

### 16.3.2. Exact Logistic Regression Analysis of Combined Withdrawal or Black-Box Warnings Measure, Stop Coding in August 2005, Drop Saquinavir.

## Binary Regression

regression (type=logit, model(sbwbbw081 = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

### Basic Information

| | |
|---|---|
| **Data file** | analysesdroppingsaquinavir20080509.csv |
| **Model** | sbwbbw081(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

### Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 25.87 | 21 | 0.2116 |
| **Likelihood Ratio** | 295.9 | 3 | 1.249e-009 |

### Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.04114 | NA | Asymptotic | 0.003026 | 0.5593 | 0.01656 |
| | | | | Asymptotic(Profile) | 0.002774 | 0.5583 | |
| **subyrctr** | PMLE | 0.9981 | NA | Asymptotic | 0.8634 | 1.154 | 0.9791 |
| | | | | Asymptotic(Profile) | 0.859 | 1.154 | |
| | CMLE | 0.9961 | NA | Exact | 0.8536 | 1.157 | 0.9958 |
| **pred01fda** | PMLE | 4.201 | NA | Asymptotic | 1.671 | 10.56 | 0.002282 |
| | | | | Asymptotic(Profile) | 1.683 | 10.97 | |
| | CMLE | 4.28 | NA | Exact | 1.513 | 12.79 | 0.004698 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

Taking the combined "Withdrawals or Warnings" Measure and excluding saquinavir from the BBW count yields an OR of 4.3 (just less than reported in the original article) and a lower bound on the exact CI of 1.51 (nearly identical to that in the original article).

### 16.3.3. Random-Effects Logistic Regression Analysis of Combined Withdrawal or Black-Box Warnings Measure, Stop Coding in August 2005, Drop Saquinavir.

Results for Deadline Approval Variable highlighted in yellow.

```
. xtlogit sbworbbwFDACZA0805_dropsaquin subyrctr pred01fda  hhospdisc hhosleng, re
i(discode) or


Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =     10.35
Log likelihood  = -66.294539                    Prob > chi2        =    0.0349

------------------------------------------------------------------------------
sbworbbwFD~n |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .9638772   .0894364    -0.40   0.692     .8036007    1.156121
   pred01fda |   6.973425   4.342355     3.12   0.002     2.057797    23.63141
   hhospdisc |   1.000001   2.11e-06     0.39   0.698     .9999967    1.000005
    hhosleng |   1.050633   .0661873     0.78   0.433     .9285977    1.188707
-------------+----------------------------------------------------------------
    /lnsig2u |   .8583714   .4872433                     -.0966078    1.813351
-------------+----------------------------------------------------------------
     sigma_u |   1.536006   .3742044                      .9528442    2.476077
         rho |   .4176383   .1185056                      .2162838    .6507877
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     4.83 Prob >= chibar2 = 0.014
```

.

Taking the combined "Withdrawals or Warnings" Measure and excluding saquinavir from the BBW count yields an OR of 6.7 (significantly above that reported in the original article) and a lower bound on the 95% exact CI of 2.05 (well above that in the original article).

### 16.4 Now Re-Analyze 12/2007 Cutoff Data, combine Warnings and Withdrawals, and Drop Saquinavir from the BBW Count as an FDA Coding Error

Now we return to the combined "withdrawals and warnings" measure examined in Section 12.3, and we drop saquinavir from the BBW count.

```
. gen CZAFDASBWorBBW1207_dropsaquin =  CZAFDAcomboSBWorBBW_dec2007

. replace  CZAFDASBWorBBW1207_dropsaquin = 0 if(ndanum_fda == 20628)
(1 real change made)
```

### 16.4.1. Cross-Tabulation with Fisher's Exact Test.

```
. tab  CZAFDASBWorBBW1207_dropsaquin pred01fda, exact

CZAFDASBWo |
rBBW1207_d |       pred01fda
 ropsaquin |         0          1 |     Total
-----------+----------------------+----------
         0 |       204         70 |       274
         1 |        22         18 |        40
-----------+----------------------+----------
     Total |       226         88 |       314

           Fisher's exact =                 0.014
   1-sided Fisher's exact =                 0.011
```

### 16.4.2. Exact Logistic Regression Analysis of Combined and Corrected Warnings and Withdrawals Measure, Dropping Saquinavir from the BBW Count as an FDA Coding Error

## Binary Regression

regression (type=logit, model(sbwbbw12 = subyrctr pred01fda), estimate(subyrctr pred01fda), method=exact, mle=firth, profile=yes, outtype=odds);

### Basic Information

| | |
|---|---|
| **Data file** | analysesdroppingsaquinavir20080509.csv |
| **Model** | sbwbbw12(Response = 1)=%Const+subyrctr+pred01fda |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 314 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

### Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 26.8 | 21 | 0.1777 |
| **Likelihood Ratio** | 201.8 | 3 | 1.433e-009 |

### Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.1154 | NA | Asymptotic | 0.01668 | 0.7984 | 0.02866 |
| | | | | Asymptotic(Profile) | 0.01624 | 0.7894 | |
| **subyrctr** | PMLE | 0.9979 | NA | Asymptotic | 0.8953 | 1.112 | 0.9693 |
| | | | | Asymptotic(Profile) | 0.8938 | 1.111 | |
| | CMLE | 0.9969 | NA | Exact | 0.8911 | 1.113 | 0.9821 |
| **pred01fda** | PMLE | 2.387 | NA | Asymptotic | 1.203 | 4.739 | 0.01288 |
| | | | | Asymptotic(Profile) | 1.196 | 4.731 | |
| | CMLE | 2.38 | NA | Exact | 1.117 | 5.031 | 0.02355 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:03**

Hence using the combined "withdrawals and warnings" measure that includes all Nardinelli et al determinations of a BBW or SBW (this was examined in Section 12.3), and dropping saquinavir from the BBW count, yields an OR of 2.4 with a exact p-value of 0.02 for a two-tailed test.

### 16.4.3. Random-Effects Logistic Regression Analysis of Combined and Corrected Warnings and Withdrawals Measure, Dropping Saquinavir from the BBW Count as an FDA Coding Error

Results for Deadline Approval Variable highlighted in yellow.

```
. xtlogit  CZAFDASBWorBBW1207_dropsaquin subyrctr pred01fda  hhospdisc hhosleng, re
i(discode) or


Random-effects logistic regression              Number of obs      =       314
Group variable (i): discode                     Number of groups   =       135

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =      8.92
Log likelihood  = -109.46869                    Prob > chi2        =    0.0630

------------------------------------------------------------------------------
CZAFDASBWo~n |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   .9789434   .0708445    -0.29   0.769     .8494886    1.128126
   pred01fda |    3.87044   1.911668     2.74   0.006     1.470074    10.19017
   hhospdisc |   1.000002   1.79e-06     1.09   0.274     .9999984    1.000005
    hhosleng |   1.029629   .0616835     0.49   0.626     .9155596     1.15791
-------------+----------------------------------------------------------------
    /lnsig2u |   1.161936   .4548797                      .2703886    2.053484
-------------+----------------------------------------------------------------
     sigma_u |   1.787769   .4066098                      1.144759    2.791955
         rho |   .4927727   .1136962                      .2848644    .7032112
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =    11.26 Prob >= chibar2 = 0.000
```

Hence using the combined "withdrawals and warnings" measure that includes all Nardinelli et al determinations of a BBW or SBW (this was examined in Section 12.3), and dropping saquinavir from the BBW count, yields an OR of 3.9 with a p-value of 0.006 for a two-tailed test.

# 17. Re-Analysis of CZA Black-Box Warnings Measure, Using Recoded CZA Pre-Deadline Approval Measure, then FDA Pre-Deadline Approval Measure.

Finally, we used our original dataset of 313 drugs and a revised just-before-deadline measure based upon a recoding of the standard-vs.-priority discrepancies. If we re-analyze the original Carpenter/Zucker/Avorn (CZA) postmarket black-box warning measure and use a recoded just-before-deadline approval measure (based upon the reclassified standard and priority drugs), we obtain the following results for a cross-tabulation and for Fisher's exact test.

```
. tab combobbw pred0410_recode, exact

combobbw_o |    pred0410_recode
   riginal |         0          1 |     Total
-----------+----------------------+----------
         0 |       214         85 |       299
         1 |         5          9 |        14
-----------+----------------------+----------
     Total |       219         94 |       313

           Fisher's exact =                 0.007
   1-sided Fisher's exact =                 0.007
```

## 17.1. Re-Analysis of Black-Box Warnings Measure, Using Recoded Pre-Deadline Approval Measure and FDA Deadline Approval Measure (cont.)

An exact logistic regression on the same data yields the following results, with a p-value of just above 0.05 for a two-tailed test.

### Binary Regression

regression (type=logit, model(combobbw_o = subyrctr pred0410_r), estimate(subyrctr pred0410_r), method=exact, mle=firth, profile=yes, outtype=odds);

**Basic Information**

| | |
|---|---|
| **Data file** | COMBOBBW-dump20080413.csv |
| **Model** | combobbw_o(Response = 1)=%Const+subyrctr+pred0410_r |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 313 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

**Summary Statistics**

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 24.49 | 21 | 0.2702 |
| **Likelihood Ratio** | 334.2 | 3 | 1.665e-009 |

**Parameter Estimates**

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.0003102 | NA | Asymptotic | 8.626e-006 | 0.01115 | 1e-005 |
| | | | | Asymptotic(Profile) | 5.783e-006 | 0.009312 | |
| **subyrctr** | PMLE | 1.273 | NA | Asymptotic | 1.064 | 1.524 | 0.00838 |
| | | | | Asymptotic(Profile) | 1.067 | 1.545 | |
| | CMLE | 1.282 | NA | Exact | 1.064 | 1.567 | 0.007871 |
| **pred0410_r** | PMLE | 3.416 | NA | Asymptotic | 1.14 | 10.24 | 0.02826 |
| | | | | Asymptotic(Profile) | 1.153 | 11.02 | |
| | CMLE | 3.538 | NA | Exact | 0.9935 | 14.2 | 0.05137 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

As the next page shows, a random-effects logistic regression on the same data yields a slightly larger odds ratio estimate, and a p-value of 0.04.

## 17.1. Re-Analysis of Black-Box Warnings Measure, Using Recoded Pre-Deadline Approval Measure and FDA Deadline Approval Measure (cont.)

```
Random-effects logistic regression              Number of obs      =       313
Group variable (i): discode                     Number of groups   =       134

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =     13.20
Log likelihood  = -48.159155                    Prob > chi2        =    0.0104

------------------------------------------------------------------------------
combobbw_o~l |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   1.311151   .1387747     2.56   0.010     1.065516    1.613413
pred0410_r~e |   3.773193   2.400124     2.09   0.037     1.084578    13.12676
   hhospdisc |   1.000002   1.99e-06     0.80   0.426     .9999977    1.000005
    hhosleng |   1.064993    .063383     1.06   0.290      .947736    1.196757
-------------+----------------------------------------------------------------
    /lnsig2u |  -.2108729   .7379722                     -1.657272    1.235526
-------------+----------------------------------------------------------------
     sigma_u |   .8999316   .3320623                      .4366445    1.854774
         rho |   .1975433   .1169833                      .0547786    .5111678
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.76 Prob >= chibar2 = 0.192
```

.

### 17.2. Analysis of Carpenter/Zucker/Avorn BBW Measure, Using FDA Deadline Approval Measure.

If we re-analyze the original Carpenter/Zucker/Avorn postmarket black-box warning measure and use a recoded (based upon the reclassified standard and priority drugs), we obtain the following results for a cross-tabulation and for Fisher's exact test.

```
. tab combobbw  pred01fda_CZAdata, exact

combobbw_o |   pred01fda_CZAdata
   riginal |         0          1 |     Total
-----------+----------------------+----------
         0 |       220         79 |       299
         1 |         5          9 |        14
-----------+----------------------+----------
     Total |       225         88 |       313

           Fisher's exact =                 0.004
   1-sided Fisher's exact =                 0.004
```

The next page shows the results of an exact logistic regression (controlling for submission year of the NME) on the same data.

## 17.2. Analysis of Carpenter/Zucker/Avorn BBW Measure, Using FDA Deadline Approval Measure (cont.)

An exact logistic regression on the same Carpenter/Zucker/Avorn measure, but using the FDA's deadline approval measure, yields an estimated odds ratio of 3.8 and a p-value of 0.04 for a two-tailed test.

# Binary Regression

regression (type=logit, model(combobbw_o = subyrctr pred01fda_), estimate(subyrctr pred01fda_), method=exact, mle=firth, profile=yes, outtype=odds);

### Basic Information

| | |
|---|---|
| **Data file** | COMBOBBW-dump20080413-2.csv |
| **Model** | combobbw_o(Response = 1)=%Const+subyrctr+pred01fda_ |
| **Link type** | Logit |
| **Weight variable** | <Not Specified> |
| **Stratum variable** | <Unstratified> |
| **Analysis type** | Estimate :: Exact |
| **Number of terms in model** | 3 |
| **Number of term(s) dropped** | 0 |
| **Number of observations in analysis** | 313 |
| **Number of records rejected** | 0 |
| **Number of groups** | 24 |

### Summary Statistics

| Statistics | Value | DF | P-Value |
|---|---|---|---|
| **Deviance** | 24.47 | 21 | 0.2707 |
| **Likelihood Ratio** | 334.7 | 3 | 1.896e-009 |

### Parameter Estimates

| | Point Estimate | | | Confidence Interval and P-Value for Odds Ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 95 %CI | | 2*1-sided |
| Model Term | Type | Odds Ratio | SE(Odds) | Type | Lower | Upper | P-Value |
| **%Const** | PMLE | 0.0003543 | NA | Asymptotic | 1e-005 | 0.01255 | 1.283e-005 |
| | | | | Asymptotic(Profile) | 6.686e-006 | 0.01046 | |
| **subyrctr** | PMLE | 1.263 | NA | Asymptotic | 1.055 | 1.512 | 0.01084 |
| | | | | Asymptotic(Profile) | 1.059 | 1.534 | |
| | CMLE | 1.272 | NA | Exact | 1.056 | 1.555 | 0.01017 |
| **pred01fda** | PMLE | 3.675 | NA | Asymptotic | 1.22 | 11.07 | 0.02072 |
| | | | | Asymptotic(Profile) | 1.233 | 11.91 | |
| | CMLE | 3.803 | NA | Exact | 1.06 | 15.35 | 0.03914 |

PMLE: Penalized MLE for bias correction (Firth's method).

**Analysis Time = 00:00:00**

## 17.2. Analysis of Carpenter/Zucker/Avorn BBW Measure, Using FDA Deadline Approval Measure (cont.)

A random-effects logistic regression on the same Carpenter/Zucker/Avorn measure, but using the FDA's deadline approval measure, yields an estimated odds ratio of 3.8 and a p-value of 0.04 for a two-tailed test.

The estimates for the FDA's "deadline approval" measure are highlighted in yellow. The random-effects logistic regression shows an estimated odds ratio of just over 4 with a p-value of 0.03 for a two-tailed test.

```
Random-effects logistic regression              Number of obs      =       313
Group variable (i): discode                     Number of groups   =       134

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =       2.3
                                                               max =        16

                                                Wald chi2(4)       =     13.62
Log likelihood  = -47.933501                    Prob > chi2        =    0.0086

------------------------------------------------------------------------------
combobbw_o~l |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    subyrctr |   1.301012   .1376919     2.49   0.013     1.057292    1.600913
pred01fda_~a |   4.069912   2.607341     2.19   0.028     1.159505    14.28556
    hhosleng |   1.065602     .06325     1.07   0.284     .9485739    1.197069
   hhospdisc |   1.000002   1.99e-06     0.77   0.439     .9999976    1.000005
-------------+----------------------------------------------------------------
    /lnsig2u |  -.2140948    .745051                     -1.674368    1.246178
-------------+----------------------------------------------------------------
     sigma_u |   .8984831   .3347079                      .4329279    1.864679
         rho |    .197033   .1178753                      .0539001    .5138292
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     0.72 Prob >= chibar2 = 0.197
```

All of the results in this Section 17, of course, use the black-box warning measure of Carpenter/Zucker/Avorn for purposes of demonstration. As we have shown in Sections 11 through 16, our results hold using a revised and corrected measure, using the FDA's 314 NMEs, using the FDA's deadline approval measure, and using the FDA's own withdrawal and BBW measures.