9th Annual FDA Scientific Computing Day

Missing Field Alert Reports

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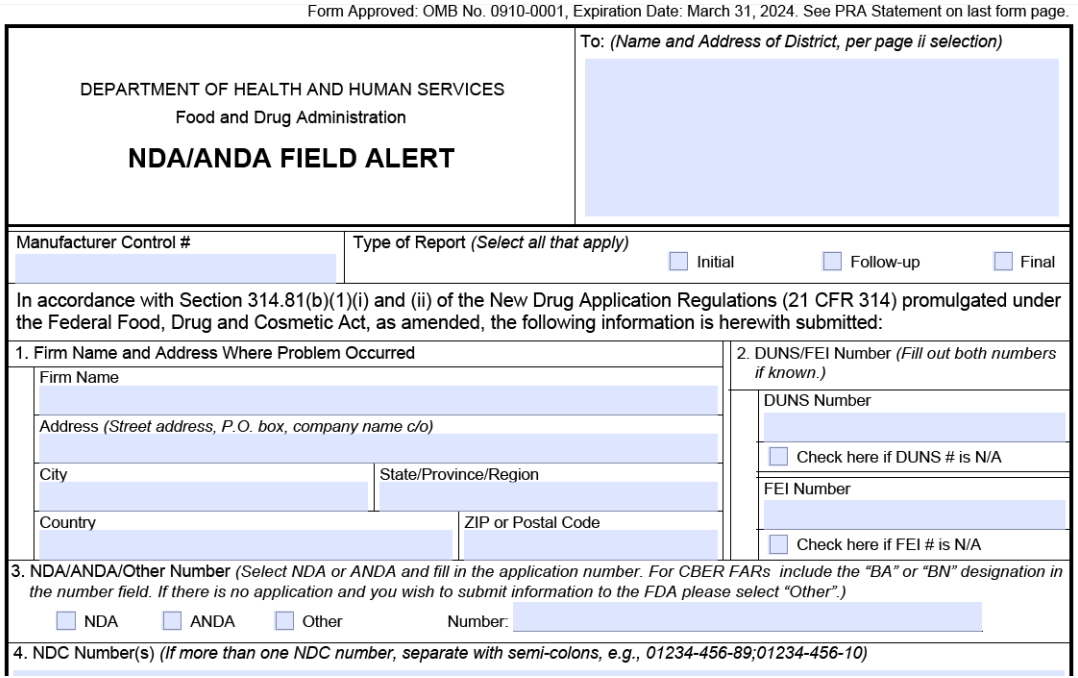
Background Information

Disclaimer: Findings and conclusions contained herein have not been formally disseminated by the FDA and should not be construed to represent any agency determination or policy.

Field Alert Report (FAR)



Form Approved: OMB No. 0910-0001, Expiration Date: March 31, 2024. See PRA Statement on last form page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

NDA/ANDA FIELD ALERT

To: *(Name and Address of District, per page ii selection)*

Manufacturer Control #

Type of Report *(Select all that apply)* ☐ Initial ☐ Follow-up ☐ Final

In accordance with Section 314.81(b)(1)(i) and (ii) of the New Drug Application Regulations (21 CFR 314) promulgated under the Federal Food, Drug and Cosmetic Act, as amended, the following information is herewith submitted:

1. Firm Name and Address Where Problem Occurred

Firm Name

Address *(Street address, P.O. box, company name c/o)*

City | State/Province/Region

Country | ZIP or Postal Code

2. DUNS/FEI Number *(Fill out both numbers if known.)*

DUNS Number

☐ Check here if DUNS # is N/A

FEI Number

☐ Check here if FEI # is N/A

3. NDA/ANDA/Other Number *(Select NDA or ANDA and fill in the application number. For CBER FARs include the "BA" or "BN" designation in the number field. If there is no application and you wish to submit information to the FDA please select "Other".)*

☐ NDA ☐ ANDA ☐ Other Number:

4. NDC Number(s) *(If more than one NDC number, separate with semi-colons, e.g., 01234-456-89;01234-456-10)*

Background Information

What	Field Alert Report (FAR)
Who	Holders of approved New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs)
When	Within three working days of receiving information concerning a quality problem with distributed drug product
Why	• Regulations in 21 CFR 314.81(b)(1) and 314.98(b) • Early warning to identify potential public health hazards

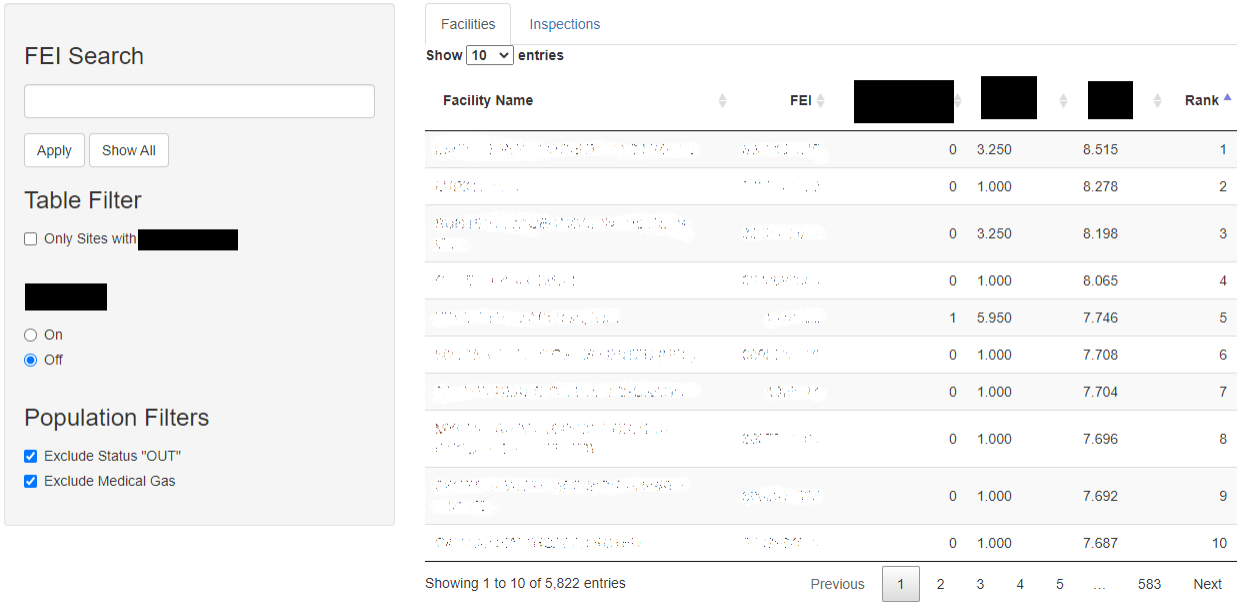
Background Information (cont.)

- Failures to submit FARs are documented in raw text of Establishment Inspection Reports (EIRs).
- Data source with raw text of over 12,000 EIRs from 2012-2020

Project Overview

1. FAR submission failure identification from EIR text
2. Exploration of prospective explanatory variables
3. Development of interactive portal

Interactive Portal



Built using R Shiny

FAR Failure Identification

13,511	raw EIR text
9,369	unique EIR keys

```
"[[:space:]()]FAR[Ss]?[[:space:]])\\.]|[Ff]ield [Aa]lert [Rr]eport"
```

675	mentions of FARs in summary section
91	describe FAR submission failures

FAR Failure Identification (cont.)

Preliminary keyword search

Specificity	85.2%
Sensitivity	93.4%
Accuracy	86.4%

Exploratory Analysis

Methods

- Response variable as count
- Over-dispersion
  - Quasi-Poisson vs. Negative Binomial
- Likelihood ratio tests
- Holm-Bonferroni procedure

Results

Variable	*p*-value
Region	0.0473
Member of PIC/S*	0.6686
ANDA Product Count	0.0029
NDA Product Count	0.5576

*PIC/S is the Pharmaceutical Inspection Cooperation Scheme

Appendix

Detailed Discussion

Text Mining

	Word	Count
1	the	13365
2	and	6961
3	of	6623
4	field	6129
5	alert	5778
6	to	5135
7	for	4713
8	a	4226
9	far	4090
10	reports	3300

The text mining technique used to automate identification of FAR submission failures from EIR text involves first tokenizing the EIR summary text into sentences. These sentences are filtered such that only sentences mentioning FARs are considered. Then counts of all words appearing in these sentences are taken.

The 10 most common such words are shown in the table to the left. Most of these words either are used to describe FARs themselves or consist of common articles or conjunctions that are of little interest. These are considered “stop words” and are removed from the list.

Text Mining (cont.)

	Lemma	Count
1	submit	2717
2	inspection	2391
3	complaint	2253
4	product	2184
5	review	1829
6	nda	1727
7	firm	1682
8	lot	1643
9	investigation	1559
10	not	1535

In addition to removing stop words, the remaining words are lemmatized, i.e., related words such as “submit,” “submitted,” etc., are all converted to the lemma “submit” for counting purposes.

The 10 most common lemmas are summarized in the table to the left. The sentences that describe FAR submission failures typically include two elements: a lemma indicating submission such as “submit” or “file,” and a lemma indicating negation such as “not,” “no,” or “fail.”

Using a search for sentences that mention FARs and have both sorts of lemmas present already resulted in fair accuracy, and with refinement could be used to automate the identification of FAR submission failures in the future.

Statistical Analysis

Because some sites have multiple EIRs that reported separate FAR submission failures, the **response variable** of interest is best treated as a **count** of FAR submission failures per site. This suggests that Poisson regression would be an appropriate analysis technique. However, the FAR submission failure count sample mean is 0.0664 and the sample variance 0.0887, suggesting there might be **over-dispersion**.

Quasi-Poisson and **negative binomial** regression are both like Poisson regression but include estimation of an additional parameter to allow for a variance greater than the mean. Since quasi-Poisson regression tends to give greater to weight sites with greater counts (Hoef & Boveng, 2007), and the sites with FAR submission failures are more important for this analysis, quasi-Poisson regression is used.

Four quasi-Poisson models, each with one of these variables as the only covariate, are fit to the data. A null model with only a constant value is also fit, and four **likelihood ratio tests** are performed comparing the fit of the null model with each of the four fits with covariates. The *p*-values reported are the results of these likelihood ratio tests. The lower the *p*-value, the lower the probability of getting the observed results given the hypothesis that the fit of the model with the covariate is no better than the fit of the null model. Thus, low *p*-values indicate strong evidence that the covariate explains some of the variation in the number of FAR submission failures.

Statistical Analysis (cont.)

The **Holm-Bonferroni procedure** is used to adjust individual type I error rates in order to achieve a family-wise type I error rate of 0.05. The type I error rate (sometimes called “significance level”) defines a kind of acceptable false positive error rate for a hypothesis test. However, when there are multiple hypothesis tests being conducted simultaneously, using a type I error rate of 0.05 for each individual test results in a higher type I error rate overall, since there are multiple opportunities for false positives. The Holm-Bonferroni procedure stipulates significance levels for each individual test that preserve an overall type I error rate across all tests.

	Variable	*p*-value
1	Region	0.0473
2	Member of PIC/S	0.6686
3	ANDA Product Count	0.0029
4	NDA Product Count	0.5576

In the Holm-Bonferroni procedure, the first individual significance level to be used is the overall type I error rate divided by the number of hypotheses. In this case, this is 0.0125. This is compared with the hypothesis test with the lowest *p*-value. Here it is the likelihood ratio test using ANDA product count as a covariate with a *p*-value of 0.0029. Because the *p*-value of 0.0029 is less than the significance level of 0.0125, there is strong evidence that the ANDA product count explains some of the variation in the number of FAR submission failures per site.

Statistical Analysis (cont.)

	Variable	*p*-value
1	Region	0.0473
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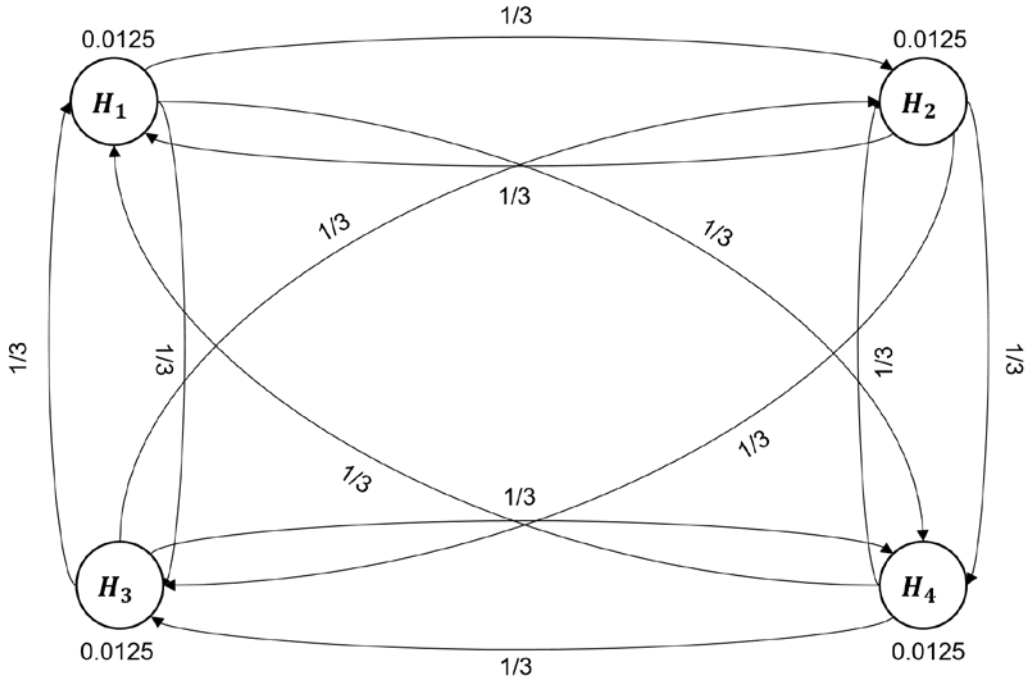
To continue the Holm-Bonferroni procedure, the significance level for the next test is recalculated. This is illustrated here way of a graphical representation. (Bretz, et al, 2009) The portions of the 0.0125 significance level for hypothesis test H_3 corresponding to ANDA product count is transferred to the other hypothesis tests along the outgoing vertices according to the fraction labeling the vertex.



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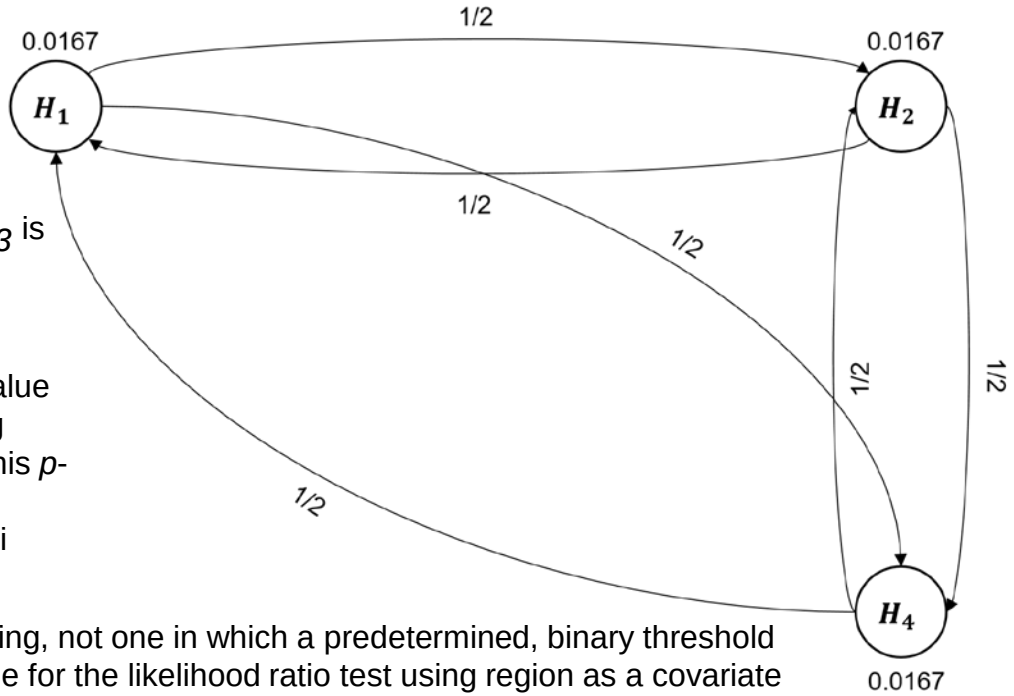

In the updated graph, the node containing H_3 is eliminated and the significance levels for the other 3 nodes updated.

The hypothesis test with the next lowest *p*-value is considered. In this case, it is the test using region as a covariate with *p*-value 0.0473. This *p*-value is greater than the significance level of 0.0167, and at this point the Holm-Bonferroni procedure ceases.

However, this is an explanatory analysis setting, not one in which a predetermined, binary threshold must be strictly followed. Because the *p*-value for the likelihood ratio test using region as a covariate is not much higher than its significance level of 0.0167, further investigation of region as an explanation of FAR submission failure might be informative.

References

Bretz, F., Maurer, W., Brannath, W., & Posch, M. (2009). A graphical approach to sequentially rejective multiple test procedures. *Statistics in Medicine,* 28(4), 586–604. https://doi.org/10.1002/sim.3495

Hoef, J. M. V., & Boveng, P. L. (2007). Quasi-Poisson Vs. Negative Binomial Regression: How Should We Model Overdispersed Count Data? *Ecology,* 88(11), 2766–2772. https://doi.org/10.1890/07-0043.1

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