Comparison of the Content of FDA Letters Not Approving Applications for New Drugs and Associated Sponsor Press Releases

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Comparison of the Content of FDA Letters Not Approving Applications for New Drugs and
Associated Sponsor Press Releases

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Abstract

Background: The US Food and Drug Administration (FDA) issues non-public Complete Response Letters (CRLs) to sponsors when FDA determines that it cannot approve their marketing applications. Thereafter, sponsors may choose but are not required to issue press releases (PRs), often the only public source of information describing FDA’s decisions and rationales.

Objectives: To describe the content of CRLs and compare them to the content of PRs.

Design: Cross-sectional study

Data Sources: All applications for which FDA’s Center for Drug Evaluation and Research (CDER) initially issued CRLs (n=61) between August 11, 2008 and June 27, 2013. CRLs and PRs were divided into discrete statements related to seven domains and 64 subdomains and assessed to determine whether CRL and PR statements matched.

Results: 48% of CRLs cited deficiencies in both the Safety and Efficacy domains, and only 13% cited neither Safety nor Efficacy deficiencies. No PR was issued for 18% of CRLs, and 21% of PRs did not match any CRL statements. PR statements matched 93 of the 687 CRL statements (14%), including 16% of Efficacy and 15% of Safety statements. Of 32 CRLs calling for a new clinical trial for safety or efficacy, 59% had matching PR statements. Seven CRLs reported higher mortality rates in treated subjects; only one associated PR mentioned this fact.

Conclusions: FDA generally issues CRLs to sponsors for multiple, substantive reasons, most commonly related to safety and/or efficacy deficiencies. In many cases, PRs were not issued in response to those CRLs and, when they were, PRs omitted the majority of CRL statements. PRs are incomplete substitutes for the detailed information contained in CRLs.
Introduction

When the U.S. Food and Drug Administration (FDA) declines to approve an application to market a drug, it informs the sponsor in a complete response letter (CRL). CRLs systematically document deficiencies FDA reviewers have identified and typically explain corrective actions sponsors can take.

With limited exceptions, the public does not receive a full accounting of FDA’s reasons for disapproval because CRLs are part of unapproved applications that FDA regulations generally treat as confidential. Some have called on FDA to publicly disclose the CRLs, arguing this would ensure a more accurate portrayal of FDA’s reasoning and would allow sponsors, researchers and clinicians to learn from previous scientific and regulatory failures. Currently the European Medicines Agency publishes refusal assessment reports detailing its reasons for denying applications. Some members of the pharmaceutical industry, however, have opposed the disclosure of any information that may be considered proprietary and confidential and have suggested that the release of CRLs would provide an advantage to competitors.

Sponsors commonly issue press releases (PRs) for CRLs they receive, presumably, in part, because US securities laws require companies to disclose information that reasonable investors would be substantially likely to consider important in making investment decisions. By aggregating data for all recent CRLs so that sponsors and specific drug products are not identifiable, we aimed to characterize (1) reasons FDA has cited for not approving drug marketing applications and (2) the degree to which sponsor PRs reflect those CRLs. Of course, given the distinct purpose and frequent brevity of PRs, it is not expected that they would necessarily cover all components of FDA-issued CRLs.
Methods

Identification and Categorization of CRLs

We obtained CRLs for all drugs that were the subject of applications classified as New Molecular Entities (NMEs) (i.e., drugs that contain active moieties that FDA has not previously approved). The CRLs for New Drug Applications (NDAs) were obtained from the FDA Document Archiving, Reporting, and Regulatory Tracking System (DARRTS), and those for Center for Drug Evaluation and Research (CDER)-regulated Biologics Licensing Applications (BLAs) were obtained from the Economics Staff in FDA’s Office of Policy and Planning. The study covered NDA and BLA applications from August 11, 2008, when CDER began issuing CRLs, through June 27, 2013. We included only the first CRL for a given NDA or BLA, thus excluding CRLs issued after sponsors responded to initial CRLs by resubmitting applications. One CRL addressing two indications for the same NME was treated as two separate CRLs. We excluded from the study supplemental NDAs (for new indications, dosage forms, doses, packaging, and labeling for already approved drugs), abbreviated NDAs (for generic drugs), and applications for radiologic agents (e.g., contrast media).

We categorized sponsors as either privately or publicly held using The Bloomberg Business Week website. We used the site’s symbol lookup function to search for sponsor names under the “public” and “private” search fields. These results were then confirmed by searching for the company name in the US Securities and Exchange Commission’s (SEC’s) Electronic Data Gathering, Analysis, and Retrieval (EDGAR) system, which only includes filings from public companies. We considered sponsors to be publicly traded if they were listed as such in Bloomberg Businessweek and were also listed in EDGAR. Conversely, a sponsor was considered private if Bloomberg Businessweek listed them as such and they did not appear in
EDGAR. We identified no discrepancies between these two sources. If company websites and PRs revealed a sponsor to be a subsidiary of a larger company, the parent company’s status was used. We used The Dun & Bradstreet Business Information database, which was used to characterize sponsors as either “large” or “small” using a cutoff of 750 employees based on the Small Business Administration classification of business size.15

We used DARRTS and data FDA’s Economics Staff provided to determine the date of CRL issuance, application status as of June 27, 2013, date of subsequent approval (if applicable), drug therapeutic area, review priority granted to the application (standard or priority), and “first-in-class” status (drugs with a new and unique mechanism of action for treating a medical condition). We defined an orphan drug as one designated as such in FDA’s online Orphan Drug Product Designation Database for the proposed indication in the application. The FDA website also indicates whether an application was referred to an advisory committee prior to CRL issuance. Posted minutes from public advisory committee meetings discuss the conclusions the committee reached. We classified these conclusions as favoring approval if the committee majorities either explicitly favored approval, stated that both safety and efficacy had been demonstrated, or concluded that the benefits of the products outweighed their risks, a method consistent with previous research on advisory committee voting.17

Identification of PRs

We identified sponsor-issued PRs describing CRL issuance through publicly available sources, including the sponsors’ websites and Internet search engines (Google, Yahoo, Bing, PRNewswire.com, and Drugs.com). Search terms were a combination of the drug’s proprietary and non-proprietary names and one of the following terms, in succession: “news release,” “press release,” “PR,” “complete response,” and “CRL.” If these sources did not identify associated
PRs, we contacted sponsors directly via mail to request copies of any PRs, stating that if we did not receive correspondence from them claiming otherwise by a designated date, we would assume that no PRs had been issued. We also entered drug names into the full-text document search function of the EDGAR system to search all US SEC filings, including Quarterly and Annual Reports, for any suggestion that PRs had been released.

Coding of CRL Content

We divided CRL contents into discrete “statements” describing specific application deficiencies. We defined statements as portions of CRLs conveying single concepts. We then assigned each CRL statement to one of seven mutually exclusive domains (these are listed in Figure 2) based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-E3) as well as an assessment of 10 CRLs included in the study that an investigator not participating in final statement extraction and coding had reviewed. These domains were designed to reflect deficiency categories FDA typically uses in CRLs, although FDA does not use a uniform approach for conveying deficiencies.

Some CRL sentences contained multiple statements. For example, a CRL might state in a single sentence that neither safety nor efficacy had been satisfactorily demonstrated. We classified this as two statements—one relating to Safety and the other to Efficacy. Conversely, multiple, even non-adjacent sentences, could describe a single deficiency.

Each statement was further assigned to one of 64 subdomains, again based on ICH-E3 and the review of 10 CRLs. If necessary, statements were partitioned to reach a level of detail sufficient to permit assignment to single subdomains. Statements that could reasonably be assigned to more than one subdomain were assigned to the more specific subdomain. We
aggregated similar statements in the Chemistry, Manufacturing, and Controls (CMC) and Labeling domains to generate no more than one statement per subdomain in each CRL because those statements were often considerably longer and more detailed than those in other domains. Any statements that were part of the standard CRL template (e.g., informing a sponsor that it had a year to respond to the CRL or that the drug product could not be marketed until the sponsor was notified in writing that the application was approved), or that otherwise did not correspond to a deficiency in the application (e.g., acknowledgment of something the sponsor had successfully demonstrated) were not considered statements for the purposes of this analysis.

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Identification of Matching Statements

Any PR statements addressing the same issues as statements in corresponding CRLs were recorded as “matching” the CRL statements and were assigned to the same domains and subdomains as the CRL statements. PR statements were not required to provide the same level of detail as CRL statements to be considered a match, and PR sentences were sometimes divided
into two or more statements to maximize CRL-PR statement matching rates. For CRLs lacking corresponding PRs, all CRL statements were considered to have been omitted. We also collected data on PR statements not appearing in CRLs. These PR-specific categories were also identified through an initial review of 10 PRs during study protocol development.

**Data Analysis**

A single investigator identified the particular statements in CRLs and PRs, classified them into domains and subdomains, and, where appropriate, matched PR statements to CRL statements. The principal investigator then reviewed all statements and their classifications. These two investigators reconciled all disagreements directly.

We compared the lengths of CRLs and PRs using Microsoft Word’s word count feature. These counts included all CRL text related to application deficiencies, but excluded CRL introductions, page headers, and wording common to all CRLs regarding labeling, the need to keep safety information current, and deadlines for resubmission. PR word counts excluded safe harbor statements, notes to editors, and media contact information.

The primary outcomes analyzed were the number and percentage of CRLs with deficiencies in each of the domains and subdomains and the number and percentage of such statements that appeared in the associated PRs. We examined the relationship between company, drug, and review process characteristics and the following: (1) whether a PR was issued; (2) whether the PR matched any CRL statements; (3) the proportion of CRL statements that were matched in associated PRs; and (4) whether the PR contained at least one CRL statement recommending a new clinical trial for safety or efficacy.

Frequencies and cross-tabulations were performed with the built-in functions of Microsoft Access. We calculated relative risks and 95% confidence intervals using MedCalc.
online statistical software. Differences between means were analyzed with a two-tailed Student’s t-test. A p-value <0.05 was considered statistically significant.

Results

CRL Characteristics

A total of 61 CRLs (48 NDAs and 13 BLAs) met inclusion criteria (Table 1, Column 2). Ninety-seven NDAs and BLAs without a prior CRL were approved during the study period. Applications for which CRLs were issued and those that were approved without first receiving a CRL were similar with respect to application type (i.e., NDA vs. BLA), sponsorship by a publicly traded company, company size, and orphan status. However, applications with priority review status were less likely to receive a CRL (RR 0.43; 95% CI 0.25-0.75). Drugs referred to advisory committees were marginally more likely to be the subject of a CRL (RR 1.45; 95% CI 0.97-2.17), although favorable advisory committee votes were associated with a lower probability of CRL issuance (RR 0.34; 95% CI 0.22-0.50).

We observed a median of four domains per CRL. Seven percent of CRLs included deficiencies in all seven domains, and 8% had deficiencies in only a single domain. The domains most frequently implicated were Safety (at least one statement in 69% of CRLs), CMC (69%), and Efficacy (67%). Forty-eight percent of CRLs had deficiencies in both the Safety and Efficacy domains, while only 13% had neither Safety nor Efficacy deficiencies.

PR Characteristics and Matching Rates

We were unable to identify associated PRs for 11 of the 61 CRLs (Figure 1). We received responses to our mailed inquiries related to five of these 11 drugs, all of which confirmed that no PRs were issued. All PRs identified were released within one week of the CRL (median of 1 day), except for two PRs published after 15 and 42 days, one of which announced that the drug
was no longer being developed. After standardized language was excluded, CRLs and PRs differed greatly in length, with a median CRL word count of 1151 (range 99 to 5974) for the 61 CRLs (the median was similar for just the 50 CRLs with associated PRs) and a median PR word count of 193 (range 78 to 532).

NDAs were less likely to have PRs associated with CRLs than BLAs (RR 0.79; 95% CI 0.66-0.95); all BLAs had associated PRs. Having a publicly traded sponsor was the only other significant predictor of PR issuance among the company, drug, and review process characteristics listed in Table 1 (RR 2.71; 95% CI 1.07-6.86).

Thirteen additional PRs (21%) had no statements matching those in their associated CRLs. Eleven of these PRs included at least one statement that did not appear in associated CRLs. The two other PRs were short documents (110 and 117 words) that included no content qualifying as a statement for the purposes of this study. Thirty-seven PRs (61% of CRLs) included one or more statements matching CRL statements (Figure 1).
from 51% to 99%, and two PRs (3%) matched all CRL statements (Figure 1). Twenty-three of 50 PRs (46%) stated that receipt of a CRL meant that marketing could not commence at that time.

Characteristics of CRLs with at least one matching PR statement compared to those with no such statements are shown in Table 1 (Columns 3-5). CRLs issued to large company sponsors were less likely to have at least one matching PR statement (RR 0.68; 95% CI 0.47–0.98), while those issued to publicly traded sponsors were more (but not quite significantly more) likely to do so (RR 6.23; 95% CI 0.97–39.90). No other predictors of having at least one matching PR statement were identified.

**CRLs and PRs: Analysis Overview of Statements**

A total of 687 statements were identified in all 61 CRLs (median 8 statements per CRL; range 1–38). As shown in Figure 2, the most frequent statements were in the **Efficacy** domain (191 statements; median 4 and maximum 17 per CRL), followed by the **Safety** domain (150 statements; median 3 and maximum 11). Together these two domains accounted for half of all CRL statements.

Ninety-three (14%) of the 687 statements in the 61 CRLs were matched in PRs. The median number of matched statements was one (range 0 to 10), and the median number of omissions per CRL was seven (range 0 to 38). CRLs with more than the median of 8 statements had a lower matching rate than CRLs with 8 or fewer statements (11% vs. 21%). Matching at the statement level (Table 1, Columns 7-9) was higher among public companies (RR 8.86; 95% CI 2.22–35.45) and lower among larger companies (RR 0.31; 95% CI 0.22–0.46), the same characteristics that predicted whether a CRL had at least one matching statement (Table 1: Columns 3-5). Still, no characteristic was associated with a matching rate exceeding 26% at the statement level. The statements most likely to be omitted from PRs were **General** statements.
(96% omitted) and Clinical Pharmacology statements (93% omitted; Figure 2). The domain with
the highest matching rate was CMC, with 25% of CRL statements matched. The matching rates
for Efficacy and Safety (16% and 15%, respectively) were similar to the overall matching rate,
although 56% of all matching statements were in these domains.

The number of matched and omitted statements by subdomain is shown in Figure 3. The
most common Efficacy subdomain was Insufficient Evidence of Efficacy (29 CRLs, 53
statements), followed by General Efficacy Concerns (17 CRLs, 32 statements). Requires New
Clinical Trial for Efficacy was the Efficacy subdomain most frequently matched (57% of 28
statements matched); there were more matched statements in this subdomain (16 statements)
than all other Efficacy subdomains combined (14 statements).

Within the Safety domain, CRLs most commonly contained General Safety Concerns (28
CRLs, 52 statements, 4% matched). Other commonly cited Safety deficiencies included
Insufficient Evidence of Safety (18 CRLs, 26 statements, 12% matched), Requires New Analysis
of Safety Data (14 CRLs, 25 statements), and Requires New Trial for Safety (15 CRLs, 17
statements). We observed higher matching rates in the subdomains Risk Evaluation and
Mitigation Strategy (REMS) Required (50%) and Requires New Trial for Safety (35%). Seven
CRLs indicated that a clinical trial had a higher mortality rate in treated subjects compared to
those in control groups, but only one of these statements had a matching PR statement.

Thirty-two CRLs (52%) contained at least one statement indicating that FDA
recommended a new trial for either safety or efficacy. No company,
drug, or review characteristic was associated with the presence of this statement. Nineteen of the
PRs associated with these 32 CRLs (59%) had at least one matching safety/efficacy trial
recommendation statement; the statement-level matching rate was 49%.
Many PRs (36%) had one or more statements that could not be matched to a CRL statement, with a total of 59 such statements, or 39% of all PR statements (Figure 4). Twelve percent of such statements raised questions about the regulatory process or standard or expressed disagreement with FDA’s interpretation of clinical data, and 5% referred to data FDA neither reviewed nor cited in the CRL.

Impact of SEC Disclosures

To determine whether companies might be using alternative routes to disclose the information in CRLs, we searched EDGAR and identified 35 annual, quarterly, or foreign SEC reports related to the study drugs that mentioned CRLs (57% of all CRLs). The median time between CRL issuance and first mention in a SEC report was 33 days. Of the 33 CRLs with both PRs and SEC reports mentioning CRLs, only seven SEC filings (21%) included a statement with more CRL information than the PR, and this information would have produced only 8 additional matches with CRLs, increasing the statement matching rate from 14% to 15%. Thus, SEC mentions of CRLs were sometimes absent, issued significantly later than CRLs (median of 33 days), and, in general, less detailed than the CRLs.

Discussion

This study describes FDA’s reasons for not approving marketing applications for NMEs and establishes that they are not being fully conveyed to the public. FDA issues CRLs for a wide variety of substantive reasons (median of 8 statements in a median of four domains). Safety and/or Efficacy concerns were identified in 87% of CRLs, and Safety and Efficacy statements encompassed 50% of all CRL statements. There was no company-issued PR for 18% of CRLs and no matching statement in an additional 21%. Overall, PRs only referred to 14% of the statements in the full set of CRLs.
The applications for which CRLs were issued were not distinguishable from applications approved without CRLs with respect to company and drug characteristics (e.g., public trading status, company size, or being a first-in-class drug), but applications were distinguishable based on certain characteristics related to their review by FDA. Drugs for which CRLs were issued were less likely to be priority review drugs, more likely to have been referred to an advisory committee, and less likely to have received a favorable advisory committee vote if they were referred.

A previous analysis of 151 NME applications receiving a CRL from 2000 to 2012 found that applications with Efficacy deficiencies were more likely never to be approved (RR 2.24; 95% CI 1.50-3.34; calculation by the authors). The study also found that deficiencies in safety and efficacy were primary reasons for non-approval (53% and 76% of applications, respectively). This study differed from ours in that it reported the primary reasons for application non-approval, based on the CRL, FDA action letters, reviews, and correspondence. In contrast, our study relied exclusively upon CRLs and did not attempt to assign primary reasons for non-approval. The earlier study did not compare CRL and PR matching rates.

Only 15% of Safety and Efficacy statements were matched, similar to the 12% matching rate in the other 5 domains. Only a minority of PRs clearly stated that receipt of a CRL meant that marketing could not commence, and even most findings associating the drug with a higher mortality rate went unmentioned in PRs. However, PRs were more likely to convey whether FDA recommended a new trial for safety or efficacy reasons (49% matched). Statements that were included in PRs were typically accurate, even though they were generally less detailed than CRL statements. In general, PRs from publicly traded (and small) companies were more likely to
communicate CRL content, suggesting that US SEC disclosure requirements may be an important driver of disclosure.

Clearly, a PR’s primary purpose is not to reveal every deficiency FDA identifies; PRs are almost always considerably shorter and less technical than CRLs. Nonetheless, they remain the predominant source of publicly available information regarding CRLs; to our knowledge, no sponsor chose to release a CRL included in this study, although nothing prevents one from doing so.

In 2009, FDA released its Transparency Initiative, which aimed to provide information regarding the Agency and its work to the public and regulated industry. In 2010, FDA’s Transparency Task Force proposed that “FDA should disclose the fact that the Agency has issued a … CRL … and at the same time, disclose the … CRL,” and sought public comment on this proposal. Our analysis of the content of PRs indicates that PRs are incomplete substitutes for the detailed information CRLs contain. Disclosure of CRLs would allow FDA to increase the overall transparency of its regulatory processes, providing greater awareness of the Agency’s role in protecting health, and combating misperceptions regarding the basis for drug non-approval. It would also allow for broader and more informed public discussion by relevant stakeholders (such as patients, clinicians, researchers, and public health advocates) of the reasons for FDA’s actions. The need for increased transparency, however, must take into consideration the legal requirement to protect sponsors’ trade secret and confidential business information.

Three potential approaches to reducing the gap between the information provided in CRLs and that provided in PRs are: 1) Sponsors could release the CRLs themselves, although they did not choose to do so for any of the CRLs in this study; 2) The sponsors could release more complete PRs; and 3) FDA could itself make the CRLs public, although this would likely
require a change in FDA’s regulations. A thorough discussion of these options is beyond the scope of this paper.

We recognize several limitations of this study. First, we did not seek to characterize the accuracy of each particular statement in the PRs. Second, our reported matching rates may overstate the correspondence between CRLs and PRs. Dividing CRLs into relatively specific statements and allowing PR statements to qualify as matching even if they were not as comprehensive as corresponding CRL statements tends to maximize matching rates. For example, one CRL statement detailed a request for a new efficacy trial in 110 words, including “you will need to provide satisfactory results from another adequate and well-controlled trial in patients with [disease] demonstrating the effect of [drug] on a short-term measure …,” while the corresponding PR noted in 17 words that the CRL recommended an additional clinical trial. Moreover, we limited CMC and Labeling statements to one per subdomain per CRL due to the length and level of detail of these statements. This was intended to avoid overemphasizing these potentially less substantial deficiencies, but it also had the effect of increasing matching rates, as even a limited mention of an issue related to these subdomains would have qualified as a match.

Third, the practice of assigning CRL and PR statements to domains and subdomains is inherently subjective and potentially limits the reproducibility of this research. However, the practice of finely dividing statements enhances reproducibility, two authors reviewed all assignments, and, given the robust findings, minor reassignments are unlikely to affect the fundamental conclusions. Finally, we included only CRLs issued by CDER, and our results cannot be extrapolated to other FDA centers involved in product approvals.

Conclusion
This study demonstrates that CRLs are issued to sponsors for multiple, substantive reasons, most commonly related to safety and efficacy. We describe, for the first time, substantial differences in content between confidential CRLs and sponsor-issued PRs. Our analysis suggests that PRs are generally an incomplete source of reasons for FDA non-approval of applications. The potential benefits of publicly disclosing the Agency’s detailed rationale for refusing approval include better informing the development of new investigational agents, drugs, facilitating a richer adding positively to public health discourse, and counteracting misconceptions regarding FDA’s reasons for denial of applications. FDA will consider these issues as it charts its future policies.
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Competing Interests Statement

The authors declare that we have received no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years (other than our employer), and no other relationships or activities that could appear to have influenced the submitted work.

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Transparency Declaration

The lead author (the manuscript’s guarantor) affirms that the manuscript is an honest,
accurate, and transparent account of the study being reported; that no important aspects of the
study have been omitted; and that any discrepancies from the study as planned (and, if relevant,
registered) have been explained.

Ethics Committee Approval

This research was not submitted to an ethics committee as it does not involve human
subjects.

Contributorship Statement

Dr. Lurie conceived the study, oversaw data analysis and played a leading role in drafting the
manuscript
Dr. Chahal helped conceive the study, designed the data collection instrument and reviewed all
CRLs and PRs with PL
Mr. Sigelman contributed to study design and write-up
Dr. Stacy contributed data analysis and portions of the first draft of the manuscript
Dr. Sclar prepared portions of the first draft of the manuscript

Ms. Ddamulira conducted the analysis related to the SEC
Table 1. General characteristics of all CRLs and predictors of matching.*

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<th>Characteristic</th>
<th>All CRLs (n = 61)</th>
<th>CRLs with at Least One Matched PR Statement(s) (n = 37)</th>
<th>CRLs with No Matched Statements† (n = 24)</th>
<th>Relative Risk‡ (95% CI)</th>
<th>All Statements (n = 687)</th>
<th>Matched Statement(s) (n = 93)</th>
<th>Omitted Statements‡ (n = 594)</th>
<th>Relative Risk‡ (95% CI)</th>
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<td>New Drug Application, # (%)</td>
<td>48 (79)</td>
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<td>20 (42)</td>
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<td>536 (78)</td>
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<td>52 (85)</td>
<td>36 (69)</td>
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<td>575 (84)</td>
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<td>Private Sponsor, # (%)</td>
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<td>6.23 (0.97-39.90)</td>
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<td>Large Sponsor (&gt;750 employees), # (%)</td>
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<td>472 (69)</td>
<td>38 (8)</td>
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<td>Small Sponsor (&lt;750 employees), # (%)</td>
<td>15 (25)</td>
<td>12 (80)</td>
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<td>17 (28)</td>
<td>13 (76)</td>
<td>4 (24)</td>
<td></td>
<td>214 (31)</td>
<td>36 (17)</td>
<td>178 (74)</td>
<td></td>
</tr>
<tr>
<td>Not an Orphan Drug, # (%)</td>
<td>44 (72)</td>
<td>24 (55)</td>
<td>20 (45)</td>
<td>1.40 (0.96 - 2.04)</td>
<td>473 (69)</td>
<td>57 (13)</td>
<td>416 (87)</td>
<td>1.40 (0.95 - 2.05)</td>
</tr>
<tr>
<td>Priority Review, # (%)</td>
<td>12 (20)</td>
<td>8 (67)</td>
<td>4 (33)</td>
<td></td>
<td>139 (20)</td>
<td>17 (12)</td>
<td>122 (88)</td>
<td></td>
</tr>
<tr>
<td>Standard Review, # (%)</td>
<td>49 (80)</td>
<td>29 (59)</td>
<td>20 (41)</td>
<td>1.13 (0.71-1.79)</td>
<td>548 (80)</td>
<td>76 (14)</td>
<td>472 (86)</td>
<td>0.88 (0.54-1.44)</td>
</tr>
<tr>
<td>First-in-Class, # (%)</td>
<td>20 (33)</td>
<td>14 (70)</td>
<td>6 (30)</td>
<td></td>
<td>229 (33)</td>
<td>36 (16)</td>
<td>193 (84)</td>
<td></td>
</tr>
<tr>
<td>Not First-in-Class, # (%)</td>
<td>41 (67)</td>
<td>23 (56)</td>
<td>18 (44)</td>
<td>1.25 (0.84-1.85)</td>
<td>458 (67)</td>
<td>57 (12)</td>
<td>401 (88)</td>
<td>1.26 (0.86-1.86)</td>
</tr>
<tr>
<td>Referred to Advisory Committee Prior to CRL Issuance, # (%)</td>
<td>35 (57)</td>
<td>22 (63)</td>
<td>13 (37)</td>
<td></td>
<td>421 (61)</td>
<td>62 (15)</td>
<td>359 (85)</td>
<td></td>
</tr>
<tr>
<td>Not Referred to Advisory Committee, # (%)</td>
<td>26 (43)</td>
<td>15 (58)</td>
<td>11 (42)</td>
<td>1.08 (0.72-1.65)</td>
<td>266 (39)</td>
<td>31 (12)</td>
<td>235 (88)</td>
<td>1.26 (0.84-1.89)</td>
</tr>
<tr>
<td>Advisory Committee In Favor of Approval, # (%)</td>
<td>18 (53)</td>
<td>11 (61)</td>
<td>7 (39)</td>
<td></td>
<td>163 (40)</td>
<td>27 (17)</td>
<td>136 (83)</td>
<td></td>
</tr>
<tr>
<td>Not in Favor of Approval, # (%)§</td>
<td>16 (47)</td>
<td>10 (63)</td>
<td>6 (38)</td>
<td>0.98 (0.58-1.66)</td>
<td>244 (60)</td>
<td>32 (13)</td>
<td>212 (87)</td>
<td>1.26 (0.79-2.03)</td>
</tr>
<tr>
<td>Days From Start of Review Cycle to Issuance of CRL, mean (range)</td>
<td>313 (179-579)</td>
<td>322 (181-579)</td>
<td>299 (179-396)</td>
<td>0.26</td>
<td>312 (179-579)</td>
<td>330 (181-579)</td>
<td>309 (179-579)</td>
<td>0.53</td>
</tr>
<tr>
<td>Application Subsequently Approved, # (%)</td>
<td>25 (41)</td>
<td>17 (68)</td>
<td>8 (32)</td>
<td></td>
<td>228 (33)</td>
<td>38 (17)</td>
<td>190 (83)</td>
<td></td>
</tr>
<tr>
<td>Application Withdrawn or Pending, # (%)</td>
<td>36 (59)</td>
<td>20 (56)</td>
<td>16 (44)</td>
<td>1.22 (0.82-1.82)</td>
<td>459 (67)</td>
<td>55 (13)</td>
<td>404 (87)</td>
<td>1.39 (0.95-2.04)</td>
</tr>
<tr>
<td>Days From Issuance of CRL to Approval of Application (if Approved), mean (n, range)</td>
<td>448 (25, 95-1309)</td>
<td>408 (17, 127-532, 8, 95-1126)</td>
<td>532 (8, 95-1126)</td>
<td>0.38</td>
<td>546 (228, 95-1309)</td>
<td>454 (38, 127-564, 190, 95-1309)</td>
<td>564 (190, 95-1309)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Percentages in columns 2 and 6 are column percentages. All other percentages are row percentages.
† Includes 11 CRLs without associated PRs.
‡ Calculated as the proportion of drugs with the characteristic with a match divided by the proportion without the characteristic with a match using MedCalc Statistical Software, Version 12.7.7, Ostend, Belgium. Available at: www.medcalc.org.
§ Percentages in this row consider only the CRLs and statements associated with applications that went to advisory committee prior to CRL issuance. One advisory committee was not directly asked whether the NDA should be approved.
Figure 1. Complete response letters by percent of statements matched (n = 61).

Figure 2. Matched and omitted complete response letter statements by domain.
Figure 3: Number of matched and omitted CRL statements by subdomain, arranged by domain. Overall matching rate for each domain is shown in parentheses.

- **General** (4% matched)
- **Efficacy** (16% matched)
- **Safety** (15% matched)
- **Clinical Pharmacology** (7% matched)
- **Nonclinical Studies** (15% matched)
- **CMC** (25% matched)
- **Labeling** (16% matched)

*Each asterisk represents four merged subdomains: Requires New Study; Study Suggests Lack of Safety; Study/Data not Satisfactory; and Requires New Analysis of Data. CMC, Chemistry, Manufacturing, and Controls; GCP, Good Clinical Practices; PK, Pharmacokinetic; REMS, Risk Evaluation and Mitigation Strategy*
Figure 4. Statements appearing in press releases but not in associated complete response letters (n = 59).

- Refers to marketing process or approval by a foreign regulatory agency: 13
- Refers to a FDA advisory committee meeting: 13
- Correctly states that no new clinical studies were requested in the CRL: 9
- Raises questions about regulatory process or standard: 7
- Indicates disagreement with FDA’s interpretation of clinical data: 7
- Refers to additional trials or data not yet reviewed or cited by the FDA: 3
- Correctly states that new studies of any type were requested in the CRL: 3
- Announces discontinuation of drug development following CRL receipt: 2
- Quotes an outside expert or published clinical trial: 1
- Emphasizes non-primary endpoints: 1

FDA, Food and Drug Administration; CRL, Complete Response Letter
References:

2. Complete response letter to the applicant, 21 CFR 601.3.
4. Confidentiality of data and information in applications for biologics licenses, 21 CFR 601.51.
5. Trade secrets and commercial or financial information which is privileged or confidential, 21 CFR 20.61.


Comparison of the Content of FDA Letters Not Approving Applications for New Drugs and Associated Sponsor Press Releases

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Word Count: 4,372 words
Abstract

**Background:** The US Food and Drug Administration (FDA) issues non-public Complete Response Letters (CRLs) to sponsors when FDA determines that it cannot approve their marketing applications. Thereafter, sponsors may choose but are not required to issue press releases (PRs), often the only public source of information describing FDA’s decisions and rationales.

**Objectives:** To describe the content of CRLs and compare them to the content of PRs.

**Design:** Cross-sectional study

**Data Sources:** All applications for which FDA’s Center for Drug Evaluation and Research (CDER) initially issued CRLs (n=61) between August 11, 2008 and June 27, 2013. CRLs and PRs were divided into discrete statements related to seven domains and 64 subdomains and assessed to determine whether CRL and PR statements matched.

**Results:** 48% of CRLs cited deficiencies in both the *Safety* and *Efficacy* domains, and only 13% cited neither *Safety* nor *Efficacy* deficiencies. No PR was issued for 18% of CRLs, and 21% of PRs did not match any CRL statements. PR statements matched 93 of the 687 CRL statements (14%), including 16% of *Efficacy* and 15% of *Safety* statements. Of 32 CRLs calling for a new clinical trial for safety or efficacy, 59% had matching PR statements. Seven CRLs reported higher mortality rates in treated subjects; only one associated PR mentioned this fact.

**Conclusions:** FDA generally issues CRLs to sponsors for multiple, substantive reasons, most commonly related to safety and/or efficacy deficiencies. In many cases, PRs were not issued in response to those CRLs and, when they were, PRs omitted the majority of CRL statements. PRs are incomplete substitutes for the detailed information contained in CRLs.
Introduction

When the U.S. Food and Drug Administration (FDA) declines to approve an application to market a drug, it informs the sponsor in a complete response letter (CRL).\(^1,2\) CRLs systematically document deficiencies FDA reviewers have identified and typically explain corrective actions sponsors can take.

With limited exceptions, the public does not receive a full accounting of FDA’s reasons for disapproval because CRLs are part of unapproved applications that FDA regulations generally treat as confidential.\(^3,4,5\) Some have called on FDA to publicly disclose the CRLs, arguing this would ensure a more accurate portrayal of FDA’s reasoning and would allow sponsors, researchers and clinicians to learn from previous scientific and regulatory failures.\(^6,7,8\) Currently the European Medicines Agency publishes refusal assessment reports detailing its reasons for denying applications.\(^9\) Some members of the pharmaceutical industry, however, have opposed the disclosure of any information that may be considered proprietary and confidential and have suggested that the release of CRLs would provide an advantage to competitors.\(^10\)

Sponsors commonly issue press releases (PRs) for CRLs they receive, presumably, in part, because US securities laws require companies to disclose information that reasonable investors would be substantially likely to consider important in making investment decisions.\(^11\) By aggregating data for all recent CRLs so that sponsors and specific drug products are not identifiable, we aimed to characterize (1) reasons FDA has cited for not approving drug marketing applications and (2) the degree to which sponsor PRs reflect those CRLs. Given the distinct purpose and frequent brevity of PRs, it is not expected that they would necessarily cover all components of FDA-issued CRLs.

Methods


Identification and Categorization of CRLs

We obtained CRLs for all drugs* that were the subject of applications classified as New Molecular Entities (NMEs) (i.e., drugs that contain active moieties that FDA has not previously approved). The CRLs for New Drug Applications (NDAs) were obtained from the FDA Document Archiving, Reporting, and Regulatory Tracking System (DARRTS), and those for Center for Drug Evaluation and Research (CDER)-regulated Biologics Licensing Applications (BLAs) were obtained from the Economics Staff in FDA’s Office of Policy and Planning. The study covered NDA and BLA applications from August 11, 2008, when CDER began issuing CRLs, through June 27, 2013. We included only the first CRL for a given NDA or BLA, thus excluding CRLs issued after sponsors responded to initial CRLs by resubmitting applications. One CRL addressing two indications for the same NME was treated as two separate CRLs. We excluded from the study supplemental NDAs (for new indications, dosage forms, doses, packaging, and labeling for already approved drugs), abbreviated NDAs (for generic drugs), and applications for radiologic agents (e.g., contrast media).

We categorized sponsors as either privately or publicly held using The Bloomberg Business Week website.\textsuperscript{12} We used the site’s symbol lookup function to search for sponsor names under the “public” and “private” search fields. These results were then confirmed by searching for the company name in the US Securities and Exchange Commission’s (SEC’s) Electronic Data Gathering, Analysis, and Retrieval (EDGAR) system, which only includes filings from public companies.\textsuperscript{13} We considered sponsors to be publicly traded if they were listed as such in Bloomberg Businessweek and were also listed in EDGAR. Conversely, a sponsor was considered private if Bloomberg Businessweek listed them as such and they did not appear in EDGAR. We identified no discrepancies between these two sources. If company websites and
PRs revealed a sponsor to be a subsidiary of a larger company, the parent company’s status was used. We used the Dun & Bradstreet Business Information database,\textsuperscript{14} which characterizes sponsors as either “large” or “small” using the cutoff of 750 employees used in the Small Business Administration classification of business size.\textsuperscript{15}

We used DARRTS and data FDA’s Economics Staff provided to determine the date of CRL issuance, application status as of June 27, 2013, date of subsequent approval (if applicable), drug therapeutic area, review priority granted to the application (standard or priority), and “first-in-class” status (drugs with a new and unique mechanism of action for treating a medical condition). We defined an orphan drug as one designated as such in FDA’s online Orphan Drug Product Designation Database\textsuperscript{16} for the proposed indication in the application. The FDA website also indicates whether an application was referred to an advisory committee prior to CRL issuance. Posted minutes from public advisory committee meetings on applications discuss the conclusions the committee reached. We classified these conclusions as favoring approval if the committee majorities either explicitly favored approval, stated that both safety and efficacy had been demonstrated, or concluded that the benefits of the products outweighed their risks, a method consistent with previous research on advisory committee voting.\textsuperscript{17}

\textit{Identification of PRs}

We identified sponsor-issued PRs describing CRL issuance through publicly available sources, including the sponsors’ websites and Internet search engines (Google, Yahoo, Bing, PRNewswire.com, and Drugs.com). Search terms were a combination of the drug’s proprietary and non-proprietary names and one of the following terms, in succession: “news release,” “press release,” “PR,” “complete response,” and “CRL.” If these sources did not identify associated PRs, we contacted sponsors directly via mail to request copies of any PRs, stating that if we did
not receive correspondence from them claiming otherwise by a designated date, we would assume that no PRs had been issued. We also entered drug names into the full-text document search function of the EDGAR system\(^{18}\) to search all US SEC filings, including Quarterly and Annual Reports, for any suggestion that PRs had been released.

**Coding of CRL Content**

We divided CRL contents into discrete “statements” describing specific application deficiencies. We defined statements as portions of CRLs conveying single concepts. We then assigned each CRL statement to one of seven mutually exclusive domains (these are listed in Figure 2) based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-E3)\(^{19}\) as well as an assessment of 10 CRLs included in the study that an investigator not participating in final statement extraction and coding had reviewed. These domains were designed to reflect deficiency categories FDA typically uses in CRLs, although FDA does not use a uniform approach for conveying deficiencies.

Some CRL sentences contained multiple statements. For example, a CRL might state in a single sentence that neither safety nor efficacy had been satisfactorily demonstrated. We classified this as two statements—one relating to Safety and the other to Efficacy. Conversely, multiple, even non-adjacent sentences, could describe a single deficiency.

Each statement was further assigned to one of 64 subdomains, again based on ICH-E3 and the review of 10 CRLs. If necessary, statements were partitioned to reach a level of detail sufficient to permit assignment to single subdomains. Statements that could reasonably be assigned to more than one subdomain were assigned to the more specific subdomain. We aggregated similar statements in the Chemistry, Manufacturing, and Controls (CMC) and
Labeling domains to generate no more than one statement per subdomain in each CRL because those statements were often considerably longer and more detailed than those in other domains. Any statements that were part of the standard CRL template (e.g., informing a sponsor that it had a year to respond to the CRL or that the drug product could not be marketed until the sponsor was notified in writing that the application was approved), or that otherwise did not correspond to a deficiency in the application (e.g., acknowledgment of something the sponsor had successfully demonstrated) were not considered statements for the purposes of this analysis.

Identification of Matching Statements

Any PR statements addressing the same issues as statements in corresponding CRLs were recorded as “matching” the CRL statements and were assigned to the same domains and subdomains as the CRL statements. PR statements were not required to provide the same level of detail as CRL statements to be considered a match, and PR sentences were sometimes divided into two or more statements to maximize CRL-PR statement matching rates. For CRLs lacking corresponding PRs, all CRL statements were considered to have been omitted. We also collected data on PR statements not appearing in CRLs. These PR-specific categories were also identified through an initial review of 10 PRs during study protocol development.

Data Analysis

A single investigator identified the particular statements in CRLs and PRs, classified them into domains and subdomains, and, where appropriate, matched PR statements to CRL statements. The principal investigator then reviewed all statements and their classifications. These two investigators reconciled all disagreements directly.

We compared the lengths of CRLs and PRs using Microsoft Word’s word count feature. These counts included all CRL text related to application deficiencies, but excluded CRL
introductions, page headers, and wording common to all CRLs regarding labeling, the need to keep safety information current, and deadlines for resubmission. PR word counts excluded safe harbor statements, notes to editors, and media contact information.

The primary outcomes analyzed were the number and percentage of CRLs with deficiencies in each of the domains and subdomains and the number and percentage of such statements that appeared in the associated PRs. We examined the relationship between company, drug, and review process characteristics and the following: (1) whether a PR was issued; (2) whether the PR matched any CRL statements; (3) the proportion of CRL statements that were matched in associated PRs; and (4) whether the PR contained at least one CRL statement recommending a new clinical trial for safety or efficacy.

Frequencies and cross-tabulations were performed with the built-in functions of Microsoft Access. We calculated relative risks and 95% confidence intervals using MedCalc online statistical software. Differences between means were analyzed with a two-tailed Student’s t-test. A p-value <0.05 was considered statistically significant.

Patient Involvement

No patients were involved in this study.

Results

CRL Characteristics

A total of 61 CRLs (48 NDAs and 13 BLAs) met inclusion criteria (Table 1, Column 2). Ninety-seven NDAs and BLAs without a prior CRL were approved during the study period. Applications for which CRLs were issued and those that were approved without first receiving a CRL were similar with respect to application type (i.e., NDA vs. BLA), sponsorship by a publicly traded company, company size, and orphan status. However, applications with priority
review status were less likely to receive a CRL (RR 0.43; 95% CI 0.25 to 0.75). Drugs referred to advisory committees were marginally more likely to be the subject of a CRL (RR 1.45; 95% CI 0.97 to 2.17), although favorable advisory committee votes were associated with a lower probability of CRL issuance (RR 0.34; 95% CI 0.22 to 0.50).

We observed a median of four domains per CRL. Seven percent of CRLs included deficiencies in all seven domains, and 8% had deficiencies in only a single domain. The domains most frequently implicated were Safety (at least one statement in 69% of CRLs), CMC (69%), and Efficacy (67%). Forty-eight percent of CRLs had deficiencies in both the Safety and Efficacy domains, while only 13% had neither Safety nor Efficacy deficiencies.

PR Characteristics and Matching Rates

We were unable to identify associated PRs for 11 of the 61 CRLs (Figure 1). We received responses to our mailed inquiries related to five of these 11 drugs, all of which confirmed that no PRs were issued. All PRs identified were released within one week of the CRL (median of 1 day), except for two PRs published after 15 and 42 days, one of which announced that the drug was no longer being developed. After standardized language was excluded, CRLs and PRs differed greatly in length, with a median CRL word count of 1151 (range 99 to 5974) for the 61 CRLs (the median was similar for just the 50 CRLs with associated PRs) and a median PR word count of 193 (range 78 to 532).

NDAs were less likely to have PRs associated with CRLs than BLAs (RR 0.79; 95% CI 0.66 to --0.95); all BLAs had associated PRs. Having a publicly traded sponsor was the only other significant predictor of PR issuance among the company, drug, and review process characteristics listed in Table 1 (RR 2.71; 95% CI 1.07 to 6.86).
Thirteen additional PRs (21%) had no statements matching those in their associated CRLs. Eleven of these PRs included at least one statement that did not appear in associated CRLs. The two other PRs were short documents (110 and 117 words) that included no content qualifying as a statement for the purposes of this study. Thirty-seven PRs (61% of CRLs) included one or more statements matching CRL statements (Figure 1).

CRLs and PRs: Analysis Overview of Statements

A total of 687 statements were identified in all 61 CRLs (median 8 statements per CRL; range 1-38). As shown in Figure 2, the most frequent statements were in the Efficacy domain (191 statements; median 4 and maximum 17 per CRL), followed by the Safety domain (150 statements; median 3 and maximum 11). Together these two domains accounted for half of all CRL statements.

Ninety-three (14%) of the 687 statements in the 61 CRLs were matched in PRs. The median number of matched statements was one (range 0 to 10), and the median number of omissions per CRL was seven (range 0 to 38). CRLs with more than the median of 8 statements had a lower matching rate than CRLs with 8 or fewer statements (11% vs. 21%). Matching at the statement level (Table 1, Columns 7-9) was higher among public companies and lower among larger companies, the same characteristics that predicted whether a CRL had at least one matching statement (Table 1; Columns 3-5). Still, no characteristic was associated with a matching rate exceeding 26% at the statement level. The statements most likely to be omitted from PRs were General statements (96% omitted) and Clinical Pharmacology statements (93% omitted; Figure 2). The domain with the highest matching rate was CMC, with 25% of CRL statements matched. The matching rates for Efficacy and Safety (16% and 15%, respectively)
were similar to the overall matching rate, although 56% of all matching statements were in these domains.

The number of matched and omitted statements by subdomain is shown in Figure 3. The most common Efficacy subdomain was Insufficient Evidence of Efficacy (29 CRLs, 53 statements), followed by General Efficacy Concerns (17 CRLs, 32 statements). Requires New Clinical Trial for Efficacy was the Efficacy subdomain most frequently matched (57% of 28 statements matched); there were more matched statements in this subdomain (16 statements) than all other Efficacy subdomains combined (14 statements).

Within the Safety domain, CRLs most commonly contained General Safety Concerns (28 CRLs, 52 statements, 4% matched). Other commonly cited Safety deficiencies included Insufficient Evidence of Safety (18 CRLs, 26 statements, 12% matched), Requires New Analysis of Safety Data (14 CRLs, 25 statements), and Requires New Trial for Safety (15 CRLs, 17 statements). We observed higher matching rates in the subdomains Risk Evaluation and Mitigation Strategy (REMS) Required (50%) and Requires New Trial for Safety (35%). Seven CRLs indicated that a clinical trial had a higher mortality rate in treated subjects compared to those in control groups, but only one of these statements had a matching PR statement.

Thirty-two CRLs (52%) contained at least one statement indicating that FDA recommended a new trial for either safety or efficacy. No company, drug, or review characteristic was associated with the presence of this statement. Nineteen of the PRs associated with these 32 CRLs (59%) had at least one matching safety/efficacy trial recommendation statement; the statement-level matching rate was 49%.

Many PRs (36%) had one or more statements that could not be matched to a CRL statement, with a total of 59 such statements, or 39% of all PR statements (Figure 4). Twelve
percent of such statements raised questions about the regulatory process or standard or expressed
disagreement with FDA’s interpretation of clinical data, and 5% referred to data FDA neither
reviewed nor cited in the CRL.

**Impact of SEC Disclosures**

To determine whether companies might be using alternative routes to disclose the
information in CRLs, we searched EDGAR and identified 35 annual, quarterly, or foreign SEC
reports related to the study drugs that mentioned CRLs (57% of all CRLs). Of the 33 CRLs with
both PRs and SEC reports mentioning CRLs, only seven SEC filings (21%) included a statement
with more CRL information than the PR, and this information would have produced only 8
additional matches with CRLs, increasing the statement matching rate from 14% to 15%. Thus,
SEC mentions of CRLs were sometimes absent, issued significantly later than CRLs (median of
33 days), and, in general, less detailed than the CRLs.

**Discussion**

**Principal Findings**

This study describes FDA’s reasons for not approving marketing applications for NMEs
and establishes that they are not being fully conveyed to the public. FDA issues CRLs for a wide
variety of substantive reasons (median of 8 statements in a median of four domains). Safety
and/or Efficacy concerns were identified in 87% of CRLs, and Safety and Efficacy statements
encompassed 50% of all CRL statements. There was no company-issued PR for 18% of CRLs
and no matching statement in an additional 21%. Overall, PRs only referred to 14% of the
statements in the full set of CRLs.

The applications for which CRLs were issued were not distinguishable from applications
approved without CRLs with respect to company and drug characteristics (e.g., public trading
status, company size, or being a first-in-class drug), but applications were distinguishable based on certain characteristics related to their review by FDA. Drugs for which CRLs were issued were less likely to be priority review drugs, more likely to have been referred to an advisory committee, and less likely to have received a favorable advisory committee vote if they were referred.

A previous analysis of 151 NME applications receiving a CRL from 2000 to 2012 found that applications with Efficacy deficiencies were more likely never to be approved (RR 2.24; 95% CI 1.50 to 3.34; calculation by the authors). The study also found that deficiencies in safety and efficacy were primary reasons for non-approval (53% and 76% of applications, respectively). This study differed from ours in that it reported the primary reasons for application non-approval, based on the CRL, FDA action letters, reviews, and correspondence. In contrast, our study relied exclusively upon CRLs and did not attempt to assign primary reasons for non-approval. The earlier study did not compare CRL and PR matching rates.

Only 15% of Safety and Efficacy statements were matched, similar to the 12% matching rate in the other 5 domains. Only a minority of PRs clearly stated that receipt of a CRL meant that marketing could not commence, and most findings associating the drug with a higher mortality rate went unmentioned in PRs. However, PRs were more likely to convey whether FDA recommended a new trial for safety or efficacy reasons (49% matched). Statements that were included in PRs were typically accurate, even though they were generally less detailed than CRL statements. In general, PRs from publicly traded (and small) companies were more likely to communicate CRL content, suggesting that US SEC disclosure requirements may be an important driver of disclosure.
Clearly, a PR’s primary purpose is not to reveal every deficiency FDA identifies; PRs are almost always considerably shorter and less technical than CRLs. Nonetheless, they remain the predominant source of publicly available information regarding CRLs; to our knowledge, no sponsor chose to release a CRL included in this study, although nothing prevents one from doing so.

In 2009, FDA released its Transparency Initiative, which aimed to provide information regarding the Agency and its work to the public and regulated industry. In 2010, FDA’s Transparency Task Force proposed that “FDA should disclose the fact that the Agency has issued a … CRL … and at the same time, disclose the … CRL,” and sought public comment on this proposal. Our analysis of the content of PRs indicates that PRs are incomplete substitutes for the detailed information CRLs contain. Disclosure of CRLs would allow FDA to increase the overall transparency of its regulatory processes, providing greater awareness of the Agency’s role in protecting health, and combating misperceptions regarding the basis for drug non-approval. It would also allow for broader and more informed public discussion by relevant stakeholders (such as patients, clinicians, researchers, and public health advocates) of the reasons for FDA’s actions. The need for increased transparency, however, must take into consideration the legal requirement to protect sponsors’ trade secret and confidential business information.

Three potential approaches to reducing the gap between the information provided in CRLs and that provided in PRs are: 1. Sponsors could release the CRLs themselves, although they did not choose to do so for any of the CRLs in this study; 2) Sponsors could release more complete PRs; and 3) FDA could itself make the CRLs public, although this would likely require a change in FDA’s regulations. A thorough discussion of these options is beyond the scope of this paper.
Strengths and Limitations of Study

We recognize several limitations of this study. First, we did not seek to characterize the accuracy of each particular statement in the PRs. Second, our reported matching rates may overstate the correspondence between CRLs and PRs. Dividing CRLs into relatively specific statements and allowing PR statements to qualify as matching even if they were not as comprehensive as corresponding CRL statements tends to maximize matching rates. For example, one CRL statement detailed a request for a new efficacy trial in 110 words, including “you will need to provide satisfactory results from another adequate and well-controlled trial in patients with [disease] demonstrating the effect of [drug] on a short-term measure …,” while the corresponding PR noted in 17 words that the CRL recommended an additional clinical trial.

Moreover, we limited CMC and Labeling statements to one per subdomain per CRL due to the length and level of detail of these statements. This was intended to avoid overemphasizing these potentially less substantial deficiencies, but it also had the effect of increasing matching rates, as even a limited mention of an issue related to these subdomains would have qualified as a match.

Third, the practice of assigning CRL and PR statements to domains and subdomains is inherently subjective and potentially limits the reproducibility of this research. However, the practice of finely dividing statements enhances reproducibility, two authors reviewed all assignments, and, given the robust findings, minor reassignments are unlikely to affect the fundamental conclusions. Finally, we included only CRLs issued by CDER, and our results cannot be extrapolated to other FDA centers involved in product approvals.

Conclusions and Policy Implications

This study demonstrates that CRLs are issued to sponsors for multiple, substantive reasons, most commonly related to safety and efficacy. We describe, for the first time,
substantial differences in content between confidential CRLs and sponsor-issued PRs. Our analysis suggests that PRs are generally an incomplete source of reasons for FDA non-approval of applications. The potential benefits of publicly disclosing the Agency’s detailed rationale for refusing approval include better informing the development of new drugs, facilitating a richer public health discourse, and counteracting misconceptions regarding FDA’s reasons for denial of applications. FDA will consider these issues as it charts its future policies.

Section 1: What is already known on this topic

☐ FDA issues Complete Response Letters (CRLs) to sponsors when the Agency determines that it cannot approve their marketing applications.

☐ Sponsors may choose, but are not required, to issue press releases (PRs) indicating that FDA has issued a CRL.

☐ These PRs are often the only public source of information describing FDA’s decisions and rationales for not approving marketing applications.

Section 2: What this study adds

☐ FDA generally issues CRLs to sponsors for multiple, substantive reasons, most commonly related to safety and/or efficacy.

☐ In many cases, PRs are not issued in response to CRLs.

☐ When PRs are issued, they omit the majority of reasons FDA cited for denying applications.

☐ PRs are incomplete substitutes for the detailed information contained in CRLs.
Acknowledgments

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Competing Interests Statement

The authors declare that we have received no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years (other than our employer), and no other relationships or activities that could appear to have influenced the submitted work.

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**Transparency Declaration**

The lead author (the manuscript’s guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Ethics Committee Approval**

This research was not submitted to an ethics committee as it does not involve human subjects.

**Data Sharing**

No additional data available.

**Contributorship Statement**

Dr. Lurie conceived the study, oversaw data analysis and played a leading role in drafting the manuscript

Dr. Chahal helped conceive the study, designed the data collection instrument and reviewed all CRLs and PRs with PL

Mr. Sigelman contributed to study design and write-up
Dr. Stacy contributed data analysis and portions of the first draft of the manuscript

Dr. Sclar prepared portions of the first draft of the manuscript

Ms. Ddamulira conducted the analysis related to the SEC
References:

5. Trade secrets and commercial or financial information which is privileged or confidential, 21 C.F.R § 20.61 (1994).


Table 1. General characteristics of all CRLs and predictors of matching.

<table>
<thead>
<tr>
<th></th>
<th>All CRLs (n = 61)</th>
<th>CRLs with at Least One Matched PR Statement(s) (n = 37)</th>
<th>CRLs with No Matched Statements† (n = 24)</th>
<th>Relative Risk‡ (95% CI)</th>
<th>All Statements (n = 687)</th>
<th>Matched Statement(s) (n = 93)</th>
<th>Omitted Statements† (n = 594)</th>
<th>Relative Risk‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Drug Application, # (%)</td>
<td>48 (79)</td>
<td>28 (58)</td>
<td>20 (42)</td>
<td>0.84 (0.55-1.30)</td>
<td>536 (78)</td>
<td>75 (14)</td>
<td>461 (86)</td>
<td>1.17 (0.73-1.90)</td>
</tr>
<tr>
<td>Biologics Licensing Application, # (%)</td>
<td>13 (21)</td>
<td>9 (69)</td>
<td>4 (31)</td>
<td>6.23 (0.97-3.90)</td>
<td>151 (22)</td>
<td>18 (12)</td>
<td>133 (88)</td>
<td>8.86 (2.22-35.45)</td>
</tr>
<tr>
<td>Publicly Traded Sponsor, # (%)</td>
<td>52 (85)</td>
<td>36 (69)</td>
<td>16 (31)</td>
<td>1.17 (0.73-1.90)</td>
<td>575 (84)</td>
<td>91 (16)</td>
<td>484 (84)</td>
<td>0.31 (0.22-0.46)</td>
</tr>
<tr>
<td>Private Sponsor, # (%)</td>
<td>9 (15)</td>
<td>1 (11)</td>
<td>8 (39)</td>
<td>20 (42)</td>
<td>215 (31)</td>
<td>55 (26)</td>
<td>160 (74)</td>
<td>0.68 (0.47-0.98)</td>
</tr>
<tr>
<td>Large Sponsor (&gt;750 employees), # (%)</td>
<td>46 (75)</td>
<td>25 (54)</td>
<td>21 (46)</td>
<td>0.84 (0.55-1.30)</td>
<td>472 (69)</td>
<td>38 (8)</td>
<td>434 (92)</td>
<td>0.31 (0.22-0.46)</td>
</tr>
<tr>
<td>Small Sponsor (&lt;750 employees), # (%)</td>
<td>15 (25)</td>
<td>12 (80)</td>
<td>3 (20)</td>
<td>0.84 (0.55-1.30)</td>
<td>214 (31)</td>
<td>36 (17)</td>
<td>178 (74)</td>
<td>0.84 (0.55-1.30)</td>
</tr>
<tr>
<td>Orphan Drug, # (%)</td>
<td>17 (28)</td>
<td>13 (76)</td>
<td>4 (24)</td>
<td>0.84 (0.55-1.30)</td>
<td>214 (31)</td>
<td>36 (17)</td>
<td>178 (74)</td>
<td>0.84 (0.55-1.30)</td>
</tr>
<tr>
<td>Priority Review, # (%)</td>
<td>44 (72)</td>
<td>24 (55)</td>
<td>20 (45)</td>
<td>0.84 (0.55-1.30)</td>
<td>473 (69)</td>
<td>57 (13)</td>
<td>416 (87)</td>
<td>1.40 (0.95 - 2.05)</td>
</tr>
<tr>
<td>Standard Review, # (%)</td>
<td>12 (20)</td>
<td>8 (67)</td>
<td>4 (33)</td>
<td>0.84 (0.55-1.30)</td>
<td>139 (20)</td>
<td>17 (12)</td>
<td>122 (88)</td>
<td>0.84 (0.55-1.30)</td>
</tr>
<tr>
<td>First-in-Class, # (%)</td>
<td>49 (80)</td>
<td>29 (59)</td>
<td>20 (41)</td>
<td>0.84 (0.55-1.30)</td>
<td>548 (80)</td>
<td>76 (14)</td>
<td>472 (86)</td>
<td>0.84 (0.55-1.30)</td>
</tr>
<tr>
<td>Not First-in-Class, # (%)</td>
<td>20 (33)</td>
<td>14 (70)</td>
<td>6 (30)</td>
<td>0.84 (0.55-1.30)</td>
<td>229 (33)</td>
<td>36 (16)</td>
<td>193 (84)</td>
<td>0.84 (0.55-1.30)</td>
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<tr>
<td>Referred to Advisory Committee Prior to CRL Issuance, # (%)</td>
<td>41 (67)</td>
<td>23 (56)</td>
<td>18 (44)</td>
<td>0.84 (0.55-1.30)</td>
<td>458 (67)</td>
<td>57 (12)</td>
<td>401 (88)</td>
<td>0.84 (0.55-1.30)</td>
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<tr>
<td>Application Subsequently Approved, # (%)</td>
<td>25 (41)</td>
<td>17 (68)</td>
<td>8 (32)</td>
<td>0.84 (0.55-1.30)</td>
<td>228 (33)</td>
<td>38 (17)</td>
<td>190 (83)</td>
<td>0.84 (0.55-1.30)</td>
</tr>
<tr>
<td>Application Withdrawn or Pending, # (%)</td>
<td>36 (59)</td>
<td>20 (56)</td>
<td>16 (44)</td>
<td>0.84 (0.55-1.30)</td>
<td>459 (67)</td>
<td>55 (13)</td>
<td>404 (87)</td>
<td>0.84 (0.55-1.30)</td>
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<tr>
<td>Days From Start of Review Cycle to Issuance of CRL, mean (range)</td>
<td>313 (179-579)</td>
<td>322 (181-579)</td>
<td>299 (179-396)</td>
<td>0.84 (0.55-1.30)</td>
<td>312 (179-579)</td>
<td>330 (181-579)</td>
<td>309 (179-579)</td>
<td>0.84 (0.55-1.30)</td>
</tr>
<tr>
<td>Days From Issuance of CRL to Approval of Application (if Approved), mean (n, range)</td>
<td>448 (25, 95-1309)</td>
<td>408 (17, 127-1309)</td>
<td>532 (8, 95-1309)</td>
<td>0.84 (0.55-1.30)</td>
<td>546 (25, 95-1309)</td>
<td>454 (38,127-1309)</td>
<td>564 (190, 95-1309)</td>
<td>0.84 (0.55-1.30)</td>
</tr>
</tbody>
</table>

* Percentages in columns 2 and 6 are column percentages. All other percentages are row percentages.
† Includes 11 CRLs without associated PRs.
‡ Calculated as the proportion of drugs with the characteristic with a match divided by the proportion without the characteristic with a match using MedCalc Statistical Software, Version 12.7.7, Ostend, Belgium. Available at: www.medcalc.org.
§ Percentages in this row consider only the CRLs and statements associated with applications that went to advisory committee prior to CRL issuance. One advisory committee was not directly asked whether the NDA should be approved.
Figure 1. Complete response letters by percent of statements matched (n = 61).
Figure 2. Matched and omitted complete response letter statements by domain.
Figure 3: Number of matched and omitted CRL statements by subdomain, arranged by domain. Overall matching rate for each domain is shown in parentheses.

- **General**
  - 4% matched
- **Efficacy**
  - 16% matched
- **Safety**
  - 15% matched
- **Clinical Pharmacology**
  - 7% matched
- **Nonclinical Studies**
  - 15% matched
- **CMC**
  - 25% matched
- **Labeling**
  - 16% matched

*Each asterisk represents four merged subdomains: Requires New Study; Study Suggests Lack of Safety; Study/Data not Satisfactory; and Requires New Analysis of Data. CMC, Chemistry, Manufacturing, and Controls; GCP, Good Clinical Practices; PK, Pharmacokinetic; REMS, Risk Evaluation and Mitigation Strategy.*
Figure 4. Statements appearing in press releases but not in associated complete response letters (n = 59).

- Refers to marketing process or approval by a foreign regulatory agency: 13
- Refers to a FDA advisory committee meeting: 13
- Correctly states that no new clinical studies were requested in the CRL: 9
- Raises questions about regulatory process or standard: 7
- Indicates disagreement with FDA's interpretation of clinical data: 7
- Refers to additional trials or data not yet reviewed or cited by the FDA: 3
- Correctly states that new studies of any type were requested in the CRL: 3
- Announces discontinuation of drug development following CRL receipt: 2
- Quotes an outside expert or published clinical trial: 1
- Emphasizes non-primary endpoints: 1

FDA, Food and Drug Administration; CRL, Complete Response Letter