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Review Article

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Decoding FDA Complete Response Letters: Regulatory Challenges and Strategies for Successful Drug Approval

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Abstract

A Complete Response Letter (CRL) is provided by the U.S. Food and Drug Administration (FDA) when a marketing application is deemed unprovable in its existing format. Although CRLs hold important regulatory implications, there is a lack of comprehensive analytical frameworks for their assessment. To develop a systematic analytical framework with CTD standards for the identification, classification, and assessment of deficiencies found in FDA Complete Response Letters (CRLs). As such, an established analytical model that was mainly used for FDA Warning Letters is adapted to fit the diagnostic framework employed for CRLs assessment. Found deficiencies were categorised according to the CTD framework, which enabled a systematic distribution in diverse fields — CMC (Module 3), Clinical data (Module 5), Nonclinical information, Labelling requirements, Facility Inspections, Drug–Device Combinations. The methodology utilised thematic grouping and trend analysis to identify ongoing regulatory concerns. Frequent deficiencies included inadequate analytical validation, weak impurity and heavy metal controls, insufficient dissolution data, clinical efficacy failures, safety concerns, labelling non-compliance, and gaps in biocompatibility, extractables/leachable evaluation, and bridging studies. A framework built on CTD enhances the interpretation of CRL, boosts the quality of submissions, identifies potential risks, and fortifies readiness for regulatory compliance in future applications.

Conclusion: The study highlights that major deficiencies in USFDA drug approval submissions, particularly in CMC and clinical areas, are commonly associated with poor data quality, inadequate validation, incomplete documentation, and insufficient safety and efficacy evidence. A systematic, proactive approach incorporating CTD guidelines, deficiency tracking, quality-focused processes, and cross-functional collaboration can improve submission quality, reduce regulatory risks, and facilitate faster patient access to approved therapies.

Keywords: Complete Response Letter (CRL); U.S. Food and Drug Administration (FDA); Common Technical Document (CTD); Regulatory deficiencies; CMC; Clinical deficiencies; Drug–device combination products; Analytical validation; Impurity control; Regulatory compliance; NDA; ANDA; BLA.

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1. Introduction

The United States Food and Drug Administration (USFDA) plays a critical role in confirming that the new drugs in the marketplace are safe, effective, and meet quality standards. The Agency sends out Complete Response Letters (CRLs) upon review of New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) if there existed any deficiencies in submissions. These letters present scientific, clinical, and regulatory concerns that should be resolved for approval They can provide important feedback regarding clinical effectiveness, safety information, manufacturing rules, bioequivalence, and documentation requirements. It makes it possible to evaluate trends in Clinical Review Letters (CRLs) and detect the common errors, regulatory challenges as well as how to enhance the submission through the process leading to lower delays and costs and risks. CRLs are evaluated in terms of content and structure to look for the same problems at issue— they are the things to keep an updated checklist for future reference, and be ready to navigate regulatory approval with fast drug development processes. (1)

2. Objectives

We analyze the contents of the FDA Complete Response Letters (CRLs) from a technical perspective in this work. Deficiencies of CRL will be systematically studied and grouped as follows:

- CMC (Chemistry, Manufacturing, and Controls)
- Clinical
- Nonclinical (Toxicology/Pharmacology)
- Labeling
- Facility/Inspection
- Drug-Device Deficiencies
- Other Regulatory Deficiencies

In the next section we will explain how often these inadequacies in each category occur and what impact they might have on delays to approve application. However, we will point out that weaknesses and how potentially these might affect how drug development happens in that context.

We will examine regulatory expectations in a broader context and study commonly produced errors or problems in a specific area that result in Complete Response Letters (CRLs) of all classifications. CRL feedback will be compared to relevant FDA guidance and industry best practices.

By grouping product and treatment CRLs into distinct product types and therapeutic strategies these will explore trends in the issuance of the CRLs to products and treatments. They will explore if the deficiency types appear similar in clinical studies for biological drugs (i.e., biologics-small molecules) as well as oncology drugs instead of CNS therapy.

This approach helps to identify and respond to weaknesses to a review of our CRLs that are identified and fixed and also promotes an organization focused collaboration processes that results in our organization resolution on a more immediate basis for CRLs that reduce these issues and also to maximize overall impact of CRLs to the organisation in general.

In addition to enhancing transparency and reducing regulatory risk throughout all phases of drug development, we shall discuss mechanisms to enhance the product transparency and risk reduction through data science, documentation, policy making to help FDA respond on proper monitoring and in advance the data quality will also be investigated.

3. Pattern of Analysis

This methodic approach to examining CRLs is similar to existing techniques that have been applied to USFDA Warning Letters, as this method facilitates the identification of deficiencies in CRL analysis to provide a more systematic process of detecting regulatory bottlenecks, highlighting the regulatory compliance problems and showing the company's standards for such applications. Our approach is similar to those on CRLs in which findings can be categorized in a formal fashion and trends identified, and generalisations drawn in order to identify trends of the errors made on CRLs are also made. This gives us information on regulatory needs and will be useful for resubmissions and future applications (e.g. with this understanding now that we more formally, robustly and uniformly identify a scope and focus on the flaws that are visible in CRLs so we can create best strategies going forward.

3.1 Different Approaches used for Analysis of Warning Letter

- **Country-Specific Approach**

  FDA Warning Letters should be evaluated for their member countries in light of the country's manufacturing rules and the overall compliance practices and quality management practices in the country that has that law. There is also a strong concern that Warning Letters have been issued to different countries for the reasons of regulatory comprehension, adherence to current Good Manufacturing Practices (cGMP), as well as personnel training and documentation and infrastructure systems. Tracking these Warning Letters geographically indicates the issues related to GMP compliance but also how to secure the data and process management system. It allows us to learn more about legal challenges and implementation strategies in every country and can lead us to develop region-based strategies in terms of training systems, quality training on the project or risk-based inspections to address those issues in that region. (2)

- **Quantitative Analysis**

  Although the most common method for analyzing FDA Warning Letters quantitatively is a numeric examination of compliance issues, quantitative approaches rely on empirical evidence. In this study, we also seek to identify issues such as data integrity defects, missing documentation, equipment failures, and deficiencies in validation. It also examines how these problems are partitioned across dosage forms, manufacturing locations, and time periods. It employs frequency distribution analyses, percentage calculations, and trend assessment to calculate the incidence and recurrence rates of these compliance issues. These analyses will help organizations to uncover high-risk regulatory compliance issues, evaluate potential remediation measures to overcome such compliance, formulate a process to help implement standard procedures to overcome such issues, and partner with different agencies on measures to improve their Good Manufacturing Practice (GMP). Additionally, this approach is intended to reduce the risk of enforcement action by the U.S. Food and Drug Administration. (3)

- **Six-System Approach**

  The Six-System Approach is a systematic approach used by the U.S. Food and Drug Administration to assess compliance with Good Manufacturing Practices (GMP) during inspections. This approach organizes regulatory findings into six major systems as follows: Quality System, Facilities and Equipment System, Materials System, Production System, Packaging and Labeling System, and Laboratory Control System. As for the evaluation of warning letters, deficiencies identified must also be mapped to these systems, and this is to identify operating areas of

failure to comply exactly. This approach allows a comprehensive analysis of recurring issues, identifies the systems that are most affected, and guides organizations in taking targeted corrective and preventive action (CAPA) to improve overall GMP compliance. (4)

- **Issues Enabling a Poor-Quality System**

  Examining the causes behind poor quality that are the basis for a poor and unsatisfactory regulatory system is about identifying the operational and organisational deficiencies, as we could observe from the warning letters from the U.S. Food and Drug Administration. And instead of listing such isolated defects, this is about tackling the deep-seated problem, where employees are not trained by the best quality management practices, lack of documentation, or lack of supervision, and corrective and preventive actions (CAPA) systems are not present. Organizations can get better at understanding how recurring defects among the various quality systems may result in the failure to maintain Good Manufacturing Practices (GMP) and reduce potential of regulation. (2)

3.2 Approaches used for the analysis of CRL

With extensive investigation into the analytical practices deployed with respect to FDA Warning Letters, the analysis of their classification and trends enabled the creation of an appropriate analytical framework concerning Complete Response Letters (CRLs). While there are significant differences in purpose and timing between these two types of regulatory communication, the systematic evaluation approach used for Warning Letters—specifically, placing deficiencies into major groups and identifying ongoing trends—did provide insight. This awareness informed the process of devising an adapted approach in accordance with the distinctive characteristics and objectives of CRLs.

The approach includes numerous subcategories specific to shortcomings evident in CRLs.

- CMC Deficiencies
- Non-clinical Deficiencies
- Clinical Deficiencies
- Labelling Deficiencies
- Facility Inspection Deficiencies
- Drug-Device Combinations
- Other Deficiencies

a) Labeling Deficiencies

Deficiencies in labeling are categorized on the basis of 21 CFR 201 for pharmaceutical items and 21 CFR 801 for medical devices, which is conducive to compliance with applicable regulations. Through listing deficiencies in line with these FDA requirements, applicants, when filing new applications or resubmissions, will gain clarity on the labelling that applies to their product category. This structured system streamlines the corrective process, ensures conformity with FDA standards, and decreases the chances of additional inquiries pertaining to labelling. (5,6)

Table 1. Labeling Deficiencies

Category	Deficiency	Examples
Prescribing Information (PI)	Non-compliance with PLR format	Missing Highlights section, Full Prescribing Info not structured properly
	Inaccurate indications and usage	Claims not supported by clinical trial data
	Incomplete dosage and administration info	Missing route, frequency, and preparation method
	Inadequate contraindications/warnings	Omission of the black box warning or known safety risks
	Improper adverse reactions listing	Not based on clinical or post-marketing data
	Missing pregnancy/lactation data	Not aligned with PLLR requirements
	Unclear drug interactions	Drug interactions are unsupported or incomplete
Carton and Container Label	Missing required elements	Strength, dosage form, Rx-only symbol, NDC number
	Font size and legibility issues	Small or blurry text, poor contrast
	Look-alike/sound-alike (LASA) risks	Design may cause medication errors
	Improper placement of barcode/expiry date	Barcode unreadable or expiration date not visible
	Incorrect storage instructions	Not aligned with stability data
Patient Labelling	Incomplete Med Guide or IFU	Missing safety warnings or administration steps
	Language too complex	Reading level exceeds FDA-recommended threshold
	Unbalanced risk/benefit information	Benefits overstated, risks underrepresented
	Inaccurate illustrations/diagrams	Image conflicts with usage instructions
	Inconsistency with PI	Content mismatch between PI and patient leaflet
Proprietary Name	Name similarity	Confusing with other marketed drugs
	Promotional implication	Suggests superior efficacy, not proven
	FDA rejection of the proposed name	Due to safety or misbranding concerns
	Misbranding under the FDCA	False or misleading statements

Regulatory/Content Compliance	Non-adherence to FDA guidance	Not aligned with recent FDA labelling recommendations
	Typographical or factual errors	Outdated information, spelling mistakes
	Failure to implement FDA-suggested changes	Sponsor ignored prior label revision requests
	Omission of REMS information	Required REMS not described or included

b) Facility Deficiencies

Deficiencies discovered while conducting inspections are grouped and categorized based on 21 CFR 211 that specify the existing Good Manufacturing Practice (cGMP) standards in pharmaceutical manufacturing. Such classification helps applicants identify precisely non-compliant issues and systematically address them. This approach ensures that corrective actions taken are consistent with the FDA's cGMP requirements, allowing for both resubmissions as well as new applications and the prevention of the occurrence of similar inspection deficiencies in the future. (7,8)

Table 2. Facility Deficiencies

Category	Deficiency	Examples / Details
GMP Non-Compliance	Failure to meet current Good Manufacturing Practices (cGMP)	Observations from Form FDA 483, warning letters, data integrity violations
	Inadequate quality systems	No SOPs, poor deviation handling, weak change control, lack of CAPA
	Contamination or cross-contamination risks	Shared facilities not properly cleaned or validated
	Inadequate personnel training	Staff not qualified to perform or supervise critical operations
Inspection Issues	Pending or failed Pre-Approval Inspection (PAI)	Facility inspection incomplete, deferred, or resulted in major observations
	Failure to respond adequately to 483 observations	Insufficient corrective actions or untimely responses
	Lack of inspection readiness	Facility not ready to produce commercial lots
Process and Equipment Validation	Inadequate process validation	Missing or incomplete data for commercial-scale lots
	Equipment not qualified or maintained	No IQ/OQ/PQ documentation, uncalibrated equipment
	Cleaning validation deficiencies	Cross-contamination risks not evaluated or controlled
Control and Testing Facilities	Unvalidated analytical methods at site	No method verification or transfer data
	Environmental monitoring inadequate	Especially for aseptic or sterile manufacturing
	Lack of control over contract testing labs	No oversight on third-party testing results
Packaging/ Labeling Facility Issues	Inadequate container-closure integrity testing	Testing not validated or not aligned with product characteristics
	GMP issues at secondary packaging site	Separate packaging lines or facilities not validated
Documentation and Data Integrity	Data integrity violations	Deleted, altered, or untraceable data
	Missing batch records or incomplete documentation	Inability to reconstruct batch history
	Electronic systems not validated	Insecure or non-auditable electronic records
Biologics/ Complex Products Specific	Inadequate viral clearance validation	Critical for monoclonal antibodies, vaccines, or gene therapies
	Improper control of cell banks	No authentication, contamination issues
	Inadequate aseptic processing controls	Air flow, gowning, or sterility assurance failures

c) Drug-Device Combination

To measure the drug-device combination product weaknesses, a comprehensive system that adheres to internationally accepted benchmarks and regulations is needed. Pharmaceutical performance standards are governed by ICH Q8–Q12, as well as ICH Q3 concerning impurities, while the Common Technical Document (CTD) organizational requirements are defined by ICH M4. (9-11)

Table 3. Drug-Device Combination Deficiencies

Category	Deficiency Description
Biocompatibility Issues	- Insufficient data to support cytotoxicity, sensitization, irritation, genotoxicity, or systemic toxicity testing. - Missing justification for long-term contact or mucosal/tissue exposure. - Lack of testing per ISO 10993 standards.
Performance / Functional Testing	- Failure to provide adequate bench performance data under simulated use. - Incomplete in vitro or in vivo compatibility with the drug product (for combination products)- Missing reliability and repeatability test results for device components.
Human Factors / Usability Engineering	- No human factors validation study for intended users and use environments. - Failure to identify or mitigate use-related risks that could result in medication errors.
Design Control & Risk Management	- Incomplete design history file (DHF) or failure to follow 21 CFR 820.30 requirements. - No documented risk analysis (per ISO 14971) linking hazards to mitigations. - Changes in device design not re-validated.
Manufacturing Process Deficiencies	- Lack of evidence that the manufacturing process ensures device consistency and sterility. - Deficiencies in cleaning validation for reusable components. - Missing packaging integrity and stability data.
Combination Product-Specific Deficiencies	- Inadequate drug–device compatibility data over shelf-life. - Missing or incomplete extractables/leachables data from device materials. - No validation that device performance remains within specifications after drug exposure.
Labelling / Instructions for Use (IFU)	- Inadequate or unclear user instructions that may lead to misuse. - Missing warnings, precautions, or diagrams required for safe operation. - IFU not reflecting actual tested conditions.

4. Result of analysis

Analysis of 150 CRL is done so far; from which the total queries listed are 200.

These 200 are subdivided into different categories mentioned in the methodology:

- CMC Deficiencies: 29
- Clinical Deficiencies: 55
- Non-Clinical Deficiencies: 11
- Labelling Deficiencies: 70
- Inspection:10
- Drug-Device Combination Deficiencies: 25
- Other Deficiencies: 05

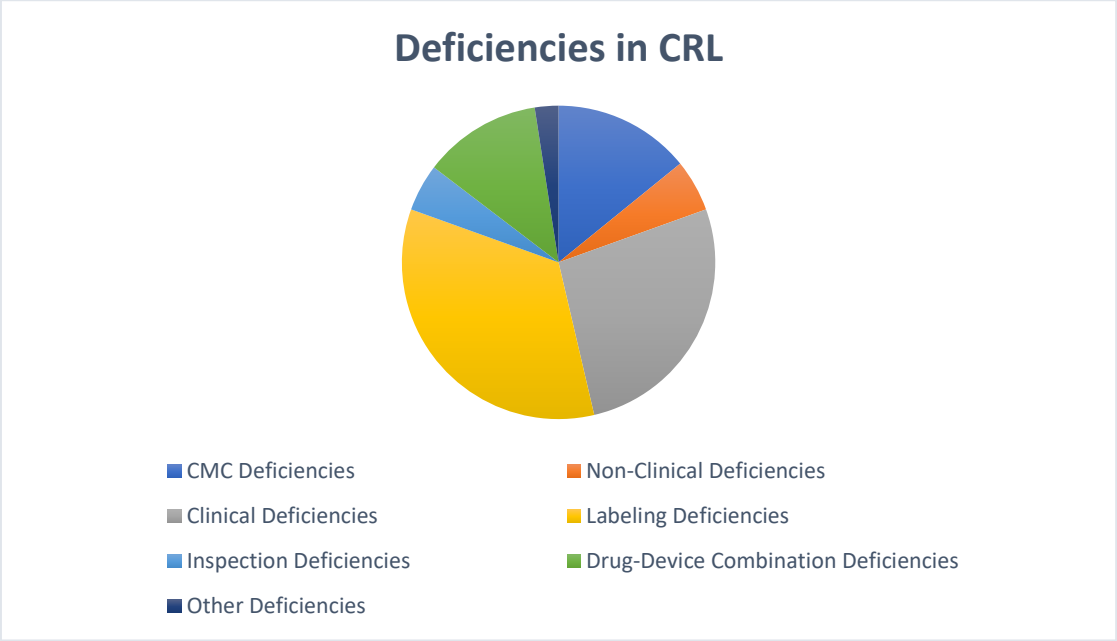


Figure 1. Deficiencies in CRL

From the above analysis of 150 CRL, we can conclude that till now, labelling and clinical queries occur more after review. Applicants should review these all section carefully and file the application accordingly to avoid further queries after review.

The major deficiencies identified in each section are summarized below for clarity and to facilitate a structured understanding of the key issues.

a) CMC Deficiencies:

- 3.2.S.2: Manufacture of Drug Substance (Control of critical step)

- ❖ 3.2.S.3: Characterization of Drug substance (Impurities)
- ❖ 3.2.S.7: Stability of Drug Substance
- ❖ 3.2.P.3: Manufacture of Drug Product
- ❖ 3.2.P.5: Control of Drug product (Validation of Analytical Procedures)
- ❖ 3.2.P.8: Stability of Drug Product

b) Drug-Device Combination products:

- ❖ Human Factor Studies
- ❖ Biocompatibility Issues
- ❖ Combination Product Specific Deficiencies (Extractables and Leachable)

c) Labelling Deficiencies:

- ❖ Prescribing information and Patient Labelling

d) Clinical Queries:

- ❖ 5.3.5: Reports Efficacy and Safety studies.

e) Inspection Deficiencies:

- ❖ GMP Non-Compliance and Inspection Issues

5. Conclusion

It highlights how important it is to obtain Complete Response Letters (CRLs) in the USFDA drug approval process. By studying all application scenarios of Chemistry, Manufacturing & Controls (CMC), clinical studies, nonclinical studies & nonclinical processes such as labeling and facility compliance, it shows common deficiencies for CMC and clinical issues leading to approval times. The study showed that most of these deficiencies resulted from poor data quality, unreliable validation tools, incomplete documentation and insufficient evidence of safety and effectiveness. The study proposes the use of systematic approaches such as categorising deficiencies, tracking trends by time and thematic assessments in warning letters such that they are presented to one set of CRL data with the regulatory parameters. Importantly, the enhanced clarity of regulations coupled with public access to CRLs present one of the best learning opportunities to the pharmaceutical industry. These insights invite applicants to mitigate risk and improve submission quality while also conformably aligning their business with pharmaceutical industry regulation. This study also proves that when a proactive strategy driven more by systematic processes focusing on quality and the need for this through working collaboratively is complemented with Common Technical Document (CTD) guidelines in the team and across teams to work, the probability of receiving CRLs disappears drastically. Following the checklist approach to the study (i.e. the one suggested in the framework proposed for this paper) could therefore increase confidence and help patients to receive treatment faster; it could help to be more prepared for regulatory scrutiny and it must also cut that process (once approved) in a good order.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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