MANAGING AN ADVERSE FDA INSPECTION:
PRACTICAL CONSIDERATIONS FOR AVOIDING REGULATORY ESCALATION

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Timing is everything...

...when managing an FDA inspection that has identified objectionable conditions. The good news is, a device manufacturer has the ability to influence the agency’s perception of and reaction to an inspection report and the associated FDA 483. Knowledge of the agency review process, including how much time it takes, is essential to doing this successfully. Equally important is an understanding of the criteria applied by the agency in assessing whether regulatory escalation is appropriate, and knowledge of issues affecting suitability of a formal FDA 483 response.

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WHAT TO CONSIDER

Responding to an FDA 483 is not always as straightforward as it may initially seem in terms of content. There are a number of business and regulatory issues that need to be considered, starting with:

- Assessing the validity of investigator findings
- Evaluating the business risk associated with potential regulatory follow-up
- Cost and feasibility of any correction under consideration

There are numerous examples of the types of deficiencies FDA compliance officers find with responses to FDA 483s, as these deficiencies are commonly noted in publicly posted Warning Letters. Review of this historical data may be very helpful in avoiding having your response rejected as insufficient.
Even during the FDA inspection (including the closing meeting) a firm has some potential to influence the perceived significance of any objectionable conditions or practices identified.

**Take advantage of this.**

Specific interactions with the FDA investigator may help ensure provision of a full and fair context for the observations, as well as provide insight into the specific control concerns of the investigator and/or agency. The goal of this white paper is to offer practical advice relating to each of these mechanisms for obtaining the best possible outcome following adverse FDA inspection findings presented via an FDA 483 form.
INSPECTION REVIEW MECHANISMS AND TIMING

Before discussing tips for managing adverse findings, some background on inspection review mechanisms and timing may be helpful. After formally closing out the inspection, your FDA investigator will write a report that is supposed to be a factual account of observations and absent of any judgment or opinions. The report will include any exhibits (collected records, etc.) that he or she chooses to include. The investigator will submit the report to their immediate supervisor and in most cases, it will be accompanied by a recommended ‘classification.’ There are three basic possible classifications / outcomes for FDA inspections:

- **No Action Indicated (NAI)**
  Occurs when no FDA 483 observations are issued

- **Voluntary Action Indicated (VAI)**
  Arises when an FDA 483 is issued but observations do not rise to the level of official action, or were not properly documented in the report

- **Official Action Indicated (OAI)**
  Applied when serious control deficiencies are identified and appropriately documented
The time frame from inspection close-out to initial classification by a local supervisor is generally 10 days or less. Review by a district or local compliance officer generally occurs in parallel to the report writing and local supervisor review. A compliance decision about escalation to a Warning Letter can occur in as little as 15 days from close-out. The subsequent creation and review cycle could take several months.
The preceding description is typical for review of routine, district-initiated work plan inspections meeting direct reference authority criteria. In some cases, a review by the CDRH Office of Compliance or Office of Chief Counsel may be required. For additional info on this process see the FDA’s Regulatory Procedures Manual¹.

Warning Letters can and do arise for other reasons, such as problems with promotional claims or the market clearance status of the product. These issues are not identified on an FDA 483 form at close-out, but can still emerge via a referral of inspection report to the Office of Device Evaluation for subsequent review. Note any suggestion of these concerns from the investigator, as they will not be cited on the issued FDA 483, but may still require a reaction.

UNWELCOME PROBLEMS

The following are unwelcome, but possible situations that may arise after adverse inspection findings.

- Significant corrective action is not possible in the time frames of interest
- Reaction has potentially significant (or even intolerable) impact on product availability or cost
- Significant disagreement with the agency regarding interpretation of the regulation arises

These situations may lead to full-blown remediation activities, alternative review negotiation, or appeal mechanisms. Remediation issues arising after escalation will be the subject of a future white paper offering from R&Q; subscribe to our blog to know when it is published.
So how do you take advantage of available front-end opportunities to reduce the risk of escalation? Let's begin with the inspection itself.

1. Daily Out-Briefs
Most manufacturers have appropriately adopted the practice of requesting daily out-briefs from their investigator to assess perceptions. Always keep in mind that recognizing issues early will maximize the time available to react to any of the issues. While the daily out-brief practice is commonplace all over the world and in third-party audits, there is no guarantee that an FDA investigator will provide daily summaries. With that said and in this author's experience, most are willing to provide daily feedback more often than you might think... if requested. It is surprising how frequently 483 observations arise simply due to poor communication between the FDA investigator and the inspected company.

Don't make this mistake.

An investigator may assume all available documentation relating to a specific inquiry has been provided, while a firm may have interpreted a request more narrowly than what was intended by the investigator. Daily out-briefs provide the opportunity to react to these issues.
A common complaint of the industry when I started 20 years ago with the FDA was the perception that FDA investigators would surprise a firm with a 483 at the end of an inspection, right as they ran out the door. Things have improved *dramatically* over the years in this regard. However, a close-out meeting at the time an FDA 483 is issued does not afford much opportunity for influencing investigator perception, or balancing business and regulatory concerns.

2. Get to Know Your Investigator
Understand and document the investigator’s basis for the adverse finding; it is fair to discuss the observations in the context of the applicable regulatory language. It is also important to know your FDA investigator: their experience level, technical background, and extent to which they are familiar with best practice in your industry. The FDA is, of course, a large organization. With several hundred device investigators nationally there will naturally be variation in experience level. Investigators make mistakes like anyone else, and there is considerable reluctance to modify or remove an FDA 483 observation once it is issued. This is due in part to human nature and in part to the cumbersome mechanics of the IT tools provided to investigators. While it may not always be doable, address possible observations prior to a formal close-out meeting.
If you have concerns about the observation or information that might temper the agency’s perceived risk significance of the observation, **express that early and often**. It is reasonable to encourage the FDA investigator to describe your position in the Establishment Inspection Report and not necessarily wait until you submit a written FDA 483 response. The reason for this is that within two to 10 days of close-out, your FDA CSO's immediate supervisor will be classifying the report with respect to the potential for follow-up for regulatory action (e.g. Warning Letter) based on their review of the report (including collected documents) and the FDA 483 that was issued. If the inspected firm’s position does not make it into the EIR, an opportunity to preclude an OAI classification will be missed. If you know in advance an FDA 483 observation is coming, it may be possible to provide evidence of completed or in-process corrections that can be described in the Establishment Inspection Report. Your early reaction can also be documented on the FDA 483 through the annotation process.

**Be proactive. It is worth it.**
Another topic for discussion during the inspection and at close-out involves attempting to ensure that appropriate context for the observation is provided by the investigator in their report. By proactively discussing these considerations with the investigator, you increase the chance they will recognize and document the context of interest. For example, a 483 observation might state that six complaint files were found to lack documented complaint investigations and/or a reason for absence of complaint investigation. It may be that six records were problematic out of 10 reviewed, or that six out of 10,000 were found to be problematic. Furthermore, it may be that the failure mode is already being reviewed under a lead complaint and the deficiency was a failure to document the existence of lead investigation. That is less significant of a situation compared to six complaints that were simply not processed. It is easy to think these distinctions are obvious; that a CSO can be expected to differentiate between these situations and describe the differences in the report.

We recommend never making that assumption.

For actions to be taken during the inspection, actively managing early perceived risk significance of observations by sharing information will likely temper concern.
This information might relate to the perceived issue being a flyer versus a systemic control issue; or related to the existence of redundant controls that mitigate risk of the observed control deficiency.

The next opportunity to impact the probability of escalation exists in the form of your firm’s written response to an FDA 483.

There have been many instances in which a potentially avoidable Warning Letter was issued due to a **failure to consider historical precedent**. There is a wealth of data available in the form of real world examples of reasons FDA compliance officers have found FDA 483 response to be inadequate, resulting in a Warning Letter that could have been avoidable. Review of these publicly available Warning Letters provides some insights on potential best practices for responding to FDA 483 observations, including many recurring themes in the reasons responses were found to be inadequate. We'll explore some of these in the pages to come.
It is an intensive effort for the FDA to issue a Warning Letter.
If a firm can convince the responsible district (or CDRH/OC, if applicable) that appropriate corrections have been made prior to issue of a Warning Letter, they may downgrade an inspection to VAI. For cases perceived as borderline with respect to seriousness of the deficiencies, indication that appropriate corrections are in progress and updates will follow may be enough to downgrade to VAI. The other reason an inspection may be downgraded is a conclusion that the observations do not meet the criteria for regulatory follow up.

The compliance program covering routine FDA inspection of device manufacturers, 7382.845, “Inspection of Medical Device Manufacturers.” specifies criteria for regulatory follow-up actions, and can be reviewed at the FDA's website². Part V of this document provides insightful information for developing strategies to avoid regulatory escalation. The compliance program provides guidance on specific criteria for escalation. This guidance is offered separately for QSR related deficiencies, MDR, Correction and Removal, and Mandatory Tracking related deficiencies. While the focus is primarily on QSR related issues, analogous considerations may be derived from the available regulatory escalation guidance on part 803 or 806 deficiencies found in the compliance program.

QSR DEFICIENCIES

The criteria relating to QSR deficiencies identifies two situations, differentiating between the two on the basis of significance.

**Situation 1**

Situation 1 applies to inspections that result in identification of one or more Major Deficiencies relative to the requirements of the Quality System Regulation (QSR). Paraphrasing from the compliance program, examples of major deficiencies may include:

(a) Failure to establish a QMS or any of the seven QMS subsystems
(b) One or more deficiencies in any element of the subsystem that the agency deems to be critical, perhaps due to a deleterious synergy between related systems (e.g., purchase controls and incoming acceptance)
(c) Presence (and especially release) of non-conforming product that has not been reacted to appropriately via CAPA mechanisms
(d) Failure to properly correct previously identified major deficiencies

*Note: Specifically excluded from this discussion are instances involving immediate health hazards and international inspections, contract manufacturers, sterilizers and international sites. Each of these situations adds layers of complication and will be discussed in a future white paper. Subscribe to R&Q's Blog to be notified when these are published.*
Situation 2
Situation 2 applies to situations where the deficiencies documented are such that FDA believes “there is minimal probability, in light of the relationship between quality system deficiencies observed and the particular device and manufacturing processes involved, that the establishment will produce nonconforming and/or defective finished devices.” Situation 2 inspections will be classified as VAI and not result in regulatory escalation.

Clearly, once an FDA 483 has been issued, the goal is to have the FDA conclude that they are dealing with a Situation 2 inspection. Review of the criteria supports the importance of taking every opportunity to provide information, suggesting that:

The observed deficiencies have not, and are not likely to, result in the release of non-conforming product. Responses - both during the inspection and in formal written response - might identify redundant controls if applicable. Historical absence of NC's due to control deficiency can be helpful, but is not deterministic.
You really have no choice but to establish the required QMS system or subsystem. The good news is, a minimalist implementation may satisfy the requirements, depending on product. For small organizations, it may be possible to make a case that correction has been made prior to the issue of a Warning Letter (or perhaps 15 days from close-out). For situations where issues were identified relative to specific subsystem problems, your response should seek to convince the agency that the deficiencies are not “critical.”

Candidate materials to be included in a formal response include:

1. **Any evidence supporting a conclusion that the observed deficiency is not systemic, coupled with evidence of correction.**

2. **Any available evidence that the deficiency has not resulted in a failure to meet the intent of the regulation.** For example, if service records for warranty repairs (likely construed as complaints) do not include all the information required by 820.198, an argument might be made that the service record and service activity effectively resulted in appropriate investigation and knowledge of potential field performance issues. In other words, the distinction is just semantics, coupled with evidence of effected or planned correction.
Failure to consider the agency’s escalation criteria and utilize it in formulating a response strategy is not the only pitfall, unfortunately. I mentioned earlier that otherwise strong responses are often rejected for specific reasons, some of which are recurring themes evident from a broad review of publicly posted Warning Letters. When issuance of a Warning Letter is preceded by receipt of a formal response to the FDA 483, the Warning Letter will generally acknowledge that and comment as to the adequacy of the response.

The response you want to avoid is the dreaded, “We reviewed your firm’s responses and conclude that they are not adequate.”
Here are multiple examples from publicly posted Warning Letters:

"...supporting documentation of the implementation of this procedure was not included..."

"...while a design control procedure was submitted in your response ... you did not provide evidence that you retrospectively reviewed all devices to ensure they had design control procedures in place as required..."

"...your correction plans do not include provisions for the training of the employees..."

"...your response did not indicate how devices that did not meet specifications but were already distributed will be handled, nor did it demonstrate that all acceptance records were reviewed to ensure that no other nonconforming products have been distributed..."

"... your response did not include evidence of the interim steps your firm is utilizing to prevent contamination prior to installation of the new filtration system referenced..."
"...Your firm described its corrective actions. However, it did not include documentation or evidence of the corrective actions and did not provide evidence of implementation with the response to FDA..."

"...After conducting a review of your firm’s revised procedure, the following deficiencies are still noted..."

"...The initiation of the added testing requirements does not appear to be timely relative to the criticality of this deficiency."
WHAT YOU NEED TO DO

Suffice it to say, anyone with enough patience to retrieve numerous archived documents from the FDA website could create a very long list. Review of this data reveals multiple recurring themes, which we have translated to best practices, as described below.

1. If you report to the FDA that you have made a correction, **prove it**. For example, if part of your correction involves revisions to procedures, do not simply describe the changes. Include copies of new releases, documented training of new procedures, and to the extent possible, evidence that the revised procedures or practices are being used and are effective. Do this and you are on your way.

2. Whatever form your response takes it is best to manage it through your formal CAPA mechanism.

3. It is critically important that your response includes not only improved practices going forward, but also retroactive consideration of the deficiency. For example, if you revise your adverse event reporting criteria, be sure to demonstrate that you have also applied the revised criteria retroactively to an extent that makes sense. If observation relates to actual nonconforming product, be sure to include an assessment of and reaction to previously fielded product (supported appropriately by risk documentation as required).
4. Your response to the FDA as well as your planned corrections need to be sufficiently broad. Control deficiencies cited on the FDA 483 may have broader implications than those specifically noted by the investigator. For example, if you receive an observation relating to failure to validate a process where applicable, do not simply validate the process, but be sure to include evidence of a new review of all processes for recurrence of the same issue. The same reasoning applies for observations relating to, for example, a single supplier; response should look across all suppliers. This concept applies to specific product lines as well. You should not only react to the example cited. A response should assess all product lines potentially affected by a similar issue and reaction must be comprehensive.

5. The FDA will expect your reaction to FDA 483 observations to be congruent with the risk significance of the deficiency and the risk profile of affected product. If you think there may be a disconnect between the agency’s perception of risk and your own, be certain to include compelling evidence to support your view. Examples could include extracts from risk file, evidence of a benign post-market experience, absence of complaints, operator expertise, etc.
CONCLUSION

These are a few of the many issues that should be considered when formulating a response to adverse FDA inspection findings. It certainly makes sense to avoid the historical recurring pitfalls. I have also suggested that certain activities as early as during the FDA inspection can facilitate being in the best possible position to respond... and possibly head-off FDA 483 observations, or influence/temper their tone.

We recognize that special circumstances can arise. For example, a manufacturer may fundamentally disagree with the findings of a specific investigator, or the agency after their further review. Alternatively, and even if there is substantial agreement, reaction may adversely affect required product availability or affordability. These situations are most critical when corrections involve significant cost or other business impacts. Should your inspection issues escalate to a Warning Letter, the regulatory risk elevates significantly. Remediation will need to be conducted in a fashion that appropriately balances business and regulatory risk, and, most importantly, in a way that can be tolerated and maintained operationally. R&Q looks forward to sharing our thoughts on these and other issues through future white papers and blogs... and welcome discussion of these topics at your convenience.
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