Handling Regulatory Inspections

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Abstract *— As per the International Harmonization Guidelines (ICH) a regulatory inspection is the act by a regulatory authority (ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority (ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or CRO's facilities, or at the other establishment deemed appropriate by the regulatory authority (ies). An inspection can happen at any time in any city or state. The mission is to protect consumers and enhance public health by maximizing compliance of regulated products and minimizing the risk associated with those policies.* Inspections can cover finished human and veterinary drugs and biologics *[9*].

Key Terms *— Board of Health (BoH), Inspections, Regulatory agencies*

INTRODUCTION

The key to effective management of regulatory inspections is effective preparation. Being well organized and confident during the inspection means that your firm gives its best possible performance which in turn gives the regulatory inspector the clear message that you know your business thoroughly [8]. However, in order to always be prepared, or inspection ready, the company should establish several guidelines. These guidelines should be as general as possible in order to match with any Regulatory Agency or Board Of Health (BOH) that perform the inspection. But, it this possible? How well can you prepared? Are all the regulatory inspections handled in the same way? Do all of them last the same time? [6] Audits and inspections by regulatory agencies can be disruptive and resource intensive. Advance preparation is critical to having a smooth inspection. Do you have a process to host these inspections? In order to provide answers to these questions, we have prepared a questionnaire to gather different companies' experiences when handling regulatory inspections.

RESEARCH OBJECTIVES

The main objective of this design project is to identify the inspection techniques and methodologies used by the regulatory agencies inspectors and provide a standard guideline that organizations can use to prepare for the different types of regulatory inspections.

RESEARCH CONTRIBUTIONS

Regulatory inspections have existed for more than 100 years. Since that time people from the applicable companies have had to deal with them too. Inspections have evolved since. More board of health agencies have been created in the different countries bringing with them different inspection approaches. However, the implementation of guidelines itself than can be use for any type of inspections are not common, why? Because not much people have all the information and it is a complex endeavor that requires significant research, preparation, and planning. Organizations in highly regulated industries, such as pharmaceuticals, must ensure that the implementation is carried out in a manner that fully complies with regulations.

Preparation for a regulatory inspection is just the beginning of the inspection management process. It is critical that everyone knows what to do when an inspector visits your facility, how to handle the inspection process, and what actions to

take after the inspector leaves the premises. This project covers how your company can design a system to prepare for a regulatory inspection, including a guideline, proper behavior of staff during the audit, as well as the follow-up process and response to possible observations. It describes the implementation process in detail so organizations understand what is involved, helps them prepare better, and avoid surprises.

RESEARCH BACKGROUND

Regulatory agencies are government or nongovernment authorities, responsible for oversight of the effectiveness, safety, manufacture, and distribution of medicines in a specific country or region of the world such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMEA). Other regulatory bodies are: Canada Health, COFEPRIS, Turkey Inspectorate, ANVISA, Russian BoH, and WHO.

Types of regulatory inspections:

- **Pre-inspection**: Inspection assignments are made to a district office, in which case the inspector might or might not announce the visit. The inspection will be either a routine or for-cause inspection.
- **Routine inspections** are performed for: Full inspection of all components of GMP, Newly establish manufacturer, Renewal of license, New product or product lines, Modifications to manufacturing methods, Key personnel, premises or equipment, History of non-compliance with GMP, Not inspected in the last 3-5 years, and Unannounced inspections. These are routine monitoring inspections, typically performed once every two years and encompassing the full-facility and associated records.
- **Concise inspections** are: Consistent record of compliance with GMP, Focus on limited number of GMP requirements, Identify significant changes, and Indicate attitude towards GMP.
- **Follow-up inspections** are performed for: Reassessment or re-inspection, Monitor result of corrective actions, 6 weeks to 6 months after initial inspection (Nature of defects and/or Work undertaken), and Specific GMP issue.
- **Special inspections** are performed for: Spot check focusing on, Complaints or recalls information challenge, adverse drug reactions, Marketing approval or export certificate, and information or investigation (Specific information or Advice on regulatory requirements).
- **Quality systems review inspections** are performed for: Assessing the quality assurance (QA) system, Description of the QA system (e.g. manual), Policy and standards to be observed, Management structure implementation, Quality standards set for products, and correctly defined manufacturing processes.
- **For-cause inspections**: These inspections may be prompted by "whistle-blowers" from within any given contract research or sponsor organization, or as a result of undisclosed or unforeseen adverse event reporting in marketed products.

An investigation or inspection is an information gathering activity conducted for many different reasons. The purpose of any investigation is to determine and document facts concerning a particular issue so the BoH can make informed and sound decisions.

How to handle the inspection

Inspections normally begin with an opening meeting at which the investigator will discuss the purpose of the inspection, cover administrative details, and provide a preliminary indication of the course of the inspection. At least one representative of management and the inspection escorts should attend the opening meeting. It is also advisable for quality and production management to be in attendance. During this meeting, the investigator should be asked to clarify any points that are not

clear, and, if the inspection is expected to last more than one day, a meeting should be requested at the end of each day to review any inspectional findings up to that point.

The investigator should be accompanied at all times by two escorts--one to lead and interact with the investigator and one to take notes. It is important that both escorts, but particularly the lead escort, be knowledgeable about plant operations; familiar with the CGMP requirements; and has an understanding of the authority and responsibility of the inspector(s). The note taker needs to accurately record the investigator's questions and comments and the answers provided.

If during the course of the inspection, the investigator wishes to speak directly to an employee, be certain that the question being directed to the employee is one that the employee is competent to answer, and that the employee's answer is factual. The employee should not be permitted to express an opinion and should confine his/her answers to the question asked. If the question is not appropriate for a particular employee or if the employee is not completely fluent in the language, the investigator should be so informed. To the extent possible, the escort, supervisors, or managers who are completely knowledgeable about the subject should handle questions.

Since there are no record keeping requirements in 21 CFR 110, if the inspection does not involve low-acid or acidified foods, investigators are not authorized to request or copy records unless the records are volunteered by the company. Even though they can demand records under the Bioterrorism Act of 2002, it is unlikely an investigator will do so absent a compelling reason. Investigators are, however, instructed to ask for formulas even thought there is no requirement to provide either qualitative or quantitative formulas. If formulas are not provided, the investigator may attempt to reconstruct them by observing production, batch cards or formula sheets, and raw materials and their location. If the company does not wish the agency to have access to its formulas, for whatever reason, it is justifiable to keep any formula-related documentation out of sight of the investigator.

Investigators are also instructed to take photographs to document violative conditions. Companies, in consultation with legal counsel, should establish a position on photographs prior to be confronted with a request during an inspection. If the company permits photographs, the escort should take an identical photograph from the same angle at the same time.

Post Inspection

The inspector prepares an inspection report and supporting documentation to be forwarded to the Center for Compliance. A final classification of the inspection is made.

Inspection Classification:

An inspection might result in several classifications, including "no action indicated", "voluntary action indicated" or "official action indicated". "No action indicated" means there were no objectionable conditions or findings. "Voluntary action indicated" means an inspector found objections, but none were severe enough to take regulatory action. "Official action indicated" requires regulatory action because serious objectionable conditions were found. Figure 5 includes an example of a decision tool for inspection findings.

Benefits of In-Touch Insights for Regulatory Inspections and Reports

Inspectors will notice the following:

- Field audit or inspection information is loaded in real-time or as soon as the inspector has connectivity.
- Faster response times that improve customer satisfaction.
- Data quality is improved by the elimination of manual transcription and paper-based records.
- History is accessible with the mobile device, as it is 'always connected', giving the inspector access to a library of information if corrective action is needed onsite and immediately.

- Ability to monitor time and location of mobile device usage and industry leading encryption enhance data security and integrity – critical considerations for governments and their agencies.

RESEARCH METHODOLOGY

The methodology use to obtain the basic information for this project was a questionnaire. The most important part of the survey process is the creation of questions that accurately measure the opinions, experiences and behaviors of the public. Accurate random sampling and high response rates will be wasted if the information gathered is built on a shaky foundation of ambiguous or biased questions. Creating good measures involves both writing good questions and organizing them to form the questionnaire. For that matter a questionnaire was created in order to understand the differences between the existing regulatory inspection agencies and created a guideline as comprehensive as possible to achieve inspection readiness.

Questionnaire design is a multiple-stage process that requires attention to many details at once. Designing the questionnaire is complicated because surveys can ask about topics in varying degrees of detail, questions can be asked in different ways, and questions asked earlier in a survey may influence how people respond to later questions.

For many years, surveyors approached questionnaire design as an art, but substantial research over the past thirty years has demonstrated that there is a lot of science involved in crafting a good survey questionnaire.

The Steps in a Survey Project

These Steps are the minimum required in order to use the survey as an analytical tool.

1. Establish the goals of the project - What you want to learn.
2. Determine your sample - Whom you will interview.
3. Choose interviewing methodology - How you will interview.
4. Create your questionnaire - What you will ask.
5. Pre-test the questionnaire, if practical - Test the questions.
6. Conduct interviews and enter data - Ask the questions.
7. Analyze the data - Produce the reports.

Establishing Goals

The first step in any survey is deciding what you want to learn. The goals of the project determine whom you will survey and what you will ask them. If your goals are unclear, the results will probably be unclear. Some typical goals include learning more about:

- The potential market for a new product or service.
- Ratings of current products or services.
- Employee attitudes.
- Customer/patient satisfaction levels.
- Reader/viewer/listener opinions.
- Association member opinions.
- Opinions about political candidates or issues.
- Corporate images.

Selecting Your Sample

There are two main components in determining whom you will interview. The first is deciding what kind of people to interview. Researchers often call this group the target population. If you conduct an employee attitude survey or an association membership survey, the population is obvious. If you are trying to determine the likely success of a product, the target population may be less obvious. Correctly determining the target population is critical. If you do not interview the right kinds of people, you will not successfully meet your goals.

Avoiding a Biased Sample

A biased sample will produce biased results. Totally excluding all bias is almost impossible; however, if you recognize bias exits you can intuitively discount some of the answers. The

following table (Table 1) shows some examples of biased samples.

Table 1

Examples of Bias Survey Samples

Sample	Probable Bias	Reason
Your Customers	Favorable	They would not be your customers if they were unhappy, but it is important to know that keeps them happy.
Your Ex-Customers	Unfavorable	If they were happy they would not be ex-customers, but it is important to know why they left you.
"Phone-In"	Extreme Views	Only people with a strong interest polls in a subject (either for or against) are likely to call in – and they may do so several times to load the vote.
Daytime	Non-Working	A majority of people who are at home during interviews the day do not work. Their opinions may not reflect the working population.
Internet	Atypical People	Limited to people with internet access. Internet users are not representative of the general population, even when matched on age, gender, etc. This can be serious problem, unless you are only interested in people who have internet access. In many business surveys this limitation might not be a problem. Another concerns is that respondents have been known to complete multiple surveys to sway results, unless the software prevents this

The consequences of a source of bias depend on the nature of the survey. For example, a survey for a product aimed at retirees will not be as biased by daytime interviews as will a general public opinion survey. Because escorts inspectors and support the inspection process can be misunderstood for most of the people that work directly with it, only people that is used to it and work directly with the inspections was selected for the survey.

Interviewing Methods

Personal Interviews: An interview is called personal when the Interviewer asks the questions face-to-face with the Interviewee. Personal interviews can take place in the home, at a shopping mall, on the street, outside a movie theater or polling place, and so on.

Advantages:

- The ability to let the Interviewee see, feel and/or taste a product.
- The ability to find the target population. For example, you can find people who have seen a film much more easily outside a theater in which it is playing than by calling phone numbers at random.
- Longer interviews are sometimes tolerated. Particularly with in-home interviews that have been arranged in advance. People may be willing to talk longer face-to-face than to someone on the phone.

Disadvantages:

- Personal interviews usually cost more per interview than other methods. This is particularly true of in-home interviews, where travel time is a major factor.
- Each mall has its own characteristics. It draws its clientele from a specific geographic area surrounding it, and its shop profile also influences the type of client. These characteristics may differ from the target population and create a non-representative sample.

Email Surveys: Email surveys are both very economical and very fast. More people have email than have full Internet access. This makes email a better choice than a Web page survey for some populations. On the other hand, email surveys are limited to simple questionnaires, whereas Web page surveys can include complex logic. This was one of the most useful type of survey used for this project.

Advantages:

- Speed. An email questionnaire can gather several thousand responses within a day or two.
- There is practically no cost involved once the set up has been completed.
- You can attach pictures and sound files.

- The novelty element of an email survey often stimulates higher response levels than ordinary "snail" mail surveys.

Disadvantages:

- You must possess (or purchase) a list of email addresses. The e-mail addresses list form this project was mostly obtained form my previous co-workers, my actual co-workers and friends that share the same type of work that I have, work in the compliance area of a company working directly with the regulatory inspections.
- Some people will respond several times or pass questionnaires along to friends to answer. Many programs have no check to eliminate people responding multiple times to bias the results. The Survey System's Email Module will only accept one reply from each address sent the questionnaire. It eliminates duplicate and pass along questionnaires and checks to ensure that respondents have not ignored instructions (e.g., giving 2 answers to a question requesting only one).
- Many people dislike unsolicited email even more than unsolicited regular mail. You may want to send email questionnaires only to people who expect to get email from you. For this matter only people that received e-mails from me and know me where used for this project.
- You cannot use email surveys to generalize findings to the whole populations. People who have email are different from those who do not, even when matched on demographic characteristics, such as age and gender. In this type of work this is not a characteristic that can affect the survey. People form different ages, experienced, genders and countries work in the same group and have the same responsibilities. However the survey was not sent to a people that work or used to work for a BoH to avoid any conflict of interest and have genuine results.
- Email surveys cannot automatically skip questions or randomize question or answer choice order or use other automatic techniques that can enhance surveys the way Web page surveys can.

Table 2

Summary of Survey Methods

Speed	Email and Web page surveys are the fastest methods, followed by telephone interviewing. Mail surveys are the slowest.
Cost	Personal interviews are the most expensive followed by telephone and then mail. Email and Web page surveys are the least expensive for large samples.
Internet Usage	Web page and Email surveys offer significant advantages, but you may not be able to generalize their results to the population as a whole.
Literacy Levels	Literate and less-educated people rarely respond to mail surveys.
Sensitive Questions	People are more likely to answer sensitive questions when interviewed directly by a computer in one form or another.
Video, Sound, Graphics	A need get reactions to video, music, or a picture limits your options. You can play video on a Web page, in a computer-direct interview, or in person. You can play music when using these methods or over a telephone. You can show pictures in those first methods and in a small survey.

From these survey methods present in Table 2 the most recommended are the ones related to the use of internet, as email or a web page survey. These methods cost less and are less time consuming.

Your choice of survey method will depend on several factors. These include:

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- How to organize the Inspection Room and get off to a good start.
- How to communicate with the Control Room
- How to manage roles and responsibilities.
- How to handle daily wash-up meetings and the close-out meeting.
- How to organize the Control Room – layout, technology and personnel.

- How to prepare staff to contribute in the inspection room.
- What documents to prepare and how to control them.
- How to communicate to the rest of the site/company.

Inspection Checklists are available as a guide to prepare for inspections; using previous inspection findings by regulatory agencies and self-inspections reports are a good starting point to prepare for inspections.

RESEARCH RESULTS

A total of Seventy two (72) persons from the Pharmaceutical and/ or Medical Devices Industry in Puerto Rico and United States participated in this study. It is important to clarify that the people selected were the ones that work with the inspection process; no anyone who work in this kind of industries.

Conclusions as per Questionnaire Information Tabulated

After tabulated all the data of the Questionnaire these were the facts/ conclusions found:

- FDA is the agency that performed more inspections (42%), followed by EMA with an 33%.
- Most of the inspections (58%) are for regular GMP, however, a lot of them have more than one purpose.
- 83% of the inspections last more than 40 hours.
- All the inspections are performed by 2 or three investigators.
- All inspections include the Quality System.
- Most of them (83%) also include the laboratories system. For more details please refer to Figure 1.
- 83% of the people that answer the survey believe that the inspectors that performed the inspection are experts or have knowledge above the average in those matters; where as 17% understand that they have just an average knowledge.
- 75% of the people interviewed have a good opinion of the investigators attitude, where as 67% consider that they are subjective, demanding or arrogant. For more details please refer to Figure 2.
- 29% of the surveyed people believe that the discussion process with the investigator doesn't need any improvement; where as 22% had to explain themselves several times in order for the investigator to understand it.
- On the other hand, 70% of the people interviewed had some complaint of the discussion process.
- As an outcome of the inspection process, 78% of the companies obtained more than 5 observations and only 17% did not obtain observations.
- 77% of the people interviewed consider that the outcome of the inspection was due to deficient systems, facts and objective information; while 33% believe that was due to subjective information and/ or investigator opinion.
- When comparing the depth of the inspection process, results are almost identical, 51% of the surveyed people understand that an FDA inspection is more thorough while 49% understand that the other agencies' inspections are.
- 100% of the people interviewed understand that FDA inspections are the most extensive ones.
- 100% of the people interviewed believe that the only value obtained from an inspection process is robustness of the systems. No one believes that their products will have more quality, that the people learned something during the process or that it has any cost savings.
- In general, 50% of the people consider that any other agency rather than FDA and EMA are more reasonable when comes to the inspection process. For more details please refer to Figure 3.

- 68% of the people interviewed consider that the language is an issue or a barrier during the inspection process.

In addition to the individual conclusions of each one of the questionnaire questions, from the survey data gathered we can conclude that in general any inspections will normally have the following characteristics:

- last 40 hours or more,
- are performed by two or three investigators,
- the quality system is always challenged,
- investigators have an expert knowledge or at least above average,
- investigators have a good attitude (for more details please refer to Figure 1),
- the outcome of the inspections is normally five observations or more,
- after the inspection process, systems are more robust,
- if the person is from a different country than the one inspected, cultural differences or language can be barriers.

The groups of persons that participate in this study come from the pharmaceutical and the medical devices industry. However, even though each one of these companies have a different regulatory profile, this distinction does not make any difference at the time of an inspection. All regulatory bodies from the study behave in the same way during an inspection for more details refer to Figure 2. Moreover, it was really clear that the differences are directly related to the agency's training, not due to the different profile of the company for more details refer to Figure 3.

Figure 1 shows the different systems cover by investigators during a regulatory inspection.

Figure 2 shows the investigators attitudes during an inspection process.

Figure 3 shows the reasonable inspectors' attitude between the different regulatory agencies.

The questionnaire results were used in order to implement a checklist for the inspection readiness in any pharmaceutical or medical device industry. In addition, could be use as a guideline for any other type of organization.

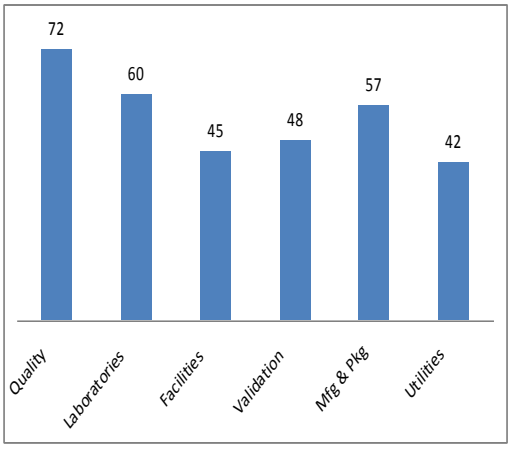

Figure 1
Systems covered by Investigators during an Inspection

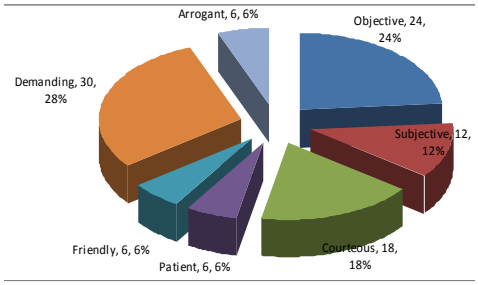

Figure 2
Investigators Attitude during an Inspection Process

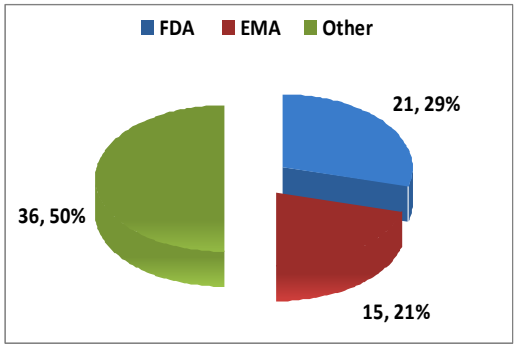

Figure 3
Survey Regulatory Agencies Classification

Inspection Readiness Tips

Know the key areas FDA will be looking at [1]:

- Complaints,
- Recalls & Field Corrective Actions (FCAs),
- CAPAs,

- MDRs,

Know the QSIT areas FDA will be looking at:

- Management Controls,
- CAPA,
- Design Control,
- Production Process Control,
- Supplier Management,
- Training,

Have an FDA Inspection Plan [4]

- Back room,
- Scribes & Runners,
- Facilitators,
- Subject Matter Experts for each QSR area,
- All of the above should be trained and rehearsed,

Have a brief but strong opening presentation

- Products, facility, organizational charts,
- Make a copy for the FDA auditors in advance.

Have the support of Senior Management during the Inspection [3]:

- Attendance at opening and closing meeting,
- Open door to be interviewed during the inspection,
- Commitments at the closing meeting,
- Have a "strategy team" to monitor the inspection and jump in as needed.

Have a planned presentation on the workings of the Quality System:

- Formal presentation,
- Handouts for the FDA auditors.

Have a "story board" with facts and data for all QSR areas and FCAs [5]:

- Show before and after complaint rates.

Work with the Facilitator and FDA to make the inspection go smoothly and quickly.

Check-in with the FDA asking if they are getting everything they need for the inspection.

Figure 4 shows the interaction of all the systems with the Quality systems.

Figure 4
Quality Systems Involved during Inspections

CONCLUSIONS

Although the specific functions covered by regulatory inspection programs may differ, the goals and objectives of these programs, the risks faced by program managers in overseeing these programs, and the control practices they implement in response to their risk assessment are generally similar.

Learn how to plan for and manage inspections by regulatory agencies is essential to your company.

Don't be caught off guard! The key to effective management of regulatory inspections is preparation. This guideline was developed to help companies determine how to build a robust system for handling regulatory inspection and ensuring that all employees follow the process [1].

This guideline will help you understand why you might be getting audited, and prepare your company to pass any surprise or scheduled regulatory inspections that might be in your company's near future. They will help you understand the purpose for the inspection, and help you make ready all the necessary regulatory filing that may be involved. They will inspect all the logistics in and around your company and will work to prepare your site according to Regulatory Agencies standards [2].

In summary, this project information will help you to:

- Understand what a site inspection readiness program is.
- Understand the regulatory authorities' audit processes and the purpose of the inspection.
- Utilize the tools needed to accomplish tasks related to inspection readiness.
- Distinguish specific roles and responsibilities and responsibilities during the inspection process.
- Evaluate the inspection intricacies associated with quality, compliance, validation, facilities, laboratories, utilities and processes.
- Establish an expert for each functional area.
- Formulate effective responses to various types of questioning used by the FDA and other regulators.
- Guide the inspectors to focus on your quality system's strengths instead of weakness.

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