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FDA INSPECTIONS OF SYSTEMS IN A PHARMACEUTICAL MANUFACTURING ESTABLISHMENT

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ABSTRACT

Since the late 1960s, and increasingly as the years have passed, FDA has been using the systems approach to establishment inspections. FDA's Compliance Programs for drug process inspections state, in effect, that if one system is out of control the entire process may be deemed to be out of control. When is a system out of control? There seem to be no two FDA Investigators who do inspections precisely the same way, but they all must follow certain defined policy during inspections. Systems inspections will be presented from the vantage point of an experienced FDA Investigator.

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The abstract of my topic touches on four aspects: the systems approach to an inspection; when is a system out of control; what policies are utilized to carry out these inspections; and why no two FDA Investigators seem to do an inspection precisely the same way.

We will start by answering the question what is a systems approach? To my way of thinking it is a look at a related series of operations. Generally in a pharmaceutical company, the systems are defined by the firm being inspected, that is, they have already divided their operations into departments or separate rooms. Systems seem to consist of logical groupings for performing manipulations so that the product in process is ready for the next stage. One of the FDA guidelines gives a number of examples of systems and these include operations for mixing, blending, granulation, encapsulation, tableting, aseptic filling, sterilization, packaging, and labeling.

Now that we know what the system approach is we might ask why FDA started using it. We started using it increasingly as it became clear that end product testing alone was not sufficient to really cover a product adequately. By concentrating, that is taking a smaller look at those aspects which closely interrelate, we hope to flush out any potential problems and be able to express them clearly to management.

The FDA Investigators are asked to determine if a firm is in a state of control, and I emphasize that positive aspect in a state of control, rather than out of control. This is because FDA's philosophy regarding control has changed recently.

The first use of the term "out of control" in regard to a drug process that I could locate seems to be in one of our guidelines, a Compliance Program from October 1978. This is when a separate Compliance Program on drug process inspections was initiated and incidentally the very first time that FDA defined the term validation in writing. More details about these Compliance Programs and validation will appear later in this paper.

Under the previous Programs, that is before October 1982, a process was considered to be out of control if it was not validated or even if it was validated if certain aspects were altered or if the written controls were not followed. While this basic concept along with the definition for validation was used for four years, it was dropped from the October 1982 Compliance Program on the same subject. As I noted, only the positive references are now used. The firm is in a state of control and we achieve that when: controls are developed; when the operations are in compliance with the Current Good Manufacturing Practice regulations; and when the finished drug product has the quality, strength, and purity

assured throughout the production operation.

That leads us to the next question, what is the goal of FDA during the inspection? Currently there are five goals. First we review the firm's quality assurances systems, then compare them to the requirements of the Current Good Manufacturing Practice regulations. Next, we audit the systems, review the written standard operating procedures (SOPs), and lastly cover all significant processes.

Next let us look at FDA policy. The Abstract notes that all Investigators must follow certain defined policy during inspections. I think I almost detect a note of a question after that, something like shouldn't they? Being a government agency, we certainly do have a lot of policies and what I would like to do is cover some of the main ones that directly influence the Investigator and his/her inspection of your pharmaceutical plant.

References

Of course we have to touch lightly on the basis for the existence of FDA, a government agency financed by the taxpayers and that is the law, the Federal Food, Drug and Cosmetic Act. I am sure you are all familiar with the fact that Section 501(a)(2)(B) in the law is the source of the term "current good manufacturing practice". That takes us on to the regulations which have been derived to interpret just what current good manufacturing practice means.

The Current Good Manufacturing Practice regulations commonly referred to as the CGMPs were last updated in 1978 when the concept of validation was introduced. The most up-to-date version is found in the current edition of the Code of Federal Regulations whose specific reference is 21 CFR Sections 210 and 211.

Another guide is the Official Compendium namely the current edition of the United States Pharmacopeia And The National Formulary. As you probably know, an "Official Compendium" is referenced in the FD&C Act (Sec 501(b)).

Working downward in priorities we have then a series of Guidelines and Directives and I am going to divide these into several categories so we can examine them, first the Internal Directives and then Published Guidelines that are generally available to the public.

Looking at the Internal Directives, we come to the most important, the FDA Compliance Programs which are collectively called the FDA Compliance Program Guidance Manual. This is a series of about 100 different programs relating to everything that FDA covers, with drugs being covered by eight to ten specific Compliance Programs. These Compliance Programs are updated annually. Some have a limited life and some are deleted after a short time.

The Compliance Programs have three specific purposes. One is uniform guidance and specific instructions to the 900

Investigators that are out in the field regarding gathering of evidence. Another purpose is to gather data on a particular industry, for instance, parenterals. A third stated purpose is to gather data on specific problems with perhaps a single product, for instance, radiopharmaceuticals or antibiotics or bulk drugs. Shortly we will examine one of these Compliance Programs to show you specific examples of what is in it and that is the one for Small Volume Parenterals.

Just who writes these Compliance Programs? There is input from FDA Field Investigators as well as the Headquarters people and in the drug area it originates with the Office of Drugs. The last stage is review by the FDA Associate Commissioner for Regulatory Affairs for agency wide consistency. In other words, we do not want to take regulatory actions in the pharmaceutical area that are vastly different from those taken for food or for cosmetics.

Next in order of importance is the FDA Investigator Standard Operating Procedures Manual which is called the Inspection Operations Manual. I suppose you figure that if we were requiring written SOP's for everyone else that we must have some for ourselves and it's true. These are periodically updated by transmittal sheets and it is Chapter 5 Subchapter 540 that we are interested in, that covers how to do a drug inspection.

Another category of guidance is from the FDA Reference Materials and Training Aides for Investigators and a good example of that is a 25 page booklet telling you all you want to know about inspecting a computer or as it is titled Guide to Inspection of Computerized Systems in Drug Processing. Shortly I'll cover some specific examples from this rather recent program also.

Guidelines

Now we go on to published works that are generally available to the public in the area of guidelines, both FDA guidelines and guidelines published outside of the agency. While we are talking about guidelines there is a very specific definition of what is and is not a guideline and what we can expect from it. The FDA has published these definitions in the Code of Federal Regulations and the reference here is 21 CFR 10.90. It shows four areas of interest, regulations, guidelines, recommendations, and agreements. The first two are the most important for the drug area. Regulations are of course are generally enforced as legal requirements, for example the Good Manufacturing Practice Regulations.

I think in terms of FDA Guidelines, there are four key issues. First they cover principles of general applicability, secondly they are not legal requirements, let's remember that. A guideline represents the formal

position of FDA on a matter and lastly you do not have to follow it, so it will not appear on a 483, for example. One of our guidelines that has been quite successful covers Compressed Medical Gases.

There are outside guidelines that are not put out by FDA and of course absolutely not enforced by FDA in any way. An example might be the Federal Standard 209B covering the clean room technology or the various military standards for drug manufacturing.

I should note that we are aware of some excellent documents published by industry associations which we do utilize for reference materials. Again let me emphasize these are not regulations, these are not guidelines, they are not enforced by FDA, and they are not put on the Form 483.

Still talking about guidelines, there are two more categories, the published and the unpublished drafts or proposals. The GMP proposal for the Large Volume Parenteral Drug Products is a good example. It was published in 1976 as a proposal and has remained as such ever since. Other guidelines have been published as proposals, one on Process Validation and another on the Limulus Amebocyte Lysate, the LAL test. Now just because these have been published as proposed guidelines does not mean that they are ever going to see the light of day as finished guidelines. However, they

have a greater chance of being published than does a regulation. To my way of thinking, the primary value of these drafts or proposals is that they offer a glimpse into the thought processes of the policy makers at FDA. They do unofficially show what is, in fact, FDA policy, at least at the time the guideline is written. For example, the LVP GMP's are used in the industry as a guideline although in a very informal way.

The last category of guidelines are the unpublished drafts that are ciruclating for review within FDA covering aspects such as aseptic processing or bulk drugs. These are not available to the public but like the Pentagon Papers sometimes manage to leak out. Whether these will ever survive their three year gestation period and be delivered some day, is strictly speculative.

Training Schools

That takes us on to a somewhat new area, still under the defined policy for Investigators, and that's the FDA training schools. We have a great variety and I'll just mention a few of them. There's a basic four week training school held at a School of Pharmacy and various specialized advanced training schools held from one to three weeks such as industrial sterilization, pharmaceuticals or antibiotics. One of the things we are always sure to do at these schools is to

include not only people from academia with excellent reputations in the field but also folks like yourself who work in the industry and know more than anyone else about it. These people are gracious enough to appear at our training schools and to share their knowledge with us.

The last category is industry training schools and one in which FDA has recently been invited to participate are the excellent series of seminars run by the Parenteral Drug Association.

Validation

Now that we've covered most of our formal guidelines, we really have to touch on another area as I promised, validation. Here I think we must begin with definitions. From my inquiries, it appears that FDA first defined validation in an October 1978 Compliance Program. This Compliance Program was the first to have the specific subject of Drug Process Inspections and the reference number for it is C.P.7356.002. The definition of a validated manufacturing process is rather simple and straightforward and one that I still favor today, namely that a validated manufacturing process is one which has been proved to do what it purports to do.

FDA carried this definition along until the October 1982 edition of this same Compliance Program on Drug Process

Inspections. (By the way, our fiscal year begins in October, that's why the Programs begin then.) In October 1982, that definition was dropped from the revision and also deleted was the concept of a process being out of control, as I mentioned earlier. Now we only use the positive term, in control.

The definition of validation did reappear in a modified form in the draft guidelines on process validation. Just for contrast, I would like to focus on the new definition and see how it differs from the earlier version. First, the word "Manufacturing" has been dropped and the order of the words reversed, coming out as "Process Validation". It seems to have three key aspects. First, it now has to be a "Documented" or written program. Next it must provide a "High Degree of Assurance" – now there is some latitude. It does not say must absolutely provide, it says a high degree of assurance, so keep that in mind. Then it continues with a specific process that will, another key word, "Consistently" produce products which meet the specifications. You should note that FDA offers this as one definition of validation in the Guideline. That is we do not say this is the only definition. I think all these nuances are important to emphasize.

Compliance Program – Small Volume Parenterals

We have covered the systems approach, we talked about

the Guidelines, I mentioned validation, now I think we can get right down to the inspectional approach itself. What I would like to do is give you two examples of a systems approach according the FDA Guidelines. One will be on what is covered for Small Volume Parenterals and the other on what we cover during a Computer Systems Inspection. The first is found in the Compliance Program reference number 7356.002A titled Small Volume Parenterals. It's interesting to note that the drug process inspection program that I mentioned earlier was reference number 56002 so this one is number 56002A shows that it is closely related to the validation aspects.

The SVP program has three stated purposes: to provide guidelines to the Investigators; to determine compliance with the Food, Drug and Cosmetic Act, the law itself; and to identify practices which need correction or improvement.

The program goes on to require that the Investigator fully review and report in five specific areas. What I would like to do is go through the types of things that we will cover under each of these five categories.

Air Quality

We will begin with Air Quality and we are supposed to evaluate the firm's aseptic processing area. There is a cross reference to the GMP's in the CFR, Section

211.42(C)(10) but that Section does not have too many specifics beyond some very basic requirements so this Compliance Program goes on to tell us what we are supposed to look at. Start with the Air Handling Systems, look at the specifications and methods for testing the Quality of the Air, and determine what type of instruments are used in checking the filters. There should be dioctyl phthalate (DOP) sampling at a rate of 1 cubic foot per minute and a reading on an appropriate instrument of 0.01% indicates that there is a leak in that filter. This integrity test of the High Efficiency Particulate Air (HEPA) filter should be carried out twice a year. We look for a velocity of about 90 feet per minute and get that figure out of Federal Standard 209B. However, as I noted earlier it is not something which we would enforce. We might ask whether you have tested for turbulence using, for instance, smoke sticks.

We look at the exposure of the sterile product and the container/closure system. We look for laminar air flow and air class 100 conditions, again these are highly recommended but not absolutely required. Class 100 air as specified in Federal Standard 209B is the maximum number of particles per cubic foot 0.5 nanometers and larger. In the metric system, for the rest of the world outside of the USA, that is 3.5 particles per liter of air.

We look at qualification and monitoring of the area served by the filtered air. We look for positive pressure with an 0.05 inch water differential between the critical area and outside rooms. We inquire about and record the alert level and the action levels for contamination and we suggest that there be not more than one viable particle per 10 cubic feet of air sampled.

How often is monitoring done is a question we will put to you. We prefer daily readings. What is done if the action levels is reached is a second question followed quickly by another, what is the disposition of the product you made under those out-of-limit conditions?

We will inquire about tests you've done to monitor both viable and non-viable particles and determine the locations where the measurements were taken. We prefer to see these taken near the open product containers.

We will inquire about the methods for viable particle air monitoring. The forced air samplers are preferred as the nutrient agar settling plates will catch only the heavy particles.

Media Fills

After a thousand or more questions related to that aspect, we will move on to the second topic sterile media fills which FDA feels closely simulates the actual production

run. As described in the USP/NF, a representative lot of containers are aseptically filled with sterile culture media and the entire lot incubated and then examined for growth. We will ask about media fill results (if you've elected to use this method) what alert and action levels you utilize, what media is used and how many units are filled and examined. We suggest that there be three separate runs for each filling line and we recommend that you fill 3,000 units in order to achieve a 95% confidence limit. We will ask how often the tests are performed – we recommend twice a year or when changes occur in the equipment or processes. We will ask what is done when the action level is reached.

Sterility Retesting

Our third area for this minimum required coverage is the laboratory testing, addressing four topics: sterility, potency, pyrogens, and particulate matter. I am not going to cover potency but I will elaborate on the other three starting with the sterility testing. We are very interested in the failure of initial sterility tests and how this is evaluated. We like to know how you make a determination of false positives and whether you do speciation of the organisms which are found. We would like to see you compare them with the organism normally found in the production areas as well as in the laboratory where the sterility testing is

done. We are going to look through your records and try to determine the retest rate, that is, when is a second sterility test necessary. In addition we will use the standard follow-up for the USP media growth promotion test and your determination as to whether the product is bacteriostatic or fungistatic. We will also inquire whether you are using the direct or membrane method, the media used, the incubation time, and temperatures. Incidentally, it is not all that uncommon to find that temperatures within incubators are not being monitored.

Pyrogen Testing

Pyrogen testing is another area for investigation and the proposed FDA LAL Guidelines were published in March 1983. We will ask whether you have validated the LAL procedures for detection of endotoxins in each product you test. We will want to know the sensitivity of the method and we will provide a copy of the FDA LAL Guidelines to you. If you use rabbits we will use the USP pyrogen testing requirements as a guideline, and ask about calibration of thermocouple leads including the method and frequency. An inquiry will be made as to whether the rabbits are screened for sensitivity to known endotoxin levels before they are used.

Particulate Matter Detection

The fourth area of concern is particulate matter and we

will examine the room seal for adequacy, the use of positive pressure, and the air filtration methods. We will look for laminar flow, check personnel for apparel and review the standard operating procedures for gowning. We will observe the handling of packaging components and the movement of employees as well as the washing and rinsing of the vials and stoppers. We will look for possible particulate generation from equipment and we will ask about the particle inspection methods and the written SOP. We will want to know the criteria for particle examination, whether it is done manually or automatically. We will want to know the degree of magnification for a manual method and the duration of duty for the operators. The rejection rate will indicate problems as well as the identification of particles when found. Interestingly, the Compliance Program requires that the FDA Investigator must do his own field examination of units which have been passed by the firm, looking at a minimum of 100 units.

Water Systems

The last system of interest under the SVP Compliance Program are the water systems and we will want to know details about all the different types of water in use starting with potable water and going through treated, deionized as well as water made by reverse osmosis or

distillation. We will take a very close look at the water for injection including sources, procedures, and written standard operating procedures. We will want to know about the monitoring, sampling schedule, the site where samples were taken, and, you knew it was coming, validation of the system. We will look at your specifications and ask for alert and action levels for microbial presence.

We will take a close look at the piping systems to see if we find any of those dreaded threaded connections that can harbor bacteria instead of the nice sanitary fittings like the dairy industry uses. We will look for dead legs (I like that term) those areas that are not drained regularly because the micro-organisms love to grow there. We will seek out water system cross-connections. Where we see them most frequently is where there is a nice little flexible rubber hose running from a faucet down into the sink. When the sink water level comes above the hose outlet, water can siphon right back into the system. Another place cross-connections are commonly seen is when drain pipes go to the sewer without an air break and when that sewer standpipe fills up, the sewer water can siphon right back into the water system or even into an autoclave.

With water for injection, we expect to see either a continous circulation loop held at a recommended 80 degrees C

or dumped every 24 hours for a non-critical use or to the drain. And of course, validation of the system is required.

The sanitizing schedule is another aspect which we will scrutinize especially for the deionizers, and also for the reverse osmosis apparatus and the stills.

You can now see how we operate during the systems inspections, zeroing in on these discrete areas and taking a very close in-depth look at the operations.

Computer Systems

I promised you a second example and I will get right into that with how we carry out computer systems inspections. I'll cover four categories, hardware, software, computerized operations, and finish with some GMP guidance.

We will begin with an overview of the hardware systems and determine the extent to which the computer controls or monitors the operations. We will look at the general loop system and determine any critical aspects. Specific manufacturers and suppliers of computer systems are identified because FDA does their own trend analysis for problems. We will evaluate the location of equipment for hostile environments such as excessive temperature, humidity, dust, or static electricity. Micro-processors in laboratories for instance can be vunerable to spillage.

In use of computer hardware, we will ask about command

overrides and suggest that these be recorded and look at inter-connected units for possible misdirected commands.

Validation, of course, will cover the operational limits and here we will look at the standard operating procedures. Have you simulated the worse case production conditions? Have you repeated the run until you are certain that it will function properly? We will look for documentation as well as criteria for reevaluation.

Moving on to software, from the key programs from the menu, we will note the language used, and look closely into the edit procedures. Here we have seen things such as rounding off of digits or truncation, correction factors, and program overrides. Details about the software development will be obtained, especially if it is a turn-key operation using proprietary programs.

Security is another area of great interest. We will look at access to the computer, the security of keys or cards, and ascertain authority and identity of personnel allowed to enter the area.

On software validation, we first look at the written SOP's, inquire as to who conducted the validation, and their qualifications, and see whether validation covered compatibility with the tasks. Can the computer handle the maximum number of variables expected, for instance, can it

cover two or three different lots of a single component that you intend to use? Again we recommend repeated runs for some statistical validity, and we will ask for documentation and revalidation criteria.

If the computer is part of a network, we will want to know the extent of the network, the information flow, the monitoring, and security procedures to prevent unauthorized entry to the network.

Manual back-up systems are another area where we will inquire about which functions are covered, documentation when back-up is used and the written standard operating procedures.

There are a number of ways we can monitor computerized operations, for example, if calculations are involved, we can perform these manually. If there is an input recording often we can take a manual reading from a gauge and verify that. If components are under computer quarantine, we will verify the actual location of the materials. We might look into accountability of tailings in automated batching systems.

Alarms- What type, (visual, audible, printed) and their locations? What is the SOP for response to an alarm? What are the alarm thresholds for critical conditions? Can these thresholds be changed by the operator? If so, are they recorded when they are overridden and what is the response to alarms?

What about that dreaded day like the New York City Garment District experience not too long ago, the shutdown, when the electricity goes off? What are the SOP's? What are the recovery procedures? Do you have manual back-up provisions?

Now let us take a brief look at GMP considerations in regard to computer systems and I will give you a few references from the GMP Regulations. Section 211.68 requires that the computer input and output be checked for accuracy. We can note that software edits tend to minimize inaccuracy and here we ask again, as in our definition for validation, for a high degree of assurance of accuracy, not 100% checking. We will look at your error handling procedures, and want to see the documentation, the error verification, the correction of the verification, and the allowable overrides.

We will want to see what back-up data storage systems you have such as duplicate tapes, discs or microfilm and evaluate data transfer and security procedures.

The next is a very important aspect of GMP requirements and that is the annual review of data referenced in GMP Section 211.180E. This must include the computer where it is utilized. You could do things like extract, for instance, analytical data for trend analysis.

Another GMP reference is in regard to double checks in Section 211.101D, and this is one that raised a question in my own mind because of the specific wording in the regulation itself. For components being added to the batch, the wording is such that component addition must be verified by a second person. It does not say by a computer, it definitely specifies a second person so the question is are computers allowed to omit this second person check? The answer is yes, if the same degree of assurance is provided. Now the computer can not do everything of course, for instance, what happens when the color and type of raw material to be selected is the same as another one? A person may be able to distinguish between these but probably not a computer, so we will look into all aspects regarding that.

Inspectional Approaches

We will leave computers now and touch on two more subjects, one of which is that no two FDA Investigators seem to do inspections precisely the same way. I think that at this point you have some good ideas why that is true. There is a lot of judgmental latitude allowed, there are a multiplicity of guidelines, there is a great variety of educational and experience backgrounds, as well as personality types. Also, we do not use checklists so each one approaches the inspection in a little different manner.

Form 483 - Inspectional Observations

My last remarks will be about that famous or infamous document which concludes many inspections, the Inspectional Observations Form given the FDA number 483. The criteria for issuing a 483 is given in our SOP the Inspection Operations Manual in Section 512 but it notes that individual judgment should be used regarding drug adulteration. It also covers reporting, that is the listing of observations, and has some very specific directives there. It says we should be concise and to the point, grouping items of the same nature. We are directed not to enlarge or expand on our observations. In regard to the CGMPs, we are supposed to report observed discrepancies and omissions. We are not to report those discrepancies which were detected by the firm and corrected before we arrived. We are not supposed to quote the regulations. We are supposed to report faulty manufacturing practices and recordkeeping. If your product is covered by a new drug applications, we consider the contents of that NDA to be commitments and will accordingly put any deviations down on the 483.

In closing, the Drug Process Inspection Compliance Program that we have talked about earlier, number 56002, has some very good advice for the Investigators. It notes, refrain from using unsubstantiated conclusions such as

"processes have not been adequately validated". The second bit of advice is "do not use the term inadequate without explaining how and why".

Try the systems approach in your pharmaceutical firm during the next internal audit. Perhaps you will uncover an aspect which can be corrected before the FDA Investigator arrives.