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GOOD? BETTER? BEST? MANUFACTURING PRACTICE*

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When is an unadulterated product adulterated? You know, it sounds like a Catch-22 situation, but the fact of the matter is that within the Federal Food, Drug, and Cosmetic Act, there are included definitions for adulterated drugs that result in the legal conclusion that although a product is not contaminated in the usual sense of the word, that is it does not have some foreign or unpermitted substance in it, the article is in fact adulterated because of the conditions under which it is produced. In one instance, a drug can be adulterated if it has been prepared, packed or held under insanitary conditions whereby it may have been contaminated with filth. It doesn't have to be contaminated, in fact, but if there is a likelihood that it could have been contaminated with filth the article is considered adulterated in the eyes of the law. It is not an easy concept to grasp especially

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when there are instances where FDA has charged firm's with producing "adulterated" drugs, yet the actual product conforms to its monograph in all respects.

Another example of an unadulterated "adulterated" drug, (and this is the one which I'm going to spend the rest of my time discussing this afternoon) is the drug which has been produced in violation of current good manufacturing practice. Again, the product itself may not in fact contain any adulterant, but the conditions of its manufacture may cause the adulteration if those conditions don't conform to current good manufacturing practice.

What is current good manufacturing practice? The statute itself doesn't say precisely what those conditions are of manufacture for, let's say, aspirin tablets. Nor, do the regulations themselves spell out with any degree of specificity what CGMP's are for the manufacture of a particular product. Yet, you know what they are and I know what they are. They are flexible; they are dynamic, they are essential to assure that drugs are what they are meant to be; they are standards which all products must meet; they are common sense; they are the drug consumer's assurance that what you make on the east coast is the same article that another fellow on the west coast is making. Above all, they are current.

Legislative History

The legal requirement for CGMP's grew out of a series of hearings held by Senator Estes Kefauver in the 1950's and early 1960's because of his concern that all drugs meet the

same standards so that a physician would have the assurance he needed while treating his patients that a drug he prescribed, whether it was brand X or brand Y, could be depended upon to produce the same effect and be of the same quality. During those hearings, the requirement for CGMP's was developed. It is interesting to note that the idea caught on and was discussed throughout the hearings and included in the "Drug Amendments of 1962" with little controversy. Even the first edition of the regulations generated little controversy.

There have been challenges many times since, however, and I would like to discuss one briefly, that occured recently. That challenge occured in the case, U.S. vs. Morton-Norwich Products, Inc., in the U.S. District Court of Northern New York. In that case, the defendant attempted to have CGMP charges dismissed on the grounds that the requirement to conform to CGMP's was too vague and that the firm had not been properly notified of what is was expected to do. In rejecting a similar challenge to the law in a case brought by another Federal Agency, a U.S. District Court said,

> "...few words possess the precision of mathamatical symbols, most statutes must deal with untold and unforeseen variations in factual situations, and the practical necessities of discharging the business of government inevitably limit the specificity with which legilsators can spell out prohibitions. Consequently, no more than a reasonable degree of certainty can be demanded. Nor is it unfair to require that one who deliberately goes perilously close to an area of proscribed conduct shall take the risk that he may cross the line."(1)

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(1) Boyce Motor Lines v. U.S. 342 U.S. 337, 340 (1952)

On one hand in this case we were accused of not being specific enough in our requirement, but on the other as a result of our February 13, 1976 proposal for revision of the regulations we have been told we are expecting too much of industry intruding into areas which should be management's prerogatives; and have no right to develop regulations which are substantive. Let me address that point for a moment.

Substantive or Interpretative?

It is clear from the legislative history of the CGMP requirement now in the law, that the intent was to set minimum standards rather than set forth an exclusive method by which a drug could be made. The regulations themselves are a means to provide for efficient enforcement by defining CGMP's in as practical a way as possible for regulatory purposes but to allow for compliance evaluations within the context of a firm's own operations. For example, there is no requirement spelled out in the regulations that there be no flies in a sterile pharmaceutical manufacturing area, yet I'm sure you will agree that the presence of flies in a sterile facility violates CGMP's. By the same token, if there are holes in a plastic battier which is relied upon to keep bacteria out of a sterile area and the plastic flaps in the breeze created each time a door in the area is opened, CGMP's have been violated even though you will find no reference to tears in plastic barriers in sterile facilities in the regulations.(2)

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(2) Affiavit of Theodore E. Byers, U.S. vs. Morton-Norwich Products, Inc., Northern District of New York, 1976.

However, in the recently proposed revisions we have in some instances spelled out in some detail what we expected to see in the way of compliance where we felt there should be no question about what we meant. In some instances this meant new requirements, but in others it meant clarification of what we had always expected to see, but which was not stated unequivocally in the regulations. The requirements for employee garb, periodic calibration of equipment yield reconciliations, time limits on manufacturing and manufacturing of products with intent to achieve 100% of the declared active component are examples of the former. Quarantine areas, equipment use logs and increased written doc-mentation of controls are examples of the former. Another is the requirement for keeping records at manufacturing sites.

Let me digress for just a moment because this was an area that bothered me as an investigator. I never understood the logic of keeping records at sites other than the one where the product was made when none were at the manufacturing point. If you are going to be evaluating compliance and problems at the manufacturing site and we are too, why ship the records off somewhere else. For this reason and sometimes others long delays have been experienced by FDA investigators in obtaining documents they needed. Failure to provide requested records only lengthens the inspection, takes up our time and reduces our productivity. But be assured that, if need be, regardless of the time it takes, the investigator will wait for the requested records. This requirement would, therefore, be an advantageous one for the industry especially

because it will get the investigator out of your hair faster and you'll save the taxpayer a few bucks too.

The question of what constitutes CGMP violations then must be answered within the context of conditions found within a particular operation just as the Court said in the case I just cited. It is interesting to note that the constitutionality of the CGMP requirement in the Federal Food, Drug, and Cosmetic Act has never been questioned by any Federal District Court or Court of Appeals which has considered or applied it.

CGMP's Well Known

In the Morton-Norwich case the Court said again that the term CGMP's is and must be flexible in application. Further, the Court said that everyone in the drug industry knows what the term means because the manufacturers participated in the legislative process resulting in the requirement in law. You know too that industry has played a substanital role in revising and updating of the regulations. In addition, colleges offer courses in CGMP's; there are publications which discuss CGMP's; and seminars and courses are sponsored by FDA and trade associations at which CGMP's are discussed. It, therefore, is apparent that Congress had no intention of including a requirement in the law and issuing FDA authority to write regulations defining the standard and thereby creating a situation which would have to be litigated and adjudicated each time charges were brought, in order to define the violation. That would not be efficient enforcement. It is a fact that, at one time the legislation was written giving

FDA authority to write regulations under the rulemaking provisions of Section 701(e) of the Federal Food, Drug, and Cosmetic Act which would have resulted in hearings and judicial reviews. This was removed in favor of the authority in Section 701(a) which would not result in hearings. The word "interpretative" was also taken out. These changes were made specifically to prevent a legal battle over meanings of words which would have crippled our enforcement of this provision of the law.

It is clear then, that the purposes of the legal requirement for compliance with CGMP's was that legal action could be brought against firms failing to meet the standard. Violations of specific sections of law cause product adulteration, but whether FDA makes such a charge is another question. The ultimate test of the success or failure of any control system is whether the finished product has the characteristics intended and whether the methods used were designed to assure that result. As the Court observed in the Morton-Norwich case; considering the end to be accomplished (that is the drug is safe and has the identity and strength, and meets the quality and purity characteristics intended), of drugs to be used by human beings to cure or prevent disease, improvements, changes and new manufacturing and control procedures are to be expected and, in fact, to be desired!

Updated Requirements

Now, let me speak for a few minutes about some of the specific changes that have been proposed. One of the changes

has been replacement of the word "minimize" with the word "prevent" in several sections of the proposed revisions. It seems to me that the word "minimize" did not really express the intent of these regulations. The point of the CGMP regulations is that manufacturers must build quality into their product from the very beginning. To me, the word "minimize" expresses acceptance of a certain amount of something which does not belong in a product. But since we are talking about a manufacturer who is building some finished product which he can control, it seems to me that he can control to a high degree, the characteristics of the finished product. It is the manufacturer who is shaping, forming, creating and making the finished product. Therefore, the manufacturer must have designed a control system which "prevents" to the maximum degree possible, errors in the formulation, production and packaging and labeling of a drug. If we understand "prevent" to mean to anticipate problems; to forestall the occurence of problems; and to develop controls to as reasonable extent as possible to keep those problems from happening then it is exceedingly appropriate that we use the word "prevent" in our regulations. We know--you know and the Courts know that no human on this Earth can prevent all problems from occuring in an absolute sense, but I don't think that anyone in FDA or industry, the Courts or the general public realistically expects that all problems can be prevented in an absolute sense. But they do expect, and justifiably so, that reasonable measured be designed into a system to prevent foreseeable difficulties.

An important emphasis that these revisions have which I'd like to highlight is the requirement for documentation of systems and controls. In both the food and drug industries in recent years, we have been surprised to find manufacturers using processes that they don't understand. Their origins are shrouded in deep mystery. Coincidentally, many worked. Not so coincidentally, some didn't. We expect now that a manufacturer will develop data that show his water system is clean instead of assuming that it is; and that his sterilization processes work; and to know why they work; of, if they don't to determine how they should be changed. We expect to see baseline data for microbial limits where appropriate rather than a number plucked from the air simply for the want of a number. What good is a specification if we don't know why we have it, and if we ignore it all the time because we don't think it really matters anyway. If you have an area that you think is aseptic we will expect to see proof. If you are using an expiration date, we will expect to see data to support it. If problems occur we expect to see that the causes have been thoroughly investigated and that responsible individuals have made sound decisions based on reliable information.

I think too you will see increased concern for environmental contamination and controls to prevent it in drug processing areas. The obvious concern is that cross-contamination of drugs or other undesireable contamination including microbial contamination and in plant "air pollution" may

occur because of the lack of control over air supplies to drug processing areas.

We will expect to see more written standard operating procedures for controls in your quality assurance system. But let me warn you too, that these should by no means be merely a collection of words on a piece of paper. The law says that you not only have to have these controls, but that you must operate and administer those controls. May I say again, (and that this is a constant revelation to FDA investigators), that the differences between policy and practice in some pharmaceutical operations are exceedingly great. While we don't believe most people intend to fib, it is apparent that many responsible individuals don't check to see that their controls are implemented. It's important to note that an individual's lack of intent to violate the law is no defense against a CGMP violation charge. It is necessary under the law that responsible individuals acquaint themselves with the requirements of the law and to take positive and deliberate action to bring about compliance. One of the most deliberate steps that I can think of is training in CGMP concepts for employees who are actually implementing your controls. Just as some manufacturers have been found ignorant of the how and why or why not of these processes, all too often employees have been found performing jobs they learn by rote with no understanding of why or what to do if something goes wrong. It is astounding how reliable and dependable and creative they become when we recognize that they are capable of thinking and create a situation

for them in which they can think because they have a congitive understanding to the purpose of their work.

The regulations themselves are a good point to start from when developing your own internal SOP's. They state what your objectives should be and in some cases even contain an outline which can be used as a frame work on which to hang your procedures. Let me emphasize that your SOP's should be written for clarity's sake so that you understand them and so that your production employees can grasp them. You can be sure too that we'll be checking to see that the employees do grasp them because that's the other part of the legal requirement I mentioned before, that the controls be administered in conformity with GMP's.

We intend to finally close the door on the processing of penicillin products in the same areas as and on the same equipment as non-penicillin products. Our observations in recent years have shown that when separate facilities are used no cross-contamination occurs. Since the use of separate facilities precludes the cross-contamination problem there is no need for a tolerance, therefore, that too has been removed.

Another characteristic of the proposed regulations, which I hope you see and recognize as valuable is the encouragement to design a facility which moves product in a single direction and where unnecessary traffic is eliminated. The kind of traffic we are particularly concerned about is the type where in-process product moves back and forth thru the same areas more than once. Such movement creates

opportunities for error to occur. Of course, we know that some equipment is used more than once in the manufacture of a single batch so there are situations where cross-overs are bound to occur, but we believe that, to the extent reasonably possible, such cross-overs should be eliminated.

"Critical Control Points"

The concept "critical control points" has been in use in the law acid canned food industry for several years now. This concept can apply equally well to the drug industry so let me take some time to emphasize just how important it is to identify critical control points and apply controls at those,-what you might call "pressure points" on the drug manufacturing body. The terminology may be new in application to the drug manufacturing industry, but the idea is not so different from what many of you have been doing all along. Basically, it amounts to a careful examination of a manufacturing process and the controls applied to that process in order to identify those points which are crucial to control in order that a finished product meets its most important criteria. Lack of control at the crucial points could cause product failure. Critical control points in a low-acid canning operation include the operating sterilization process and the controls on the retorting equipment such as the mercury-in-glass thermometer, the venting cycle, and can closing operations among others. There are obviously critical control points in every drug manufacturing operation and different points in each different kind of operation. It seems to me that the first priority of every drug quality

control operation should be identification of the critical control points. The controls then applied should revolve around these points and should assure that they are firmly under control to increase the likelihood that the finished product complies with its specifications. A manufacturer who is unable to identify his critical control points is only going to produce a complying product by chance not design. If you want to increase the likelihood of producing a good product and build quality into the product, critical control points seem to be the most sensible means of assuring that.

Challenges Ahead

Underlying several sections of the revision you can see an emphasis on increased use of statistics. I think we all recognize that there has to be a more rational basis for our sampling, testing and product acceptance criteria. FDA is using statistics more and more in the design of some of our compliance programs. Use of statistics is an attempt to formalize what the point of our current good manufacturing practices regulations has always been, that is to build confidence into drug products. The specific requirements themselves are in some cases causing a good deal of comment. But, don't you think it's just a matter of time? If sound statistical principles were not used in designing the protocols for Investigational New Drug Products, it is likely that you would not learn from them what you expected--and likely too that they wouldn't be approved. The same is true of the sampling and testing plans in many New Drug Applications. The time has come to apply these techniques to the everyday

business of drug manufacturing. Many of you already do, But many don't. Many know too that FDA investigators have looked in the past at some of these controls, where we found them. You'll see more interest in these controls in the future.

Arising out of this I expect to see more concern in the future in FDA about your validation and/or certification of manufacturing techniques, test methods, plant facilities and equipment.

This would entail evaluation of the effectiveness of these areas from a different perspective then ever before. It will mean your determining ahead of time, the likelihood that you have designed a plant, product or process to work the way it is supposed to. It will mean that you will be able to spot with more preciseness problems as they are developing. And it will mean that you will see with more clarity, from a historical perspective, the particular successes and failures of your efforts. The start of this is the requirement for batch summaries and product profiels. As you know, under the Government Wide Quality Assurance Program for Drugs, FDA has developed a system of profiling drug firms. It has proved to be extremely useful in providing us with a concise, succinct description of a drug dirm's compliance status. I think, you'll find the technique useful also if you're not already using it in assessing your processes and products.

One emphasis in the revision which may not be apparent at first is the one on in-process testing. This control must be considered hand-in-hand with the bioequivalence

question. The Office of Technology Assessment of the U.S. Congress issued a report entitled Drug Bioequivalence in July 1974. Among other things, it criticized the relative lack of sophistication of many of the in-process control tests described in the United States Pharmacopeia and the National Formulary. It recommended a tightening of the CGMP requirements for these kinds of tests and improvement of the tests so that they were more specific, the point being to not only develop better in-process controls, but to minimize lot to lot variations.

There is a challenge here then for the industry to develop these better methods. Many new drug manufacturers have developed unique tests for their products. I don't see anything stopping the development of tight, more specific tests for all drug products above and beyond those called for in the Compendia. We have expanded the requirements for testing of inactive components as a step in this direction. As I said, we will be looking more carefully at in-process controls and you know too, that we are at work on the problem of bioinequivalence.

Conclusion

I hope it is apparent to you now that CGMP's are a number of things. They are a baseline. They are a means of efficient law enforcement. They are a means of promoting generic equivalency. Hopefully, they will be a means of preventing bicinequivalency. Above all be assured of this,--noncompliance with current good manufacturing practices involves a constant risk of failure. That's a risk that's not worth taking and one which can and should be avoided.