

There is no “Silver Bullet” to complying with the US FDA GMPs

by Alan Schwartz

Recently, we participated in a seminar on United States (US) Food and Drug Administration (FDA) regulations to the Hebei Pharmaceutical Association in Shijianzhuang, the capital city of the Hebei province. This seminar was presented by CCUS, (Chinese Committee for US Standards) a government agency that is responsible for assisting Chinese companies in understanding and complying with US as well as other foreign regulations. There were about 50 companies with over 70 attendees attending the seminar. The seminar covered how to deal with a future FDA GMP (Good Manufacturing Practice) inspection as well as how to comply with the cGMPs (current GMP).

In the 28 years that we have consulted to the FDA regulated industries, both medical device and pharmaceutical, we have been involved with assisting many companies/industries in many different countries understand and implement FDA GMP regulations.

The first time mdi was involved in assisting a foreign industry understand and deal with FDA regulations was when the FDA instituted a new set of regulations on the ‘examination glove’ industry, requiring pre-market notification (510(k)) as well as enforcing the cGMP. This was as a result of the US Congress upgrading the standards for these products because of the AIDS and Hepatitis scare and they wanted to assure the medical community that examination gloves were safe for their intended use. At that time in 1986, one of the main countries seriously hit with the possibility of being shut out of the US market was Taiwan. With over 400 companies registered with the Taiwanese glove association, compliance with FDA requirements became a major challenge.. Over 90% of the 400 manufacturers were either not up to the task of meeting the requirements or didn’t have the interest to do so and hence gave up the idea of exporting examination gloves to the USA.

The other 10% of the companies were able to successfully implement a quality system, validate their processes and understand how to deal with FDA inspections. They were thus able to retain and grow their US market share.

The next situation occurred in 1990. It involved the hand surgical instrument industry in Pakistan. In the early 90's it came to the attention of the FDA, that the single use disposable hand surgical instruments from this one city in Pakistan, Sialkot, did not meet the standards for stainless steel but were stamped "stainless steel". This forced the FDA to visit several companies in Sialkot along with the supplier of the steel. The FDA regulations required that these instruments were exempt from the pre-market notification (510(k)), but they were required to be manufactured under GMP compliance. FDA determined that none of the companies that they audited knew anything about GMP compliance. As a result of the FDA audit of the industry, they put out a notification stating that all hand surgical instruments from Pakistan were not to be allowed to be imported into the USA until full GMP implementation was obtained. This GMP compliance had to be certified by an FDA recognized expert. As with the Taiwan glove industry situation, a very large percentage of this industry could not understand and/or implement the FDA requirements and went out of business. However, many others took our expert guidance (we were recognized as a GMP expert by FDA) and were able to successfully understand the requirements and bring their operations back into compliance with the GMPs. Many of these companies are still successfully exporting their devices to US.

While giving the above examples, let me clarify that it is certainly not the intent of the US Congress or the FDA to put companies out of business. The FDA's only aim is to assure that medical device and/or pharmaceutical products being sold in the USA meet their specifications and are manufactured under GMP regulations.

In each of these two cases, the companies that succeeded in working towards understanding and implementing GMP regulations only became stronger and more competitive. Many of these companies are still in business and prospering from their hard work and dedication to understanding and assuring full FDA compliance.

But in both the cases listed above, the Taiwan Glove Association and the Sialkot Hand Surgical Association, each was looking for the "Silver Bullet" to compliance. What is a "Silver Bullet"? A silver bullet would be considered "a simple guaranteed solution for a difficult problem".

Everyone that we met felt that there must be an easy path to follow to get into compliance and back into business. Many of the companies we initially met with asked for the “quality manual” and a GMP certification letter so that they could start exporting to the USA again. None of the companies understood that getting a company in GMP compliance was a process and had to be implemented in a systematic approach. There was no magic wand that could automatically take a company down this path to compliance.

In Sialkot, we had to work with these companies over a period of a month to set up their quality systems and train their staff, implement their quality system and then we had to follow up with a review of their documentation prior to certifying them to the FDA as being in GMP compliance. Without this process, there was a very good chance that FDA would audit their initial shipment and were they to fail, it would have put them in a more precarious position with the FDA and prevented future shipments. Many companies who did not understand what the GMPs were really about and why they were beneficial to follow, fell into this pattern of having shipments held and rejected as they entered the USA.

This was also true of the Taiwan glove industry. But, for the most part now, after over 10 years of these companies implementing a good quality system and following the GMPs, many of them have been successful in shipping high quality medical products to the USA without problems.

So, now we are working with another industry, in another country, that wants to export their products to the USA and are having a hard time understanding the US GMPs. They too are looking for that “silver bullet” to FDA compliance. The Chinese pharmaceutical industry is looking at the US market as the “pot of gold” at the end of the rainbow. It was explained to me that the whole “western medicine” industry in China at this time is approximately US\$2Billion which is smaller than any one US pharmaceutical company’s sales. The potential market is enormous and the Chinese pharmaceutical industry is eager to enter this market. But, there is one major obstacle, the US FDA, and those “ambiguous” cGMP regulations.

However, it is refreshing to see that there is initiative and interest at some level to ensure that things are done the right way. During this recent seminar in Shijianzhuang, many questions

concerning specific and unique problems of various participants came up and we were happy to address them. We even had the opportunity to visit several of the larger pharmaceutical companies and meet with their management staff and discuss their issues and concerns.

We learned when we visited each company that they were already manufacturing both “western medicine” as well as “traditional Chinese medicines”. Each of the manufacturing facilities were new for the most part (less than 5 years old). From discussions with the management teams, their future intentions were to manufacture API (active pharmaceutical ingredients) for the US (which required a Drug Master Record (DMF)) or to sell either the generic drug products (requiring an ANDA (abbreviated new drug applications)) or a propriety drug requiring an NDA (new drug application). Each company knew that these types of drug applications would require that they would have a pre-approval inspection (PAI) by the FDA to determine if their cGMPs were in place.

The fear factor of dealing with an FDA inspection and the possibility of failing an FDA inspection was causing these companies to push their business plan further and further back making their success to launching a finished dosage form in the USA a moving target with the chances for success becoming more and more difficult to accomplish in a reasonable time frame.

While visiting these new facilities, we were impressed with the architecture and the detailing in their planning to make sure that they would be able to pass the FDA GMP in the future. But, in each case there always seemed to be questions related to the simple concepts of GMP compliance. This led us to think that their basic understanding of the US GMPs and how to implement them is still a long way off.

We took a short walk down some very clean corridors of the production facilities and they asked us our opinion of their operations and whether they could pass an FDA inspection. We were not given any opportunity to review any documents or procedures. Basically, it was as if they were asking us to tell them how a beautifully presented dish of Chinese food would taste by just looking at it. In either case, we could guess as to what the results would be but that guess would

mean nothing without getting a change to make a true assessment of the procedures, process validations, and the necessary documentation or with the Chinese dish, taste it.

We were asked many questions that started with “Can’t we just.....” or “is this enough.....” or “do we have to validate this machine and process if we already”.

We responded to these inquiries the only way we could with the limited information at our possession, “it appears that you are moving in the right direction and if you do that should meet the FDA requirements”.

First of all, each plant we visited was manufacturing different types of products making the compliance issues specific to that operation. Each product and process had critical parameters that were specific to that operation thus requiring different levels of scrutiny.

As we have stated, there is no “silver bullet” for achieving FDA cGMP compliance, whether you are a Chinese, Taiwanese, Pakistani or for that matter a US company. For each of these companies as well as the Chinese pharmaceutical industry as a whole, there is path to compliance that should be followed that could bring them to a successful conclusion of achieving their goal.

Here a few of the steps to move your operations towards GMP compliance:

1. Each company should set up a team that would be responsible for this project.
2. This team should be trained in the FDA cGMPs as well as have an understanding of the FDA policies related to their operations and products.
3. A project timeline should be agreed upon for achieving these goals.
4. An evaluation of the processes and products that the company would like to export to the USA and whether they want API and/or the finish dosage form approved for export.
5. Most companies should start with manufacturing and exporting APIs and then move to the finish dosage form.
6. A flow chart of the operations should be made defining the critical operations.
7. A gap analysis should be made to determine how far the company is from achieving FDA cGMP compliance by someone who has a thorough understanding of the FDA cGMP issues and what would be required to pass an FDA on-site inspection.

8. A list of the corrective actions required to bring the company into compliance should be prepared defining:
 - a. Who will be responsible for making the corrective action and implementing it
 - b. When it should be completed
 - c. The date completed
 - d. The date verified
9. Weekly meetings should be held to monitor the process and determine delays and rectify unexpected issues.
10. If process validations are required have a validation expert assist in preparing the validation protocols and monitoring the validation process.
11. Upon completion of the process and implementation of GMPs, have an outside audit conducted by someone with extensive and up-to-date FDA experience, to determine your compliance to the cGMP.
12. Stay prepared for your upcoming FDA, pre-award audit.
13. Have a GMP expert, who is familiar with your system on site during the FDA inspection to assist with monitoring the audit and provide guidance and assist with responses to the FDA.

In reviewing the Chinese pharmaceutical GMPs, they are very similar to the US FDA GMPs. The Chinese government understands the importance of pharmaceutical companies implementing a quality system and following defined procedures. They even put a time table for Chinese companies to achieve compliance to their GMPs or they would not be allowed to maintain their domestic registration. We were told that many of the Chinese pharmaceutical companies were in fact closed down as a result of lack of compliance.

That said, the Chinese government is new to this, whereas the US FDA has over 40 years of experience enforcing and implementing the regulations. The “c” in the cGMPs stands for current and allows the US FDA to adjust their policies on how they will interpret the GMPs as they learn and become aware of changes in the industry that could affect the processes and products. This ability for the FDA to make policy changes is very confusing to the US industry. For foreign

companies to be abreast of what is happening, would be particularly challenging, especially with the language differences.

The type of products that a company wants to export to the USA, would determine the time required to achieve cGMP compliance. The time for an API could be substantially less than for a sterile injectable, while a solid dosage form could take sometime in-between both of these.

We estimate, from our experience with working with similar situations that the time required to get your system into compliance would be anywhere between 6 and 12 months for an API and/or a solid dosage form product, while a sterile liquid could take up to 6 months longer. Of course these times are based on what the company's system was already like, what processes required to be validated and the company's commitment to this process and addressing all the issues in a timely manner.

With the quality of the people we have been involved in at the various pharmaceutical establishments this is not an insurmountable task. There is no "silver-bullet" to achieving FDA cGMP compliance, but there is a road map that if followed will lead to successful conclusion.

About the author: Alan Schwartz, Executive VP, mdi Consultants, Inc., Great Neck, NY, was formerly a US FDA Supervisor of Field Operations. Since 1978, Mr. Schwartz has been providing consulting services to the healthcare industries worldwide. He has been an invited speaker to many foreign industry associations on FDA compliance matters. He has had numerous articles published on Dealing with the USFDA and has been recognized as an expert by the US FDA. mdi has been the official consulting company on FDA matters to CCPIT/CCUS for over 5 years.