

## Good Manufacturing Practices Should Not Be “Skin Deep”

Quality control in manufacturing, and the lack thereof, is being written about more and more, and is becoming increasingly more obfuscated.

On February 5, 2008, an Associated Press wire story highlighted “the lack thereof” in pharmaceutical quality control, revealing the incidence of blue flecks that were found dotting the finished drug capsules Diltiazem, that matched the paint on the factory doors of a Biovail pharmaceutical plant. The plant began placing covers over the carts of capsules in its manufacturing areas, but inexplicably never tried to find out whether past shipments of the drug were contaminated – or prevent contamination in the future, according to the FDA.

Teva Pharmaceutical Industries exported its drug products from Israel to the United States even though they were known to contain small amounts of metal particles. Teva’s quality control unit said the presence of small amounts of metallic material was to be expected because the manufacturing equipment is made of metal, according to the FDA report quoted in the AP wire story. A Teva spokeswoman insisted the medicine from the now-closed plant was safe and effective, despite the contamination.

The AP wire story also disclosed that GlaxoSmithKline PLC had produced tablets of the popular antidepressant Paxil CR that split apart, potentially causing patients to take an incorrect dosage. When the company would not recall the affected pills, U.S. marshals raided the plant in March 2005, in the largest drug seizure in FDA history and also collected tablets of the diabetes treatment Avandamet, after some tablets were found to contain inaccurate doses of the active ingredient.

These are problems in the highly regulated pharmaceutical industry, in companies that are regularly inspected by trained FDA inspectors. Yet the AP wire story very clearly demonstrates that even a highly regulated industry can still have numerous quality control problems once the inspector walks out the door.

I have written before on quality control problems in the dietary supplement industry and it seems I have started a popular trend. Two naturopathic-based journals have, with good intention, allowed authorship on the subject of quality control by the owner of a small dietary supplement company. Now one journal’s editor-in-chief has written an editorial on quality control that recounts his tour of Manufacturers A and B and outlines what he considers to be highlights of the superior quality of Manufacturer B.



This highly respected doctor, medical writer, and editor, has, with incredibly good intention, volunteered to visit other manufacturers and report on those he believes meet the standards clinicians can trust.

A person without experience in quality control Good Manufacturing Practices (GMP's) and Standard Operating Procedures (SOP's) should not evaluate a facility and pass judgment. Especially with a three- or four-hour visit when it takes at least three days for a qualified government inspector to properly inspect and audit a manufacturing facility.

As I will demonstrate, the same problem exists when the inexperienced "evaluate" companies based on questionnaires such as the one this editor directs people to on his website. The owner of the small dietary supplement company mentioned above developed this questionnaire.

The questionnaire was sent to the owner of that same dietary supplement company by a doctor to determine how the "expert" on quality control would respond when asked the same questions he wants other companies to be asked. The response to the doctor's inquiry took almost two months to receive. The doctor, having no experience in evaluating quality control procedures, thought the paperwork looked impressive. When I saw it I was less impressed.

Here is a partial list of what I found:

The owner of the company (and author of the questionnaire) lists himself as CEO as well as the director of Quality Assurance (QA). In one article he authored, he also lists himself as the director of Quality Control (QC). If he were complying with any qualified GMP, he could not possibly hold these multiple roles. QC and QA cannot be the same person and must be independent of management.

In providing data for "stability" testing on one of its product, the laboratory that performed the testing at 12- and 24-month intervals for activity is different than the laboratory that performed the initial testing. His SOP calls for storage of the product to avoid "excessive heat, moisture, and/or light," yet there is no mention of validation of the levels of heat, moisture, or light. This may be accomplished by using a validated climate-controlled storage cabinet for accurate stability. If you have an in-house laboratory you have control of this. If it is an independent laboratory, they may retain and control the sample, but you should not change laboratories in mid-stream.

His "stability" program requires no finished product testing if the product is encapsulated within 90 days of raw material assay, with testing then at 12 and 24 months. But if you have no finished product "baseline," you don't have a starting point for stability testing. That's very improper GMP.



The same product was accompanied by bacterial analysis that contained the most glaring errors. The report of testing for *E. coli*, *Salmonella*, *Staph. aureus*, and *Pseudomonas* all showed “less than 10 CFU/gram” on 6/18/02 and 6/24/03. The correct reporting should be “Absent.” If any of these bacteria are present, even at less than 10 CFU, you have a problem. It took two years for the laboratory to realize their mistake and start properly reporting the levels; nevertheless, the paperwork was reviewed by the company owner and signed off by him.

One of the facility’s receiving forms shows receipt of 32 drums of a raw material; however, only one sample was taken and sent for analysis. What are the contents of the other 31 drums? Proper GMP requires sampling and analysis of all 32 drums until such time as the vendor has been validated, after which you still must sample and analyze the square root of the number received, round up, and add one. In this case, seven drums should have been randomly sampled and analyzed if this were a validated vendor – if not, all 32 drums should have been sampled and analyzed.

Virtually all of the “quality control” writing by this author/company owner excoriates anyone who doesn’t test for solvents, etc. Therefore, I was surprised to find an analysis of his Green Tea Extract in his paperwork, which showed 168 ppm of acetone; yet his company approved the product for use.

In reviewing the “Equipment Use/Cleaning and Maintenance Log” provided for the capsule polisher, it shows start date of use and time, with no finish time of “use,” just a “finish” time. So it does not show the actual time used differentiated from the actual start and finish of equipment cleaning. No a.m. and no p.m. are listed.

The log shows a “3:00” start time on 3/28/06 for a product “*Acidophilus*,” with a finish time of “12:30 3/29/06,” with a “type 1” cleaning checked off as being performed by TJB. But there is no time recorded that it took to clean the machine. The machine is then entered into service at “12:40” of that same day, apparently 10 minutes later, to run product “Oximax.” A government inspector would not know whether 10 minutes or two hours or more were used to clean the machine of *acidophilus*, an organic organism. Yet another major GMP flaw.

There are 17 line items on the cleaning log, each with potential problems. On some lines the cleaning of TJB is “checked” by RM, on other lines the cleaning of RM is “checked” by TJB. In a proper GMP environment, the QA department, which does not do cleaning, actually “inspects” in-process cleaning, as well as the finished cleaning, at which point the machine is properly tagged and the appropriate log paperwork is generated. Not a 10-minute process – and another major GMP flaw.



I have continually stressed that Quality Control is not just manufacturing; it begins with raw material choice. This company provided a certificate of analysis that was provided by their raw material supplier of vitamin D. It shows a range of 100,000-110,000 IU per gram of vitamin D activity and was independently analyzed as having 103,000 IU of vitamin D per gram. The problem here is that pure vitamin D starts out at about 40,000,000 IU per gram. So, is the commercial preparation used by this company the lactose-diluted one that contains BHT, BHA, sorbic acid, and sodium benzoate – the same vitamin D preparation that is used by many other companies? His company has not responded to the follow-up inquiry from the doctor who submitted the initial inquiry.

This company has actually promulgated a letter dated April 25, 2006, stating that in the “last month, the following raw materials failed potency testing.” They then list products that were found to be sub-potent by up to 36 percent. They then stress that they, “(at our cost) ADDED SUFFICIENT MANUFACTURING OVERAGES to ensure that the products that contained these raw materials met the specified label claim.”

If a product analyzes at 64 percent of the manufacturer’s claim, why are they not questioning what the remaining 36 percent is? What is wrong with this picture? If an ingredient received is sub-potent by more than standard laboratory deviation in testing methods (a few percent, at most), or by a slight, but acceptable amount of moisture, the material is rejected, not just supplemented with “overage.”

So, here we are. This is from a simple one-hour review of documents carefully selected and sent out by this company in response to a questionnaire they themselves developed. You, the practitioner, can easily see how many GMP issues I have raised. The recipient of this data, the inquiring doctor, does not have the experience to see the glaring GMP errors present. GMP’s are not superficial documents. This is why the FDA needs to be the inspectors, not a well-intentioned person whose only knowledge of GMP’s and manufacturing may come from a source that, in my opinion, lacks true GMP’s, SOP’s, and independent QA.

As outlined above, it is not just the dietary supplement industry that has quality control issues; it is also the pharmaceutical industry. People in the dietary supplement industry need to quit using smoke and mirrors, invest the money, and do the job right.

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