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Compliance in Quality and Validation - CQV #4: Animal Tales

By Michael H. Anisfeld Nov 20, 2018 8:43 am PST

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CQV – Compliance in Quality and Validation – presents real-life stories reflecting compliance problems in the pharmaceutical, medical device, and related industries. Previous discussions have included:

CQV #1: Overview and Invitation to Participate. JGXP V 22, #5.

CQV #2: Like-for-Like Problems. JVT V 24, #3.

CQV #3: More Like-for-Like Problems. JVT V 24, #5.

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Editor's Note:

The following "Animal Tales" by Michael H. Anisfeld was previously published in JVT. This paper is one of the most requested papers ever published in JVT. It truly exemplifies "Do we really know what's going on?" in our sites or in the sites of our contractors. It is reprinted here in CQV #4 with permission of the author.

INTRODUCTION

I was recently performing a mock-FDA inspection on behalf of a client and it hit me again -- another instance of animals coming into the inspection. So bear with me as I explain some animal tales, and I am not talking veterinary GMPs. And, I assure you that no single incident related here is from my imagination (I could not invent this stuff), nor is it exaggerated in anyway. What you will read is what happened -- exactly as it happened.

Reflecting over many years of performing GMP audits worldwide there have been many occasions that animal issues in pharmaceutical or in active pharmaceutical ingredient (API) manufacturing facilities have taught me lessons.

LESSON 1: ISO 9000 IS NOT GMP

I was auditing a French API manufacturer and was standing in the 2nd floor conference room waiting for some equipment qualification files to be delivered. Looking out of the window and admiring the skyline I happened to look down into the company yard below where open reaction tanks were staged, each of which bore a green colored label stating "Propre" -- French for "clean". As I looked it started to rain and I wondered how they could claim the tanks were clean when they had been exposed to the elements and the rain. Perhaps, I said to myself, it rains Perrier in France.

Later in the day I was walking past the tanks, still labeled "Propre" and decided to look inside to see how clean they still were. I stood on tippy toes and looked inside to see the rain streaks but also to see a cat asleep under one of the tank's baffles. I advised the QA Director of the presence of the cat. He looked inside and exclaimed "Ah Charlotte, that's where you have been hiding." When I advised that GMPs do not allow animals on the premises let alone in the equipment, he expressed surprise and then stated that this was allowed in the company's ISO 9000 Quality Manual as their method of dealing with rats. He insisted on showing me the manual, and on the way to the office advised "Funny you should have picked up on this as our ISO inspection was last month, and they also commented on Charlotte". At last I thought sanity prevails. "What did the ISO inspector say?" I asked. "Oh, he cited us for not keeping our manual up-to-date. Our manual stated that we had two cats, Charlotte and Francois, but Francois had died and we had not updated our manual" he answered.

Time did not allow me the chance to evaluate how they qualified Charlotte especially in a worst case study –if she saw the rat immediately after having a large meal, would she run after it? The lesson learned: Compliance to ISO 9000 does not mean compliance to GMPs. In fact, in my experience, the larger and more loudly a company proclaim and advertise that it is certified to ISO 9000, the poorer their GMP compliance profile.

LESSON 2: BE CAREFUL WHAT YOU SAY AND HOW YOU SAY IT

Many clients do not want to pay consultants for several days of audit as they believe a good auditor can provide a comprehensive assessment in just one or two days. When I face these time constraints I typically start by getting a feel for the facility by "following the flow" – start in the raw materials warehouse, and then moving on to dispensing, production, etc.

About three years ago working for a pharma company in the tropics, I followed the flow, and started in the warehouse. Disconcerting to say the least, especially for someone scarred of animals, was the mongoose running around the released raw materials area. When asked why the mongoose was in the facility, I was advised that its job was to catch the snakes. I then said that "GMPs do not allow animals to run around the facility", implying they should get rid of the mongoose.

Two years later I was invited back. This time when in the warehouse I found not one mongoose but three, each locked into its own cage and the cages distributed about the warehouse. I asked why the mongoose and got the same answer. OK, I understood that, but how I wondered can a mongoose be effective when they are in a cage? The answer I got was that a mongoose projects an aura that the snakes can detect, and they thus stay away. This time I asked how they qualified this assertion, and I was shown studies that a mongoose can project its aura for about 10 metres around itself (I still do not know how a snake senses a mongoose, but the study seemed to show that they do). Using this qualification data they had mapped the warehouse, and determined the optimum position for the placing the three mongooses in their cages.

The lesson learned, be very specifically precise when providing audit feedback. Rather than stating "GMPS do not allow animals to run around ….", I should have stated that "GMPs do not permit animals to be on the premises."

LESSON 3: THERE'S ALWAYS A HIDDEN AGENDA

Auditing a pharmaceutical company in a central European country and short of audit time, I again followed the flow. This time there were birds flying about the warehouse, and at no extra charge leaving gifts deposited on drum tops. In my mind my mental root cause analysis went: Birds are flying because of holes on the wall/ceiling junction where they enter to nest; block the holes and eliminate the problem. When I asked the warehouse manager why they had not done this, he related that this caused a problem with the forced air circulation system. According to him, placing the mesh screen caused temperature fluctuations and control problems. He then advised that the company had a different approach to tackling the problem, and one that he felt was innovative and cost effective. The warehouse supervisor showed me the pest control SOP describing how they did it. The SOP stated that every Saturday morning the local cross-bow club would come on-site, and shoot down the birds. Additionally they needed to employ a staff member to daily clean the drum tops, and he extolled the concept of the dignity of labor and claimed this was a way to provide a salary to a worker in a region of extremely high unemployment. He then said that as an extra bonus the cross-bow club provided their services at no charge, as they regarded the dimensions of the warehouse a very good indoor shooting range.

It was not until I mentioned this to senior management at the exit interview it emerged that the warehouse supervisor was the founder, and president of the local cross-bow shooting club. About a month after my audit I heard that when he was advised that his Saturday morning club activities had to find a new home, he resigned. I also heard that quite astonishingly, when they then blocked the holes with mesh, there was absolutely no impact on the temperature distributions in the warehouse. Lesson learned: There is always a hidden agenda.

LESSON 4: MINDLESS ROTE GMP COMPLIANCE

I audited an API facility that jet milled the corticosteroid API to ensure that the API's particle size met very narrow particle size limits (3? - 7?). To enter the jet milling area I had to change from street clothes to plant uniform through a change room with a differential pressure of 40 Pascal to the outside world. Then walk down a corridor and take off the plant uniform, take a total wet body shower, and change into a different plant uniform. Then along another corridor for a third gowning change followed by an air shower, to finally enter the jet milling room. Three clothing changes and four airlocks, each following a pressure cascade – to finally enter the Class 100 classified jet milling room with stainless steel walls and ceilings. I personally thought this was gross overkill, but who am I to criticize someone for doing more than they need.

And there on the wall, drilled into the stainless steel was a flying insect death trap (those blue lights thingies that sit behind an electrified fence). The logic defied me. Faced with what I had to go through to get to the holy grail – the jet mill room – and considering that the room's single pass 99.997% terminal HEPA filter was leak tested every six months, how I wondered could a flying insect get into the jet mill room. I asked if in the six years of operation they had ever found a flying insect. "No" they responded, "they never had". Lesson learned: Frequently people just do not think through the rationale for their actions – the company had always traditionally had flying insect death traps in the production area. Surely a case for benefiting from risk assessment if ever there was one.

LESSON 5: THERE ARE MANY WAYS TO TACKLE A PROBLEM

I audited a medical device facility where in the clean room they assembled complex electronic products for later implantation into patients. I was introduced to Jim, their "best assembler", who had been born blind. As I leaned over the assembly table to see the complexity of Jim's task (and it was complex -- and a tribute to Jim's skills that he handled it so dexterously), my leg brushed against something soft under the table. Looking down I saw a guide dog quietly sitting at Jim's feet. Connie, the dog, was a beauty with a lustrous soft auburn coat; which all the clean room workers would routinely pat as they passed Jim's desk. I was assured that the dog was of the "non-shedding" variety.

I flippantly mentioned to the QA Director that if he wanted to allow the guide dog into the clean room he would need to find suitable clean room gowning for the dog; assuming he would get my message. A few weeks later I got a phone call asking for advice – the company had spent a lot of effort trying to find canine clean room gowns but to no avail – what should they do? Here was a case where GMP regulations said one thing, but regulations on employing the handicapped said exactly the opposite. We spoke to FDA who were adamant that a dog had no place in a clean room; we spoke to the State's Labor Department who were equally adamant that accommodations had to be made for handicapped workers. So absent the availability of sterile canine clean room gowns; and the intransigence of two state agencies, we got creative and found a solution. We built a carpeted air conditioned (and 99.95% HEPA filtered) kennel outside, but adjacent to, the assembly building where the dog could comfortably rest all day (of course this was built in full accord with the prevailing Humane Society guidelines); and installed guide rails along the walls for Jim such that he could easily gain access to the clean room. Lessons learned: If you get creative, great things can happen, and everyone remains happy; well almost everybody – Jim's clean room co-workers complained that they missed patting Connie every day.

LESSON 6: A LITTLE KNOWLEDGE IS A DANGEROUS THING – ESPECIALLY IN THE HUMAN ANIMAL!

The pharmaceutical professional body of a third world country wanted to upgrade the GMP compliance knowledge and profile of the local industry, and together with the Ministry of Health, organized a "GMP Week" where they invited me to lecture for 5 days on GMP topics. Most of the audience was very senior management from the local industry: CEOs, MDs, Presidents, and a sprinkling of owners.

The training went well with lots of good questions, especially as I stressed the cost of GMP implementation and the financial impact to the company of not following GMPs. (I have found that you can never sell GMPs just by quoting the regulations; company managers and owners only speak the language of money, and this is how you need to make the GMP compliance sales pitch). After the 3rd day, one of the company owners present, who had been asking lots of questions and making lots of notes came to me and said "I believe that even though we are a 3rd world country, my company is a world class company in the manufacture of sterile injectables – I would be honored if I could show you my company". I always like to see world class companies and we agreed to a tour after I finished the next day's lectures.

Looking through the window into the aseptic sterile fill room of the "world class company", two things immediately caught my attention. First, the five male workers in the room were, with the exception of a mask covering their mouth and nose, stark naked with not a stitch of clothing anywhere from their entirely shaved heads to their toes. My jaw must have visibly dropped, as the owner said "You see. I told you we are cutting edge". I asked how he had determined this innovation, to which he responded – "we are members of the American PDA and a recent publication stated that sterile gowning for clean room use sheds particles, so we thought about it and decided to eliminate the gowns". When I pointed out that gowning sheds several log levels of particles less than bare skin, he retorted "our SOPs require all our staff to take a shower prior to entering the room, and to put oil over their entire skin surface – thus preventing skin particles from being released." Lesson learned: Innovation can be found when you least expect it – especially when I later checked his claim with several PDA members, experts on the topic, who all agreed that the approach would be very effective in eliminating non-viable particle shedding. Second lesson learned: NIH syndrome (not invented here) – I have yet to convince anybody in any American or European company to even consider

this innovative approach. Very strange!

I also noticed that there were no terminal HEPA filters in the ceiling, and asked about this. The response was “we are an ecologically minded company dedicated to using local resources”. “Look at our laminar flow system” he said and pointed at a small 10 inch diameter fan (a Ventaxia type device) in the wall at one end of the room, and another in the opposite wall. Laminar flow was being achieved by having one fan suck air into the room, and the other pulling the air out of the room. I asked “How do you filter the air”, to which we went outside and he showed me the densely packed straw mat that acted as a filter. I was intrigued; this could put the world’s HEPA filter makers out of business. When I asked for the room qualification data to demonstrate that the room was class 100 as they claimed; there wasn’t any data – they were not aware of the concept of HVAC qualification. When I asked how successful they were in the media fills they performed, turns out that they did not do any either. Lessons learned: A little knowledge is a dangerous thing, especially when it comes to the human animal.

FINAL THOUGHTS

I have been a GMP auditor for about 27 years, and I find that I learn something new, and often challenging, every day. I guess when the day comes that I do not, it will be time to pack it in and retire to a beach somewhere. I hope this review has been educational.

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