

Compliance Newsletter

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General Comments

Warning Letters to big names in healthcare are always of interest, and in this issue we have WLs to Sandoz, GE Healthcare, and Ranbaxy Laboratories for insight into the compliance world. One would expect that big firms more or less define what current GMP is. These letters show another reality.

For those new to the newsletter, it is built from hyperlinks. You can view the linked documents when you are on-line.

Compliance Problems at Sandoz

In August, [Sandoz's tableting operations in New Jersey](#) got caught for controlling their processes the old fashioned way, (by hand and on the fly). Pharma is well-known for processes which are difficult to control, or just plain poorly understood. (See the past July issue). Production of Metoprolol looks like another good example. The settings of the tablet press for each batch must be determined after a complicated analysis of pre-compression samples, and sometimes the batch still goes OOS (Out-of-Specification).

Sandoz apparently tried to conceal the process variability by not setting targets and even excluding the IPC testing from the batch records. OOS results for dissolution of the tablets however brought the variability of the process to the visibility of the inspectors.

A number of other compliance problems emerged during the course of the inspection:

- Excluding failing validation lots from the process validation studies;
- Accepting a process as non-validated and reliance upon only QC release testing;
- Quality Control is not following up on investigations of nonconformances;
- Master Production Records are not being maintained;
- Noncompliance of QC Lab computers to Part 11.

If this was India, Sandoz's products would be banned, (see Ranbaxy below).

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Regarding the lab computers, we see the situation where all users have common administrative privileges, including editing and deleting raw data, coupled with the absence of an audit trail, (wild west scenario).

The FDA also hammered Sandoz with the expectation for a “global approach to the implementation of manufacturing controls”. They don’t have it yet, but Trackwise® is being used at other sites. The FDA will be following up on the global implementation, (and integration) of this system. Since Sandoz is now part of the Novartis concern, I hope somebody has forwarded this expectation to headquarters in Basel.

Compliance Problems at GE Healthcare

WLs are not new to GE Healthcare either. [GE Healthcare Integrated IT Solutions](#) supplies software, which is regulated as medical devices. The problems at GE overlap considerably with those reported in the June issue for Philips Medical Systems. These firms have extensive databases for defects, complaints, etc., and they are not managing them well. The FDA starts with CAPA records and finds abundant compliance problems, such as:

- Lack of global management of CAPA, (particularly when software is common to multiple products);
- Specifications are not updated with new requirements before implementation;
- Release notes are incorrect regarding the status of defects;
- Product releases are not documented with final inspections;
- Complaints are not investigated adequately (or at all).

Besides these GMP problems, GE is lax with reporting to the FDA. Medical Device Reports (for malfunctions and/or injuries), as well as Corrections and Removals Reports, (for recalls, patches, etc.) are either not being submitted, or are submitted too late. With software it is easy, to fix a bug and distribute a “hot fix”. But this software is considered a medical device, and such actions require informing the FDA with at least a Corrections and Removals Report. When a number of these accumulate, you can expect the FDA to be knocking at your door.

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Apparently, GE will acquire expertise in conducting retrospective reviews, since a number of retrospective reviews have been promised. There are sure to be gaps or cover-ups, and the FDA will use them for its next round of investigations. The lesson to be learned here, is that medical device software cannot be managed like typical software via frequent software upgrades and fixes.

Compliance Problems at Ranbaxy Laboratories

Ranbaxy first ran into trouble with the FDA in 2006, with poor record keeping of stability testing, leading to a rejection of their expiration dating. Now 2 more WLs have been issued. For a foreign manufacturer, an import ban is usually a consequence of such noncompliance. [The Washington Post](#) published that 28 products have been banned. Because of the size and importance of Ranbaxy to India, other government agencies on both sides have been activated.

There are too many issues in these WLs to cover in this newsletter, and they apply more to operations which are manual and documented by hand. Most of our clients have automated, closed processes which reduce the potential for human errors and/or subsequent data manipulation.

Notable, in the [WL directed to the Paonta Sahib site](#), is the reliance upon the manual security logs for checking whether an employee was present during the time of his signature on a record. Although this operation cannot be considered completely reliable, the FDA doubted many signatures because the person was not registered as present at the time. Because of the weight of evidence, Ranbaxy acknowledged that some employees do not believe that they have to be physically present during an activity for verification. Backdating of signatures is implicit in this admittance. This might not be so serious for checking a document, but not for checking a manual activity such as cleaning.

Even worse perhaps are the [observations at the Dewas site](#), which show that production records do not always identify the persons performing or have the appropriate verifications from a second person.

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Finally, the FDA practically says that many of the manual operations are not cGMP in that, "it is not appropriate to try to overcome major flaws in clean room design and equipment by attempting to validate difficult to perform, intensive manual procedures... Furthermore, design concepts and use of contemporary equipment and automation technologies should be explored and assessed for suitability to prevent unnecessary activities.." These comments are in reference to aseptic operations. Pharma was able to implement on a large scale aseptic operations as well as multi-product plants via modern, automated, and closed operations. Ranbaxy is being told to do the same.

Although the compliance case against Ranbaxy is pretty convincing, the press version of the action is less so. Ranbaxy is one of the 10 biggest producers of generic drugs in the world, and the working people in the US need cheap drugs. Ranbaxy is not admitting any guilt, and the Indian Commerce department is treating this as a trade dispute.

Are you as unsure as I am about what is current GMP?

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If you have any further questions or comments, please don't hesitate to contact me directly via phone or email!