



COMPLIANCE NEWSLETTER

10/2016

## Compliance enforcement trends for the health care industry

### ISPE GAMP Data Integrity Europe Conference

During the two-day conference in Copenhagen earlier this month participants from GMP / GLP / GCP businesses, consultancies, health authorities and universities discussed several aspects of the hot topic 'Data Integrity'. There was common agreement in seeing Data Integrity as a change of focus within the pharmaceutical quality management, rather than as a new topic. During the opening talk by D. Churchward (Expert GMP Inspector, MHRA) it was pointed out that emphasis should not only be put on IT systems but should first of all be put on the process and the holistic understanding of the data life cycle. Later talks focused on the investigation of Data Integrity incidents, issues with outsourcing, Data Integrity in Clinical Trials and many more.

On the technical side, quick-wins for the improvement of Data Integrity have been identified – among others these are proper implementation of access controls for computerized systems and implementation of a process for the review of audit trails. When assessing data integrity within processes it is strongly recommended to take the whole data life cycle and product life cycle as well as the whole supply chain (from vendor to patient) into consideration.

### Automated Logins under Windows

Recently, in the ISPE GAMP community a lively thread was started regarding this subject. Harmlessly, it started with the question as to whether a second login for the GxP application is required when already logged in under a Windows account. There was no consensus here because it all depends upon the configuration and environment of the GxP application. The goal of course, is to ensure that access is appropriately restricted, and users are registered so that their actions can be recorded.

The thread quickly moved to a common theme in Warning Letters: "A standalone HPLC is connected to a PC with LAN connection. Logon is only to access the PC..." This infers that the HPLC software is not configured to manage user accounts, and at best could only record the User ID but not restrict his privileges. WLs typically fault group accounts in this scenario, which prevents even identifying the user. System owners should assess their computerized systems whether they are supporting user rights management or not. Restricting the execution of a GxP application by use of the operating systems access control is more an additional safety measure rather than a justified data security measure on application level. Ensuring access to GxP applications solely through the windows logon is not sufficient as long as the access levels of the windows user are not passed through to the GxP application, to ensure appropriate access to GxP data and support of a compliant audit trail.

## New EU Regulation for Personal Data

There is a flurry of interest in this [new EU regulation](#) which will force firms soon to allow people, employees, etc. to control their personal data. This extensive regulation (11 chapters) mandates a huge administrative effort for both regulators and processors of personal data. Its arm will extend beyond the EU, just like California's emission standards raised the bar globally for automobiles.

The protected rights of persons over their data are listed as: Right of access; Right to rectification; Right to erasure; Right to restriction of processing; Right to data portability; Right to object (stops processing); and Automated individual decision-making, including profiling (prohibited). There is an entire section devoted to security of personal data. Most firms will need to look at their use of HR systems to check on compliance, and it is anticipated that checking and modifying such systems will be a considerable burden, or opportunity, (depending upon one's perspective). The deadline for compliance is May 2018. The fines for noncompliance are limited to 20,000,000 € or "up to 4 % of the total worldwide annual turnover of the preceding financial year, whichever is higher".

## Warning Letters of Interest

PADE (Post-marketing Adverse Drug Experience) reporting is the subject of the WL issued to [Elite Laboratories](#). PADEs are specified in regulation 21CFR314.80 for holders of drug licenses, and is an important tool for identifying problems with drugs, once they have gone on the market. The 15-day "Alert Report" must be submitted within 15 days of receiving

knowledge of "each adverse drug experience that is both serious and unexpected, whether foreign or domestic". Elite's SOPs for handling complaints and other information from which to recognize a PADE were clearly inadequate, resulting in failing to report and investigate at least half of the 15-day cases, which the FDA found. Although the regulation is directed to the license holder, such reporting is also required for, "any person other than the applicant whose name appears on the label of an approved drug product as a manufacturer, packer, or distributor (non-applicant)".

Interestingly, FDA has the authority under subpart k) of the regulation to simply revoke the drug license, when this program is deficient, such that the firm may no longer legally market the drug. The WL basically provides the justification for such an action.

Poor investigating is also a deficiency in the WL to Chinese API manufacturer, [Cheng Fong Chemical](#). Complaints of foreign particles in product must be followed with investigations of the affected batch and any related batches. The identity of foreign particles must be determined, and preventive actions to reduce contamination are expected.

At another Chinese manufacturer, [Hebei Yuxing Bio-Engineering](#), root cause analyses of microbial contamination were faulted in the WL. The WL documents that, "microbiological contamination has been a persistent and unresolved problem at your firm since 2013". Although the firm identified potential causes, it did not determine the actual root cause(s), and thereby did not undertake effective corrective or preventive actions.

To address the ubiquitous data integrity problems uncovered, the FDA specified the following measures:

- “A detailed investigation protocol and methodology... and a justification for any part of your operation that you propose to exclude;
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.;
- An assessment of the extent of data integrity deficiencies at your facility...;
- A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses. ;
- A current risk assessment of the potential effects of the observed failures on the quality of your drugs...;
- A management strategy for your firm that includes the details of your global corrective action and preventive action plan....”

The WL to Indian drug manufacturer, [Pan Drugs Limited](#), documents another sighting of lizards in a controlled area. They also have a data integrity problem: “For example, the computer in your quality unit area did not have controls to restrict access and prevent unauthorized changes to data files and folders. All employees had access to your Annual Product Review (APR) spreadsheet. The desktop computer containing the APR was not locked.”

The FDA's recommendation is (repeatedly mentioned in both WLs) to use services of a qualified consultant to resolve data integrity issues that have been uncovered by the inspectors: “We strongly recommend that you retain a qualified consultant to assist in your remediation.”