Regulatory Compliance Considerations When Outsourcing Information Technology (IT) Operations in the Pharmaceutical Industry

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Abstract

Outsourcing is one way that some pharmaceutical companies have approached containing or reducing their overall IT costs. However, if outsourcing is considered solely from a financial perspective this will lead to regulatory headaches as at least one pharmaceutical company has found out. When selecting and setting up an outsourcing contract, the service level agreement (SLA) must include the mandatory requirement that the service provider will meet the applicable GXP predicate rules and 21 CFR 11 requirements. Does the outsourcing organization have the understanding to meet this requirement?

Introduction

Information Technology (IT) is essential to the operations of all pharmaceutical companies; it can be used for basic operations as well as to reshape and facilitate change. However, in this paper I want to focus on the force that can reshape the Information Technology in many pharmaceutical companies: finance.

The main driver for IT outsourcing is to reduce the overall cost, especially as this is not seen as a core operation for many pharmaceutical organizations. The view of many senior managers is that IT is expensive and does not work. However, let us explore the rationale for outsourcing in general industry; here, labor costs are approximately 70% of total overhead. In contrast, labor costs in pharmaceutical companies average 50% as the infrastructure and compliance costs are higher than in general industry. On the face of it, there may be scope for cost savings but not as much as in other industry sectors. Outsourcing IT operations has been occurring in several industries over the past decade and a number of major computer and outsourcing companies can be contacted to provide these services.

Outsourcing is defined as the transfer of management and operation of IT operations to a third party and the scope of this can include one or more of the following:

- All IT operations
- Operation of a data center and/or networks
- Operation of specific tasks, systems and/or business applications
- Application development

There are issues to consider when outsourcing the IT function such as:

- Regulatory compliance must be considered as part of the contract
- An outsourcing contract can be a hindrance when it binds a firm into an unhappy working relationship
- Outsourcing IT can remove key parts of the decision making process from a company
- Costs could exceed those of the original IT department before outsourcing

For the majority of multinational pharmaceutical companies the IT network, infrastructure and services are the essential mechanism to allow many sites, often located in different time zones and continents, to collaborate effectively. For example, in clinical research, an effective IT global network is the means to enable collation of clinical data and adverse events quickly and effectively. Therefore, data transfer and communications are the essence of faster research and development and hence faster time to market as well as coordinating global manufacturing.

When entrusting the IT operations to a third party, it is

essential that aims of lower operating costs are achieved but also the networks and infrastructure are operated in a compliant manner otherwise the regulatory implications will be huge. This paper will explore the issue of regulatory compliance when outsourcing the IT function.

Regulatory Compliance

The pharmaceutical industry has been subject to regulations for many years in the guise of the GXP regulations (GLP = Good Laboratory Practice, GMP = Good Manufacturing Practice and GCP = Good Clinical Practice). These regulations have focused on the respective business area and not on the IT Department; regulatory agency inspections have been carried out in these business areas and the way the business uses computer applications only. The IT Department has traditionally not been the focus of regu latory inspections.

This is now changing; the publication of 21 CFR 11 (Electronic Records and Electronic Signatures final rule) [1] has included the IT Department under the regulatory umbrella. The use of the word "system" network and infrastructure is covered by existing predicate rules (GMP, GLP and GCP) and where applicable 21 CFR 11. For some IT departments, this now means that they must comply with requirements of not only GMP but also GLP and GCP. If not already aware, this will come as a shock to some IT personnel and their management.

One way that an inspector can access the IT department is simply by asking during an inspection of the business how the electronic records of a specific computerized system are preserved as required by 21 CFR 11 [1]. If a system owner responds by saying it is the responsibility of the IT department, then the path is clear for an inspection of the IT department. As we shall see below, not all IT Departments have been ready for a regulatory inspection.

A key question occurs; are senior managers who decide if the IT function should be outsourced or not aware that the rules of the game have changed? If they are not, then major problems will await those companies that outsource this function without the checks and balances for regulatory compliance in place.

Outsourcing Responsibilities

First, any pharmaceutical company that outsources any function still retains responsibility for actions taken by any outsourcing company (this includes a contract research organization, raw materials supplier or primary manufacture of active ingredients). If the outsourcing company operates in a way that results in regulatory non-compliance, then the contracting pharmaceutical company will have a regulatory compliance issue as well.

There is no excuse blaming the outsourcing company, as it is the responsibility of the pharmaceutical company to find suitable business partners:

- FDA GMP regulations require that personnel have the appropriate combination of education, training and experience to perform their assigned tasks [2], plus there is a specific requirement that "training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them."
- European Union GMP Annex 11 [3] in clause 18 states: "When outside agencies are used to provide a computer service, there should be a formal agreement including a clear statement of the responsibilities of that outside agency (see Chapter 7)". Chapter 7 discusses extensively the roles of the contract giver and the contract acceptor.

Therefore, sufficient due diligence on behalf of the pharmaceutical company must be undertaken to ensure that the work carried out by the outsourcing company covers not only the technical ability to perform the desired job but also that any outsourcing company meets the appropriate regulatory compliance criteria.

With this background, how do IT departments and outsourcing companies in particular stand up in respect to regulatory compliance? Not particularly well as we can see now.

Audits of Outsourced IT Operations

To illustrate some of the regulatory compliance issues that can occur with outsourced IT, I have selected some observations from internal audits as well as the findings from the FDA during inspections of a major multinational pharmaceutical company.

Internal Audit Observations

Case Study 1: A multinational pharmaceutical company outsourced their IT infrastructure. The contract negotiations by the pharmaceutical company had included regulatory compliance into the contract and had conducted GXP training of the IT provider's staff before the release of the outsourced service. However, the outsourcing staff did not follow the written procedures and this led to observations during the internal audit such as basic GXP issues of having procedures and then following them:

- Engineering software applications:
  "…. the user acceptance testing did not follow a correct plan."

  "Errors found during the tests were not followed up and there was no judgement of the GMP impact of errors."

- Change control and configuration management:
  "Change management is out of control and the change procedure is not followed. There is missing documentation for more than 50% (= 43) of all the change requests and the configuration baseline has not been updated."

  "The users are not informed about bug fixes that may affect their validated systems."

- Definition of roles and existence of training records:

"The roles of the personnel involved in the operation do not match with the organization chart of the qualification plan. There is no explanation of the differences."
"There are no training records nor CVs / resumes of the outsourcing IT personnel."

Pharmacia Warning Letters and 483 Observations

The FDA found similar observations during audits of two Pharmacia manufacturing sites during the summer of 2000 that led to the issuance of two warning letters in January 2001 [4,5].

Both of the warning letters outlined some computerized system deficiencies such as:

- Document control:
  Significant deficiencies regarding documentation controls were reported. Documents were either not dated, missing, lacked a document control number, were reported in pencil on uncontrolled pages, or dates were crossed out with no initials, dates, or explanation.
- Wide Area Network (WAN) documentation:
  …..documentation (of the WAN) was not included in the validation of the [deleted] and [deleted] application and therefore documentation controls were incomplete.

However, the problem of any warning letter is that it is the Agency's viewpoint and the inspector's perspective presented on the form 483 inspectional observations which can be omitted or edited. From the regulatory compliance debate on outsourcing perspective, the most interesting IT related observations are found in the 483.

- Local Area Network:
  "Local Area Network diagrams (LAN) with appropriate definition documentation identifying the locations on site that use XXXXXX have not been included in any XXXXXX validation documents."

- Wide Area Network:
  "The firm utilizes a Wide Area Network (WAN) to connect all Local Area Networks (LAN's). The WAN is used to run network applications, which perform a variety of critical manufacturing and testing functions. Examples of network applications that run across this WAN include XXXXXX, the XXXXXX systems, and the XXXXXX system. Examples of functions performed by these applications include recording and approval of testing data, materials management functions to include approval/rejection of raw materials, in-process materials, finished API, and finished drug products. The WAN is not validated as described below:

  a. Complete system definition documentation has not been maintained. For example, the firm produced no approved WAN diagrams.

  b. The Quality unit has failed to ensure that procedures are in place which define all system definition documentation, which must be maintained for the WAN."

- Outsourcing Company:
  "There are no records to document that the Information Technology (IT) service provider staff personnel have received training that include current good manufacturing practice regulations and written procedures referred by the regulations."

Obviously care must be taken when interpreting individual 483 observations and warning letters. The outsourcing company's non-compliance noted in the 483 was presumably addressed in the correspondence with the agency between the inspection and the issue of the warning letter.

However, in the author's opinion, this will be an expanding area of regulatory action in the future and serves as a warning to all pharmaceutical companies who either have or are considering outsourcing their IT operations. The IT outsourcing house must be put in order: the cost of getting it right is far cheaper than the cost of correcting problems found during an FDA inspection.

IT Outsourcing Considerations

In light of the previous section, the following issues are some that must be addressed when considering outsourcing IT operations within the pharmaceutical industry:

Determine expertise with other pharmaceutical companies

Before committing to an agreement or contract, any pharmaceutical company considering IT outsourcing must ensure that the outsourcing company has both the technical expertise and regulatory compliance knowledge for an effective operation. Technical expertise must be assessed both at the network and application level as appropriate to the service being outsourced. This can be monitored via an effective service level agreement with agreed upon and effective metrics. Discuss with other pharmaceutical companies their experiences of potential IT outsourcing organizations and ask them for pharmaceutical company references. If possible, visit each company and get a better understanding of the key issues in successful outsourcing.

Training of staff including regulatory compliance

Technical expertise of IT staff must be documented in their curriculum vitae or resumes and training records: each member of the outsourcing company's staff must include their education, training and expertise gained on various jobs.

The same situation applies when a pharmaceutical company uses contract IT staff (self-employed staff who are recruited using contract agencies). In some circumstances, the contract staff cannot give resumes or curriculum vitae as this would negate their contacts with the agency; however, any pharmaceutical company must be able to override this and obtain the staff CVs to avoid citation during an inspection.

However, any IT service provider must ensure that its staff is trained in the appropriate regulatory compliance for one or more predicate rules and the impact of 21 CFR 11 as well; so that if an inspector calls they are able to answer regulatory questions. Failure to do this leaves any pharmaceutical com-

pany open to adverse regulatory comment and critique.

- Writing and Following Procedures
  Following on from documented regulatory compliance training is the ability to document and follow procedures for the outsourcing company staff. This is not just an issue of having SOPs or work instructions but also producing documented evidence that the procedures were followed. Coupled with this is the need to train outsourcing staff effectively: as IT personnel spend much time working on keyboards their writing skills can often lapse and therefore the legibility of writing can be questioned. Furthermore, software engineers frequently use pencil and are not trained, as noted in the Pharmacia warning letter, in GXP documentation practices when correcting information. The use of typewriter correction fluid, post-it notes and regulatory data written on scraps of paper is very common in many IT departments: staff must be trained accordingly to comply with GXP regulations.
- Change Control
  As outlined earlier in this article, an effective change control process is essential to demonstrate confidence in the IT operations. In many organizations, it is easy to make undocumented changes in the IT infrastructure; however, this will lead to non-compliance issues relatively quickly. It is important to demonstrate unequivocally that the change control process works well to ensure that an inspector does not investigate further into an IT organization.
- Technology Refresh
  Once the infrastructure has been handed over to the outsourcing company, how frequently will the technology platform be updated or refreshed? This is important to know as a too fast and a too slow refresh rate can be problematic. A fast refresh rate is usually dictated by changes in the network operating system and general or non-GXP business applications where this usually operates on an approximately 18 month – two year cycle. However, in a regulated environment, the network operating system and general business applications need to be designed, engineered, tested and rolled out in a compliant way; otherwise the validated business applications that run on top of these will remain validated. General applications and operating systems change faster than validated applications; therefore, care needs to be exercised as the platform out develops the application. Too slow a refresh rate can result in obsolete and unsupported operating systems and business applications and rising operating expenses from the outsourcing company.
- ISO 9000 Certification is not a Substitute for Regulatory Compliance
  Never accept ISO 9000 accreditation as a substitute for regulatory experience or compliance from any IT outsourcing company. If you are in any doubt read comment 65 from the preamble of 21 CFR 11 and this should leave no doubt about the way the FDA regards ISO 9000. There are critical differences between ISO and GXP regulations that will mean an ISO 9000 certified company would be unable to fulfill GXP requirements, as they cannot supply staff resumes as a minimum. It is important that the pharmaceutical company does not take the ostrich approach and hide their heads in the sand; they must audit the outsourcing company and investigate any claims of technical and regulatory made before the contract and service level agreement has been signed.
- Open or Closed Systems?
  One issue that merits scrutiny is where will the outsourcing services be sited: in-house or remotely? The former is relatively easy to define as a closed system from a 21 CFR 11 compliance perspective. However, if the outsourcing company wants to manage say data center operations or help desk from a remote location, it will be difficult to argue that this is a closed system. For example, if the help desk is located remotely or in a different country and shared with other companies (pharmaceutical and non-pharmaceutical), then the help desk would appear to be open and it needs to be subject to controls for open systems as defined in §11.30 of 21 CFR 11 [1]; this is the case if changes to validated applications were coordinated using the remote help desk. The pharmaceutical company must evaluate each outsourcing situation and monitor to ensure that there are no open systems involved.
- Validated IT Applications?
  It is important to ensure that validated business applications are not disrupted by changes made by an outsourced IT department, this relates to the changes in the infrastructure such as installation of a new service pack of the operating system without informing the system owners of validated applications or conducting a proper and effective change assessment. Equally so, there are IT applications that may need to be validated to ensure that they function correctly; if they contain records required by predicate rules. For example, if data are backed up by the IT department, has the backup software been validated? What happens if there is a new service pack or version of the software installed: was change control applied and was revalidation necessary?
- Application Service Provider (ASP)
  Applications can be served from centralized locations and here is further potential for classification as an open system as well as uncontrolled changes made by the ASP under the euphemism "keeping the system current with the latest service pack releases." Approach application service providers with great caution, there are benefits that can be obtained but these can be greatly outweighed by the disadvantages of regulatory non-compliance.
- Service Level Agreement (SLA)
  Define the scope of the outsourcing carefully: what are the boundaries of the agreement? What roles are there and what are the responsibilities of each role; this must include regulatory compliance. What are the communications between the pharmaceutical company and the outsourcing organization and are these defined? How are the service levels defined and most importantly how are they monitored and reported, as this is a major key for success.

Either the contract or SLA must allow a pharmaceutical company quality assurance staff to audit the outsourcing

company operations, procedures and documented evidence of actions. Some outsourcing companies claim "proprietary information" as a reason for excluding audits by a pharmaceutical company. This is inexcusable and unprofessional. Any outsourcing company claiming this must be rejected as unsuitable; imagine the situation that would result if this happened to an FDA inspector?

It is interesting that one pharmaceutical company who outsourced part of its IT operations to reduce the total cost of ownership (TCO) has actually taken the function back in-house after poor experiences. Caveat emptor!

Summary

Each pharmaceutical company is responsible for the regulatory compliance of its IT operations regardless of who delivers the service. Before signing an outsourcing contract, ensure that regulatory compliance is included in your evaluation of potential partners and that you have the right to audit their operations at any time. Claims that procedures and practices are "company confidential" are unacceptable from a service provider and you should walk away from any s uch agreement.

Due diligence by any pharmaceutical company in evaluating potential IT outsourcing companies is critical and must be carried out before signing any agreement. When regulatory compliance is taken into account, the potential cost savings may not be as much as senior management imagine, providing a suitable outsourcing company can be found.

References

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3. *European Union Good Manufacturing Practice for Pharmaceuticals, Medicines Control Agency, 2002.*
4. *Pharmacia Warning Letter, WL 320-01-07, dated 10th January 2001, available from www.fda.gov*
5. *Pharmacia Warning Letter, WL 320-01-08, dated 10th January 2001, available from www.fda.gov*

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