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Standard operating procedures revisited: a 2014 perspective

Approximately 50 years after the good manufacturing practice (GMP) regulations were first issued, regulatory inspections of firms operating under GMP are still uncovering cases of non-compliance with the rules concerning written operating procedures and the need to follow them. These rules are fundamental to GMP and are simple to understand. Future changes to GMP will emphasize risk management and the need to have an effective quality culture in the firm. SOPs will still form an essential part of the quality system. This article examines the principal problem areas in standard operating procedure management and provides recommendations for correcting them.

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"Documentation" as the term is applied to drug manufacture, is defined by the European Medicines Agency in its Good Manufacturing Practice (GMP) Guidelines [1] as "Instructions, i.e., directions and requirements, and records/reports." The agency further states that "Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements."

This article is concerned with the first of these two definitions, "Instructions", and specifically the need to have written procedures, as laid down in the GMP regulations and guidelines issued by all major regulatory agencies. But, these regulations date from 1963 in the USA and not much later than that from other authorities. Surely after 50 years there cannot be anything new to be said on this subject? Well, there may not be anything new to be said, but it seems that some of the old advice on this topic needs to be repeated.

The US FDA publishes warning letters that it has issued to companies on its website [101]. Of the 20 Warning Letters issued between January and September 2013, eight (40%) include mention of either a failure to have certain written procedures in place or, more importantly, a failure to follow these procedures. These warning letters are the tip of the iceberg, describing those problems of GMP non-compliance that have not been adequately addressed by the companies concerned, after an inspection report required corrective action. The observations of noncompliance with the rules on SOPs reported in the actual post-inspection report, Form 483, are much more numerous. According to Janet Bowen, VP of Compliance and Regulatory Services at Commissioning Agents Inc., in 2012 there were 1361 observations on "absence of written procedures" listed in Form 483 by FDA inspectors [2].

Other authorities, such as the European Medicines Agency, do not publish similar warning letters, but a review of inspection findings from 1995 to 2005 was published by this agency in 2007 [3]. This found that "Concerns over documentation of quality systems and procedures head the list (of non-compliance findings) by a significant margin, representing 14.1% of the total number of deficiencies. However, if all deficiencies relating to documentation were grouped together, they would make up 24% of the total. This is a significantly high value meaning that one out of every



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four deficiencies observed relates to a problem with documentation."

If one were to assume that all the European Medicines Agency reports were related to SOPs, then between 24 and 40% of companies currently being inspected are deficient in their observance of the standard operating procedure (SOP) requirements in the relevant GMP regulations. In my opinion, this topic is definitely worth revisiting now.

What the rules say

The creation of SOPs and their observation is mandatory under the GMP legislation. Throughout the texts of the rules, regulations and guidelines published by the various regulatory authorities appears the requirement that procedures, processes and methods be written down so that comprehensive documentation of the manufacture and testing of a specific drug product exists. An example is shown in Box 1. Note that this requirement includes the statement "Written... procedures shall be followed ... " and that SOPs should be written for "...all requirements in this subpart". The "subpart" referred to is "Subpart F: production and process controls." There are similar requirements in other sub-parts of 21CFR211, referring to the quality control unit, facilities sanitation, equipment cleaning and maintenance, materials management, the control of microbial contamination, reprocessing, packaging and labeling control, warehousing and product distribution, laboratory controls, staff training and recordkeeping. The GMP regulations of other regulatory agencies contain similar lists.

The regulatory agencies augment this requirement by specifying that there be a 'master formula' or 'master production and testing record' for each product, documents which will usually contain specific instructions on materials, measurements and processing conditions. However, SOPs are required for more than just the drug production and testing. A company that is in full compliance with GMP will have written procedures for every aspect of its operations that may affect the quality, safety or efficacy of its products.

The SOPs are considered by the regulatory agencies to be critical GMP documents and as such they are regularly the subject of review by official inspectors. Paul Bellamy, an Investigator for the FDA's New Jersey district, gave a presentation in which he stated that SOPs form the starting point for his investigations, as they provide a blueprint of the firm's day-to-day operations and show what the firm is documenting and what it is not [4]. This approach was confirmed by Anne Marie Montemurro, who was a Supervisory Chief Scientific Officer in an FDA Biologics Core Team, when she gave a presentation discussing the Team Biologics inspection approach [5]. In her presentation she explained that the risk-based approach to inspections identified the six key facility systems that must be examined, as shown in Box 2. In each of these systems, there are three critical elements that are common to all biological operations, and which must be inspected. These are SOPs, training and records. SOPs come first.

The results of non-compliance

A company is well advised to respond as quickly as possible to the initial observations of potential noncompliance by an inspector, with corrective action that can be shown to be effective. If this is not done, or if it is not done correctly, the next stage may be the issue of an FDA warning letter, or similar action by other regulatory agencies. This indicates that the firm's problems with GMP are sufficiently worrying that immediate remediation is needed. Failure to respond to these warnings with plans and commitments that satisfy the agency that the problems will be promptly corrected may lead to product recalls or court actions that may result in the closure of plants, fines or even imprisonment. As in most cases, prevention of these occurrences is much cheaper than correction after the event.

Where the problems are

During his inspections, in common with all inspectors and GMP auditors, Paul Bellamy always reviews a company's SOPs in critical operating areas. He stated in his presentation that, not surprisingly, the problems he found most often in SOPs were that they were absent,



(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.

» (b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified. or they were not followed, or they were not specific. It is worth examining each of these faults in more detail.

» Lack of critical SOPs

Lack of critical SOPs is most often reported today in inspections of the quality system. The firm's quality culture is now considered to be central to its GMP compliance. As reiterated in September 2013 by Janet Woodcock, Director of the Center for Drug Evaluation and Research at the FDA, in her keynote address to the Parenteral Drug Association/FDA joint regulatory conference [6], the responsibility for the quality of pharmaceutical products rests with the industry; the agencies are responsible for ensuring compliance. A lack of clear instructions in performing the quality unit's functions results in a report like this: "The Quality Assurance Unit failed to determine that no deviations from SOPs were made without proper authorization and documentation." The expectations and recommendations for a Pharmaceutical Quality System are clearly laid out in the Guidance Q10 from the International Conference on Harmonisation (ICH) [8]. The European Medicines Agency and the FDA are both committed to the aims and objectives of ICH and incorporate these guidances into their approach to GMP compliance. Failure by a firm to follow Q10's guidelines will lead to agency concerns about its quality system.

» Failure to follow SOPs

Failure to follow SOPs is reported for most areas of a facility's operations, but particularly in manufacturing procedures, quality control (QC) sampling and testing, and Quality Assurance Unit functions such as the investigation of deviations and the corrective and preventive action, which should follow the investigation. Here is a specific example of a warning letter detailing a major manufacturing failure: "The operators at your facility have repeatedly failed to comply with your procedures for aseptic operations. Specifically, your operators have been observed to not comply with standard operating procedure '#...' [specific SOP identifier was redacted]. Our review indicates that there are on-going problems with your personnel failing to comply with procedures. In your response, you state that your SOPs are inadequate and do not reflect actual practices." Clearly this is a case where the quality system is in urgent need of improvement.

» Ambiguous SOPs

Ambiguous SOPs are a frequent cause of failure to follow the instructions correctly, if at all. If the instructions are not sufficiently detailed or specific, the SOP cannot be followed, even by a trained person. Paul Bellamy described unsatisfactory "boiler-plate" SOPs that looked

Box 2. Key operating systems identified by risk-based analysis.
Quality system
Materials management system
Facilities and equipment system
Production system
Packaging and labeling system
Laboratory control system
Note: The quality system is always inspected
Other systems will be inspected according to a priority list developed from risk analyses and the results of previous inspections

as if "they had been downloaded from the internet". As a result, a warning letter may state: "We also note that your current standard operating procedure, Quality Control Regulation '#...' [specific SOP identifier was redacted], regarding the responsibilities of the quality unit is inadequate." Or, "Your firm's corrective and preventive action procedure is not adequately defined."

» Solutions

The key to compliance in this situation, as with all regulatory compliance, rests with senior management. Unless there is full commitment to a quality mission at the top of the firm, a functioning quality culture will not be established. GMP regulations require that a quality unit, independent of production and reporting directly to senior management be established, with sufficient staff and authority to ensure the quality of any product the firm issues for use. It is usual to divide the functions of the unit into QC and quality assurance (QA). QC is responsible for the testing of raw materials, in-process and final drug samples, to ensure that these comply with pre-set quality specifications. A major role of the QA unit is document control, especially the management of SOPs. This function can be split into several areas of action: creation or amendment, approval, distribution, training and cancellation. The first SOP to be written under this system is that which lays down rules for each of these activities.

» Creating, approving & distributing SOPs

The European Union's Eudralex Volume 4 [1] provides basic GMP guidelines, which include the requirement that "Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided." Anyone responsible for writing these documents must acquire the necessary skills that ensure that the SOP is readable, accurate, complete and unequivocal. The use of document templates is highly recommended, as these will create SOPs with a structure that will become familiar to those affected by the instructions, and ensure that all

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critical information is included. The outline of a template for a production SOP is shown in **Box 3**. There should be a formal approval process, which is documented on the cover page of the SOP, along with the date on which the SOP will become effective.

The best person to write a procedural SOP is someone familiar with the process, preferably an experienced scientist or technician. Here are some simple recommendations for clear SOP writing:

- » The document should be written in simple, plain language. In our multicultural world, English is now accepted as the principal language for regulatory documentation, but not everyone has English as their first language. This fact must be taken into account.
- » Always use the active tense: "Add the solution to the tank", not "The solution is added...".
- » Avoid lengthy descriptions. If the process includes the operation of equipment, and the manual for operating this is available, then the SOP need only

reference the manual without repeating all the operating instructions.

Avoid 'house jargon'. The SOP must be capable of instructing any suitably qualified person, who does not need to be familiar with the fact that in this facility it has become the habit to refer to a specific process by an acronym peculiar to this firm. In fact, it is a good practice to explain all acronyms and abbreviations at the beginning of an SOP, as shown in Box 3.

Every section of the SOP template should be completed, unless it is not applicable. The author's supervisor, or another person in a position of responsibility in the specific area of operations then checks the draft for accuracy, completeness, readability and lack of confusing instructions. The approved draft is submitted to QA, where it is checked for GMP compliance, and then to the senior quality manager, preferably a VP or equivalent, for authorization to issue. SOPs concerned with non-production issues, such as general staff instructions or training, should be initiated and

Box 3. Standard operating procedure template: manufacturing operations.			
Standard operating procedure: manufacturing operations			
Cover sheet	sop# XXX.		00.00
Originated by:	Date:		Effective: Date:
Approvals			
Supervisor:	Date:		
QA manager:	Date:		
Senior management:	Date:		
Revisions			
#1: By:	Date:		
Supervisor:	Date:		
QA manager:	Date:		
Senior management:	Date:		
Add further revisions, as necessary			
Following pages: text			
» 1.0 Title))	8.0 Procedure
» 2.0 Purpose and scope))	8.1 Safety precautions
» 2.1 Purpose of procedure))	8.2 Special handling procedures
» 2.2 Scope of procedure		»	8.3 Calibration of equipment
» 3.0 Responsibilities))	8.4 Process steps
» 3.1 Operator responsibilities		»	8.4.1 Step 1
» 3.2 Supervisor responsibilities		»	8.4.2 Step 2(and so forth)
» 4.0 Definitions and acronyms))	8.5 Data to be recorded
» 5.0 Principle of procedure (if applicable)		»	8.6 Samples to be taken, labeling
» 6.0 Reference documents))	9.0 Next processing stage
» 6.1 Batch record		»	9.1 Description of next stage
» 6.2 Other standard operating procedure		>>	9.2 Storage and labeling of processed lot
» 6.3 Other process references (e.g., equipme	nt operating	>>	10.0 Countersignatures required
manuals)		»	11.0 Attachments, forms (test request forms,
» 7.0 Materials and equipment			equipment, printouts, deviation reports, and so on)
» 7.1 Previous process stage (characterization)		
» 7.2 Chemicals and reagents			
» 7.3 Equipment			

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approved by the responsible department, for example, human resources. All SOPs should pass through the QA system. A suggested list of SOPs for a manufacturing facility is shown in **Box 4**.

There must be a central record of all SOPs, past and present, and each document should be identified by a unique alphanumeric code. It is usual to include in the code two or three letters identifying the affected function, the SOP serial number and a serial number indicating the version, for example, PRO 103.02, describes the one hundred and third SOP concerning the production department, in its second version.

The information is best kept in a master SOP file, containing the description of each SOP, its effective date and all revisions. Most companies now maintain the master file and copies of all SOPs (with their archived earlier versions) as electronic records, which are printed out as needed. In most cases, the personnel responsible for the activity now access their SOPs via computer monitors, so that the maintenance of past and current versions can be done by a central computer. It then becomes essential to ensure that the computer system complies with the specific GMP rules governing electronic records, such as Eudralex Volume 4, Annex A.11, or the FDA's 21CFR11. These require that access to the records is controlled by a username/password or similar security system and that all activities performed in creating and maintaining the records are recorded by the computer. This will provide what is termed an "audit trail", whereby any change to a document is permanently recorded and can be accessed by an auditor or inspector.

QA is responsible for the distribution of SOPs to the relative department and for ensuring that only the current version is available, and only to those persons authorized to access it. If paper copies of the previous version were issued to the factory or laboratory, these must be collected by a QA person and their destruction recorded. Then it is essential to ensure that the current SOP can easily be accessed by an operator at the point of the activity.

Always ensure that the files of print-outs of the SOPs that are made available to inspectors and auditors only contain the latest versions. GMP audits of companies discover master files containing hundreds of SOPs, of which up to 30% may be out-dated versions. This does not create a good impression. The usual reason given by a QA manager is that they are planning to review the files, but have not yet got around to it. But, if the system is followed, revision of the Master File should be an ongoing activity and should not need a 'blitz'.

» Amendments

Managing changes in SOPs should be part of the overall QA change control procedures and there should be written instructions for this. An amendment to a SOP can be made at any time, using a set process that is documented on forms issued and managed by QA. The form will record the proposed amendment, with justification for this, and the usual series of approvals or further amendments, until a final agreed version is

Box 4. Recommended list of sops for a manufacturing facility.

Organization and personnel

- » Personnel responsibilities, hygiene, movement control
- » Personnel qualifications and experience
- » Personnel training
- » Quality management
- Responsibilities and duties of quality assurance
- » Document control, including SOPs
- » Approval of intermediates, DS and DP specifications
- » Master and production batch records
- » Process and analytical method validation oversight
- » Batch production record review and product batch release
- » Change control
- » Internal audits and reports
- » CAPA
- » GMP training
- Responsibilities and duties of quality control
- » In-process and final container sampling and testing
- » Analytical equipment calibration and maintenance; log books
- » Analytical method qualification and validation
- » Approval or rejection of test results and samples
- » Formal investigation of out of specification or out of trend results
- » Issue of certificates of analysis
- Stability testing
 - Environmental monitoring and reporting of deviations
- Materials management
- » Receipt, sampling, warehousing, control and distribution of accepted or rejected raw materials, components, packaging materials, drug substances and drug products.

Facilities and equipment

- Facility safety and security procedures
- » Facility cleaning and maintenance
- » Critical systems qualification and validation (e.g., WFI, clean steam, compressed air, HVAC for clean rooms)
- » Equipment cleaning and maintenance; log books
- » Equipment qualification for process validation
- Production
- » Personnel safety and security measures
- » Control of cross-contamination
- » Performance of all production processes, work instructions
- » Operation of process equipment
- » Reporting and investigation of process deviations
- » Final container filling, inspection and packing
- Aseptic processing (if appropriate), including media fills
- » Packaging and labeling control
- » Batch production records: data entry, checking and completion *Quality control*
- » Laboratory safety and security
- » Sample receipt, storage, distribution, archiving
- » Analytical methods (one SOP for each type of test)
- Laboratory investigations of OOS, OOT results

created. This is given a new version serial number and again QA is responsible for ensuring that this version replaces the previous one and no two versions are in operation at the same time.

» Training

The ICH Q10 guideline emphasizes the importance of knowledge management as part of the overall quality system. An essential part of knowledge management is ensuring that all personnel have the experience and training that enables them to perform their duties and responsibilities correctly and effectively. This requirement is actually built into the GMP regulations, for example, as in 21CFR 211. Box 5 shows the text of section 211.25, specifying this. The European regulations contain similar language.

The SOP cannot be effective unless all personnel affected by its instructions are properly trained. Some companies do not release a new SOP or an amendment to an existing SOP until all affected personnel have been trained. This is an excellent practice. The document will stay at the 'approved', but not 'effective' stage until this is achieved. Since the documents are usually maintained in electronic format, the most common form of training is 'read and understand', which is done by the person looking at the document on paper or on the monitor screen and signing a form to state that they have read and understood its contents. For an experienced operator and a relatively small change in the SOP, this may be sufficient. However, for a new process, or the training of a new or inexperienced person, it is necessary to go beyond reading to doing. The staff must demonstrate their understanding by performing the operation under supervision, or at least by successfully answering a questionnaire. The testing should be repeated after 1-3 months, to ensure that the knowledge was retained. This is probably the most important part of the training process.

Control by the quality system

If the QU is functioning properly, any lack of adequate SOP documentation or instances of not following these should be identified during QA's routine auditing of the GMP operations. Such internal audits are an essential part of QA's responsibilities and the reports

Box 5. US code of federal regulations, 21CFR 211. Current good manufacturing practice for finished pharmaceuticals. Sec. 211.25: personnel qualifications.

» (a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice..." generated by this activity must be reviewed by the senior quality executive. It is important to note that the internal QA reports cannot be accessed by regulatory inspectors unless they can show good cause for doing so. This provision should ensure that the reports are comprehensive and unaffected by concerns of regulatory action. It is far better for potential non-compliant activities to be identified internally than to leave it to an outside inspector to discover them.

Sometimes it is a good idea to have an outside auditor check the results of internal audits, to ensure that all necessary activities are being inspected, and deviations are correctly identified, investigated and resolved. If a firm feels that the internal QU is not capable of providing sufficient insight into potential problems, it is possible to have an outside consultant perform a 'mock inspection', using the same methods and criteria as an official inspector. That same consultant should also be able to provide suitable solutions to any problems uncovered.

Future Perspective

It should be apparent by now that SOPs will remain an essential part of GMP documentation in the future. No other GMP requirement is more fundamental that having written instructions for people to follow. Looking forward, there have been indications that the FDA and European Medicines Agency will be collaborating on revisions to their respective GMP regulations and guidelines, to achieve greater harmonization in wording and requirements and a greater emphasis on risk management. Janet Woodcock said that the FDA has been working on upgrading its own quality systems and that the agency wants companies to be able to control their own futures and reduce regulatory oversight by having a strong quality culture in place [6]. Having a new look at the GMP rules is part of this project. It is likely that the section of these new rules that deal with documentation will not change significantly in respect to having SOPs and following them. Any firm that is not sure about their ability to comply with these should pay attention to them immediately. The quality management system is the place to start, and it is the responsibility of the most senior managers in the company to ensure that it is properly staffed and operating effectively.

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Executive summary

- » Lack of compliance with the good manufacturing practice regulations that govern the creation and use of written instructions, usually known as standard operating procedures (SOPs), continues to be a concern of the regulatory authorities.
- » As SOPs are considered to be critical documents, they are always reviewed by regulatory inspectors
- » The most common faults observed are lack of adequate documentation, ambiguous writing, and a failure to follow the instructions.
- » Correction of these faults is the responsibility of an effective quality management system, which must be supported by the company's senior management.
- » Key correction points are adequate training in writing and in the understanding of the instructions, along with comprehensive oversight by the quality management system.

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» Website

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