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REVIEW ARTICLE

REGULATORY ASPECT OF PHARMACEUTICAL CHANGE CONTROL SYSTEM

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ABSTRACT-
The change control is "A process that ensures that changes to materials; methods, equipment and software are properly documented, validated, approved and traceable". The process requires eight basic steps: Identification, documentation review, change proposal, change classification, implementation plan, installation, verification, closure. Changes are outlines as Major, Moderate & Minor. A compliance of regulatory group within the company determines the filing impact and submits it to FDA,-A prior- Approval supplement (PAS) for major changes, A CBE -30 or CBE-0 for moderate changes or Annual report for Minor changes. Firms are expected to write adequate Standard Operating Procedure (SOP) for the change control & be in total compliance with proper documentation. Considering the regulatory prospective of change control procedures, it is important to note that there are many guideline which describe the control of changes in manufacturing few references includes 21 CFR Part 211: Sec. 211.100, 21 CFR Part 211.194 (Laboratory Records), ICH Q7A and USFDA Guidance for Industry: Change to an approved NDA or ANDA (April 2004- Revison-1).
Key Words: Change control, Standard Operating Procedure, regulatory prospective, ICH Q7A, USFDA

INTRODUCTION

Change control is the most critical element in a pharmaceutical or biotech company's quality management system - inadequate change control procedures end up creating a huge risk of non-compliance. The FDA's guidance for Industry clearly reinforces the importance of implementing an effective change control procedures as a critical component in an overall quality system - see "Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations (CGMP)". It's important for FDA-regulated companies to be able to implement a quality system that automates change management and change control procedures and ensures that they are in compliance with GxPs and 21 CFR Part 11.

INITIATIVES TO CHANGE

Change control is a formal process used to ensure that changes to a product or system are introduced in a controlled and coordinated manner. The goals of a change control procedure usually include minimal disruption to services, reduction in back-out activities, and cost-effective utilization of resources involved in implementing change. It would be very difficult to carefully manage change control in a large company or a fast growing organization without an enterprise-wide change control system One of the most important aspects of change control is to maintain a history of changes for audit trail purposes - a capability better facilitated by such systems.

ESSENTIAL REQUIREMENTS OF CHANGE CONTROL SYSTEM

The change control system requires a structured approach towards managing change in an environment focused on continuous improvement. The system must manage the end-to-end change control process including initiating, reviewing, approving, distributing and storing change history. Such a system can provide evidence of compliance to FDA. In addition, the system should also help capture relevant information about the objective, nature and scope of change. The scope of the change control program must also cover a broad set of possibilities including changes to product formulation or design, upgrades to facilities, utilities, equipment and computer systems, manufacturing instructions, SOPs, test methods and specifications, any new raw materials as well as any changes in policy.

Change control system maintains a history of the lifecycle of all change requests. Such information is used by FDA during audits to ensure change control procedures are working well and facilitates regulatory filings and prior regulatory approval. Best practices and industry standards, as well as regulations imposed by regulatory bodies, require companies to demonstrate control over change management. Change control systems must ensure consistent procedures and informed decision-making by qualified individuals as well as assure traceability back to the justifications behind the change process.

BENEFITS OF CHANGE CONTROL SYSTEM

- Careful planning helps to ensure that the change process is started and managed by the right people at the right time
- Planned change management allows us to include specific tasks and events that are appropriate for each stage in the change process
- Change management ensures that customers, suppliers and other stakeholders understand and support the change
- Change control reduces disruptive aspects and emphasizes positive opportunities in the change process
- Change control allows easy tracking of changes and compliance to FDA regulations.

Overall, companies can see improved benefits for all their stakeholders including QA/QC managers, regulatory affairs specialists, documentation managers, production specialists, facility managers and engineers, operations/maintenance specialists, compliance auditors and R&D tech transfer managers. The benefits are accrued across the extended enterprise. The system also ensures continued compliance with regulations.[1, 3, 4]

MANAGEMENT OF CHANGE AND CONTINUOUS IMPROVEMENT

Changes to process, equipment, procedures, technology, material and organization are necessary for continuous improvement and a MOC system must also be continuously improved. The process requires eight basic steps:

- Identification
- Documentation review
- Change proposal
- Change classification
- Implementation plan
- Installation
- Verification
- Closure

Applying these steps, the system can be designed for managing the configuration and controlling the change, and then the necessary procedures and forms can be prepared. It is important that the system design come first. Specifically:

- Identify the change to be made
- Accumulate and review the baseline documentation, including drawings, procedures, P&IDs, equipment data sheets and MOC forms.

Prepare a Change Proposal

The change proposal is the vehicle used to document the changes in the specific application area. It is assigned a change proposal number, identifies approval authority, defines security, and establishes issued date, effective date, and distribution. The baseline configuration and documentation are verified. From this point on, the change proposal must be controlled throughout the lifecycle.

Classify & Approve Proposed Changes

The Change Control Board must review, evaluate, and approve changes and then classify the change as normal, urgent, emergency, or temporary. In some cases, changes which are low-risk and low-cost may be approved by the Configuration Manager.

Develop an Implementation Plan

The implementation plan describes how the change will be put in place. Baseline documentation is updated. Operators and maintenance personnel are trained in the change.

Install the Change

This step speaks for itself.

Verify Installation

Track the status of the change. Verify that each step in the process is completed and the documentation matches the "as-built" configuration. Conduct a system audit.

Close Out the Change

Everything is completed and the cycle is repeated for the next proposed change. Managing change requires that the purpose and justification of the change be documented; change be reviewed for impact on safety, health and environment; cGMPs be reviewed for impact on GMP values; additional risk is not introduced into the process; authorization be documented; process information be updated; operating and maintenance procedures be revised; personnel who are affected by the change be trained; and configuration of the plant be maintained.

Sometimes changes can introduce new hazards or compromise safeguards built into the design of a process. Situations may occur that require an immediate change to protect the health and safety of the employees, facility or community. Immediate changes should have their own procedures that list steps to be taken and requirements.[2, 3, 4,5,6,7]

STANDARD OPERATION PROCEDURE

The purpose of a Standard Operation Procedure is to ensure that all changes related to any aspect of manufacture, testing, holding and distribution are assessed and consequently addressed for their impact on the identity, strength, quality, and purity of the drug product including the assessment of the qualification and validation status and the regulatory situation.

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Deviations (Failure Investigations, Non-Conformances)

The purpose of this procedure is to ensure that all Deviations are: Investigated within 30 working days, all investigations are completely documented, assessed by the responsible line units and QA, corrective actions if applicable are implemented and implementation is tracked, the complete process is managed, monitored and

controlled.

1. Regulatory Basis, Reference Documents

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3.Purpose / Aim

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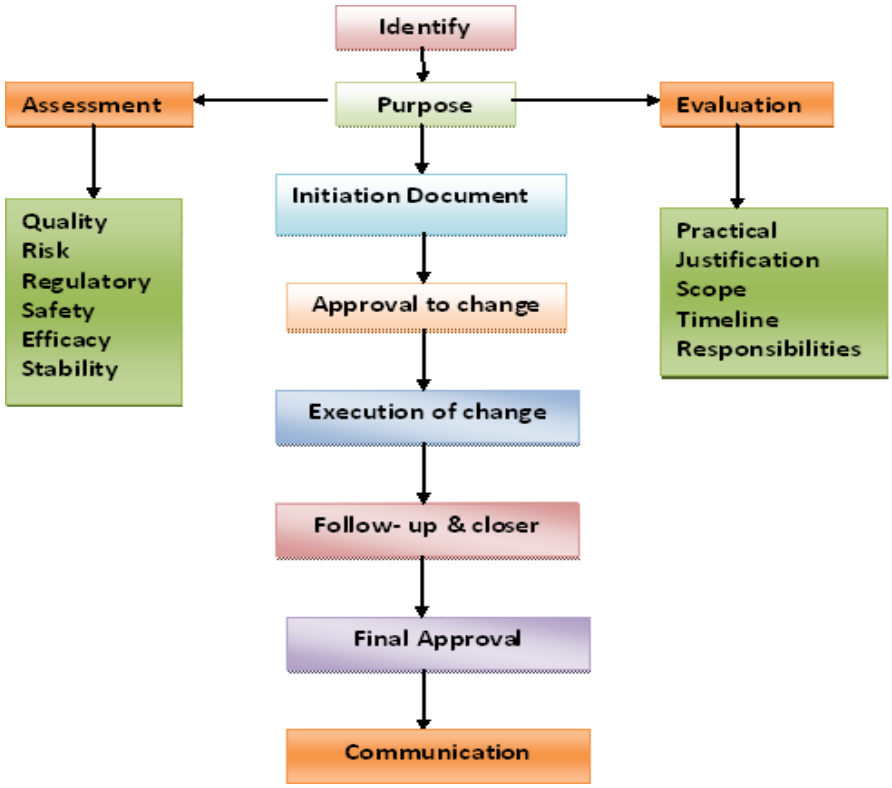

Figure 1: Flow Chart of Change Management System

Handing of OOS Results

FDA considers the integrity of laboratory testing documentation records to be of fundamental importance during drug manufacturing. As a drug manufacturer you have to assure that your laboratory investigation in cases of failures (OOS results and confirmed OOS results) is done without compromising products quality or current authority expectations. This SOP (13 pages plus attachment) guides you step by step through the process of investigating and documenting OOS results. It describes the responsibilities of laboratory personnel, the QC supervisors and QA Managers. Attached to the SOP is an easy understandable from reflecting the OOS process where you put the relevant data and assessments in three logical sections, the Preliminary Assessment, Investigation Plan and Results and the Final Approval. This SOP only needs little site-specific modification before you can adopt this SOP to your operations.

1. Regulatory Basis, Reference Documents 21 CFR 211.165, 21 CFR 211.160, 21 CFR 211.192, FDA Draft Guideline “Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production

2. Purpose / Aim

3. Scope

4.Responsibilities and Accountabilities

4.1 Analyst

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7. Distribution

8. Attachment (4 pages)

· Section I Preliminary Assessment

· Section II Investigation Plan and Results

· Section III Final Approval

GMP - STANDARD OPERATING PROCEDURES (SOP)

Investigation of Complaints

Insufficient customer complaint handling was and still is one of FDAs top findings in the published warning letters under FDAs Freedom of Information. In addition FDA starts to review not only US related customer complaints for products on the US market but since the New Quality System Approach is used during inspections also complaints for non US – products may be investigated to challenge the companies complaint system. This SOP including a investigation form attached guides you step by step through the process of investigating, documenting, reporting and follow up customer complaints. Also the responsibilities for the complaint investigations are clearly defined, which is a crucial prerequisite for any functional system. This SOP only needs little site-specific modification before you can adopt this SOP to your operations.

1. Regulatory Basis, Reference Documents
2. Purpose
3. Scope
4. Complaint categories
4.1 Commercial Complaints
4.2 Product Technical Complaints (PTC)
4.3 Adverse Drug Event (ADE) Complaints
5. Responsibilities and Accountabilities
5.1 Quality Assurance
4.1.1 Complaint information
4.1.2 Complaint registration
4.1.3 Internal Notification
4.1.4 Complaint Tracking and follow up
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7. Distribution[8, 9]

CATEGORY OF CHANGES

Impact assessment of changes is extremely important to the agency & changes are outlines as Major, Moderate & Minor. A compliance of regulatory group within the company determines the filing impact and submits it to FDA,-

- A prior- Approval supplement (PAS) for major changes,
- A CBE -30 or CBE-0 for moderate changes or
- Annual report for Minor changes.

Major Changes-

- Is likely to have a detectable impact on the critical attributes of the product, significantly.
- Could shift the process in a discernible manner (Such as: quality, yield, stability, impurity profile, crystal form, particle size, bulk density)
- Warrants definite additional/ major testing & suitable revalidation studies to justify changes.
- Reviewed by QA at the facility level & approved by corporate groups.
- Requires prior FDA approval.

Few examples of Major Changes-

- Change in type of solvent used for final crystallization (affects impurities profile, physical attributes & other critical quality attributes of API)
- Change in equipment type (Dryer, configuration, Blender type, crystallizer type, tablet compression machine, coating equipment)
- Change in critical process parameters.
- Revision of critical quality attributes (specifications), such as assay limit, dissolution profile, related substance test.
- Related substance limit.
- Revision of standard test procedure for assay (potentiometric to HPLC) for related substance (TLC to HPLC), for residual solvents (GC to Head space)
- Change in facility (site of manufacturing)
- Change in batch size by more than 10%
- Change in route of synthesis
- Change in isolators, RABS or C-RABS systems. Change in API source.
- Change in validation sterilization process.
- Change in sequence of operations.

Moderate changes-

- Is usually for improvements to process, materials, product or procedure
- Therefore, no reason to wait for approval
- Does not require prior approval by regulatory /FDA before implementation
- The agency will want to review it
- Can go in annual report to FDA
- Can be evaluated by QA, at the facility & then approved by corporate groups.
- These are called " change being effected"
- Categories are CBE-30 & CBE-0

Few examples of moderate changes-

- Improvement in yield
- Improvement in critical quality
- Improvement in attributes
- Improvement in process capability/efficiency
- Cost- effectiveness

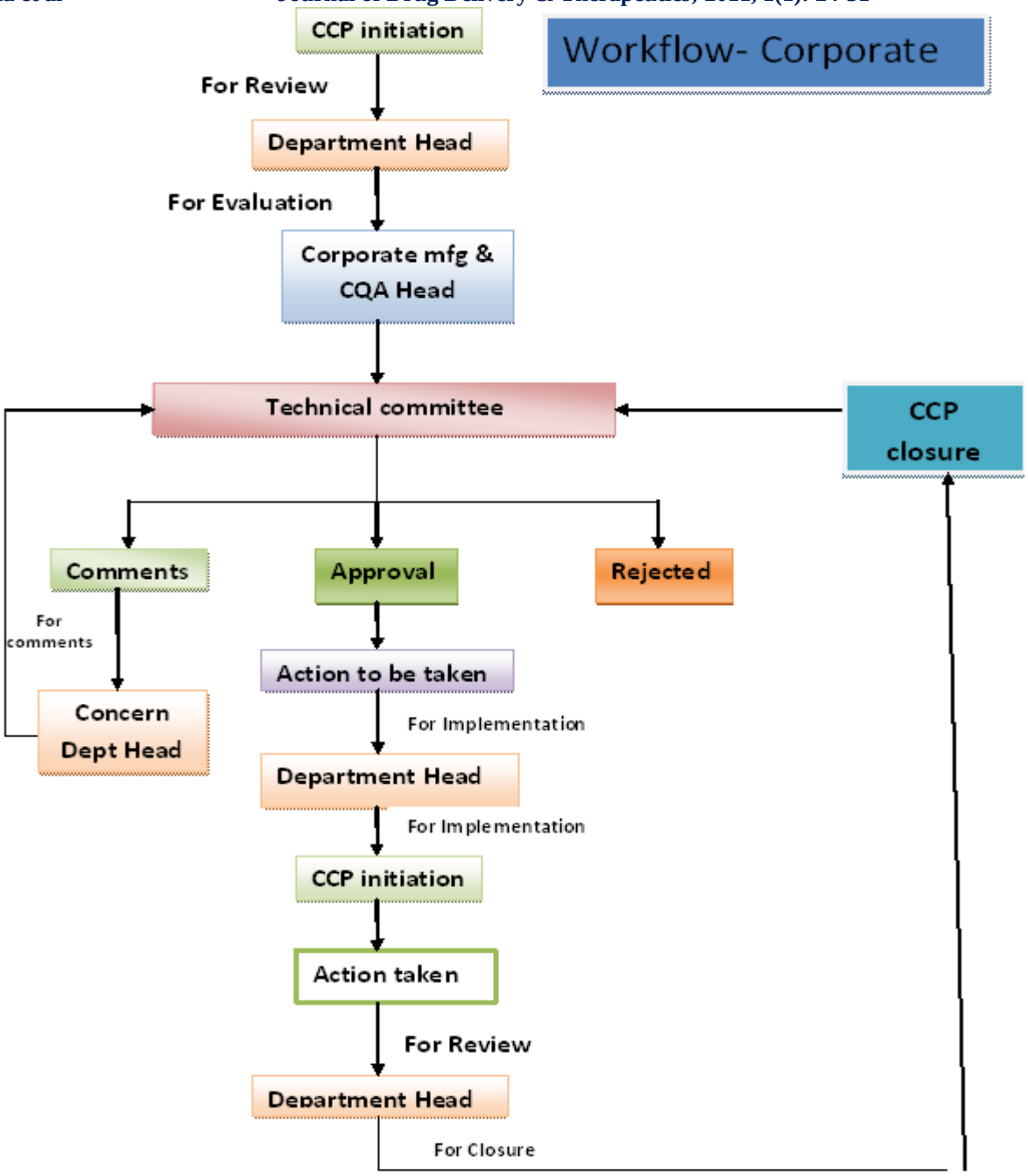

Figure 2: Change work flow task from initiation to closure from traceable authenticity

Minor changes

- Is unlikely to have a detectable impact on the critical attributes of the products.
- Does not shift the process in any discernible manner
- Can be implemented with minimal testing and revalidation
- Can be reviewed and approved by QA at the facility level
- Is reported in annual reports to FDA and does not require FDA approval

Few examples of minor changes

- Like for like equipment replacement
- Noncritical process parameter
- Revision for specifications (such as noncritical parameters) as per process capability.
- Revised quality of components and reagents, marginally in case of API intermediates
- Revised operating procedure to add safety
- Revised cleansing procedure to enhance GMPs
- Editorial changes[10,11,12,13,14,15,16]

Scientific judgment should determine what additional testing & validation studies are needed to justify a change in a validation process.

In the future, the comparability protocols will be required to support and justify the changes. This will improve the approval timing for the agency and also will reduce the risk of having an adverse affect on the SQIPP o f the product. This requirement will also ensure that no adulterated product ever gets released. Comparability protocols will be a submission to the agency and, as such, any change to the protocols must go through the change control process.

When developing a change control procedure, following points must be considered

- Developing a robust change control system
- Educate users of the change control system, and
- Enforce change control system policies and procedures

A change control policy must be in place with supporting SOPs and a Process Map that will guide users through the process so as not to deviate or work outside of the process. Stakeholder Matrix is also important so that it will provide guidance on the distribution for assessment of impact. The process must be user friendly and efficient or it will be unacceptable to the users. After a robust manual process been developed and implemented it must be owned by the Quality Organization as it is a part of compliance requirements.

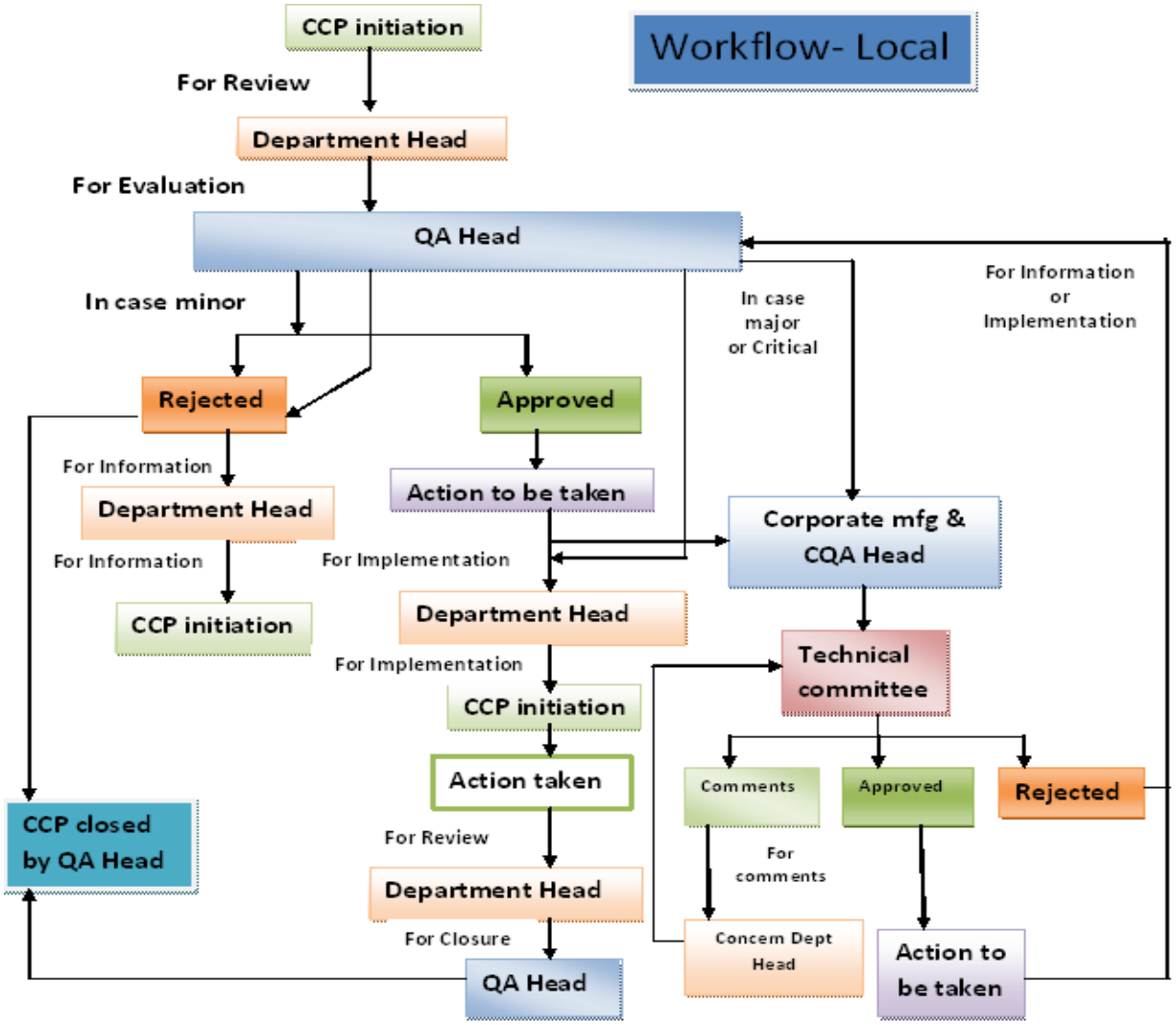

Figure 3: Change workflow task from initiation to closure with traceable authenticity

All the document s should be complete, accurate, detailed, unambiguous, credible, verifiable, and defendable and supported by scientific evidence, as they will be accessed by Federal Regulators. It is also important to make sure a tracking system in place so that document can be located and retrieved at any time.

It is important to understand not only the type of changes that will be a part of change control process, but also the priority of those changes. Change should never be expedited, but should either planned or unplanned. Almost all changes can be planned; only those that are emergencies occurring after hours, on weekends, or are safety-related should be considered as unplanned. in all cases they should be submitted through change control and any required validation / revalidation must be completed before the change is fully implemented.[10]

ENSURING TRAINING AND PROCEDURES IN A MANAGEMENT OF CHANGE PROGRAM

A large part of Management of Change is maintaining up-to-date documentation. Situations occur where personnel are not aware of changes to documentation that could indicate training does not keep pace with changes in job functions. Typical problems include not being aware of changes in training or procedures, not maintaining up-to date documentation, and lack of a detailed procedure that describes the MOC process.

In order to eliminate these problems, corrective or preventive actions may be necessary, such as: auditing the training program and/or the procedure program for deficiencies; making training part of the MOC program; developing a detailed procedure that describes a process for initiation, review and approval; and documentation, training in change, and implementation of any changes. The lack of agreement between training and procedures is a major industry problem, especially in a regulated environment. The question becomes which is correct — the training or the procedure?

Training in change is required for all changes in process and operation; technology; facilities and equipment; and procedures. It may be as simple as reading and initialing simple changes in a procedure if it does not affect skills or knowledge. In other cases, it could require developing new lesson plans to teach the new skills and knowledge, or developing and delivering structured on-the-job training. Reinforcement training, an FDA requirement, is targeted for performers to maintain their skills and knowledge. Training in change should be critical and may cover much of the reinforcement training.[7]

LEVEL OF APPROVAL-

The change control proposals are formal documents and must be initiated by the affected group. For eg production unit is the effected group for changes to equipment and facility expansion. in this eg, production unit will initiate the change proposal .This proposal could reviewed and discussed by other responsible persons from departments, such as R & D ,QA ,Regulatory and affected client. However, the final approval is granted by Quality Unit. It is important to assign levels of approval within departments .for changes categorized as Major, the review and approval must be dealt with by senior experts from stakeholder department and Quality Unit. in contrast ,for the change categorized as Minor, the review and approvals can be delegated to trained personnel who are not necessarily from senior management.

Once a manual process has been implemented, one of the stakeholder groups such as Regulatory needs to conduct an internal audit once a year. Based upon business needs, it may be necessary to automate the process with validated software. if process is not working well, this software should not be purchased to fix the problems. it will only waste of time and will make the situation worse. in order to find the software that will fit the process; a functional requirement specification outlining what is expected of the program should be written. From there, a matrix is used to evaluate the right software for correct environment.

When all of the pieces, are in place, change control process /program will provide the ability to submit, evaluate, approve, communicate, correctly implement and document all change that impact SQIPP.

HANDLING AND CONTROLLING CHANGES-

Handling and controlling change initiator call for a meeting of change control team and puts the proposal for change with the problems and consequences and advantages.

Team reviews through Brainstorming session-

Should the change be allowed?

Partly or Wholly?

Regulatory impact?

GMP & safety impact?

Need for requalification or revalidation?

Customer/ Agency to be informed?

Category of the change? Reporting category?

Documentation requires & documents affected?

If the team has decided on above points, the CCIF (change control initiation form) is processed by the team members for a sign-off & each member understands her/his responsibilities .the initiator coordinates the change process at all levels.QA checks the adequacy of the process data, impact and follow up closure and communicates to the customers/clients and management. Regulatory prepares the reporting document for the agency.

REGULATOR PROSPECTIVE OF CHANGE CONTROL

Considering the regulatory prospective of change control procedures, it is important to note that there are many guideline which describe the control of changes in manufacturing few references includes

21 CFR Part 211: Sec. 211.100

There shall be written procedure for production and process control designed to ensure that the drug product have the identity, strength, quality and purity. They purport or are represents to process.

These written procedure, including any changes, shall we drafted, reviewed, and appointed by the appropriate organizational units & reviewed & approved by the quality control unit.

21 CFR Part 211.194 (Laboratory Records)

Complete record shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for the modification & data to be verify that the modification produced results that are at least as accurate & reliable for the material being tested as established method.

ICH Q7A

A formal change control system should be established to evaluate all changes that could affect the production & control of the intermediate or API. Written procedures should provide for the identification, documentation, appropriate review, & approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment, processing steps, labeling & packaging materials & computer software.

USFDA Guidance for Industry: Change to an approved NDA or ANDA (April 2004- Revison-1)

This guidance provides recommendations to holders of new drug applications (NDAs) & ANDAs who intend to make post approval changes in accordance with section 506A of federal Food, Drug & Cosmetic Act (the act) & $314.70 (21 CFR 314.70) The guidance covers recommended reporting categories for post approval changes for drugs other than specific biotechnology & specified synthetic biological products.[10, 17, 18]

CONCLUSION

Change is inevitable, and because continuous improvement is impossible without change, progress is built on change. The key to making successful change in the pharmaceutical world is to manage it, both from internal and external perspectives. Changes can happen at any time during a product's lifecycle. The impact of the change

needs to be balanced against the cost of making the change (safety, time and money). Impact of change may require amendments to registered details. Changes must be formally documented and approved via a change control process. It needs to evaluate risk assessments throughout change control process.

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