

Chapter 2

Organization

Abstract In this chapter, an organizational structure is proposed which will allow for a more efficient and effective Analytical Department. The organization is based on a project team model. Discussions on how the team is formed, managed, and the utilization of team dynamics are presented in detail. A process for project risk evaluation based on the project plan is proposed. Among the most basic essentials, and a requirement, in any successful GMP Analytical Chemistry Department is the establishment of Standard Operation Procedures (SOP's) and working Guidelines. This is the most efficient way to communicate best practices within the group. The essential SOP's that should be included within a GMP Analytical Chemistry Department is listed within the chapter, along with a template for writing SOP's.

2.1 Department Structure

The Organization of an analytical department has a large impact on its efficiency. Having a good exchange of information and good interaction between staff personnel is extremely important. The organization structure is the starting point for creating an effective and efficient analytical department. The structure should contain process owners or expert groups to ensure the expertise is available for all members of the department. The backbone of the department is the **Project Teams**. The teams are resourced from the staff population and exchanges can be made as the project moves through the various stages of development. Within the staff, individuals are identified as team leaders, process experts, and team representatives. The team leader and representatives make up the project team. Process experts are utilized by the teams, but can also be part of the team as a team leader or representative. Individual team leaders, process experts and representatives can contribute to several project teams simultaneously. A structure for the Analytical Department is shown in Fig. 2.1.

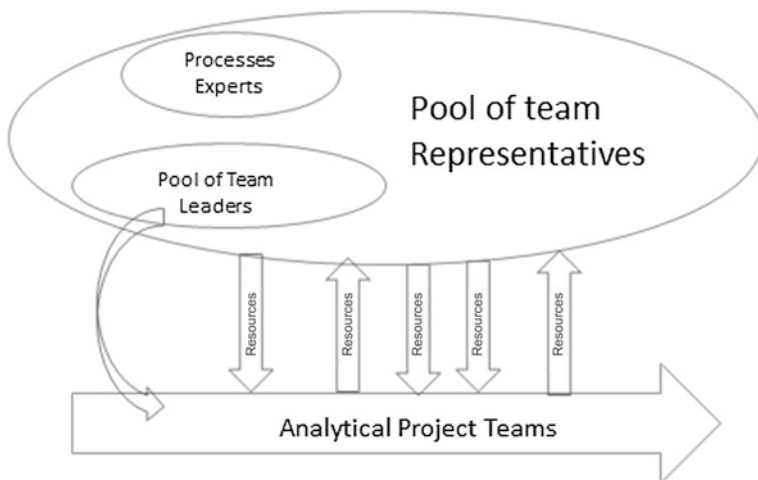


Fig. 2.1 A structure for the Analytical Department

The Process Experts interact with the project teams as shown in Fig. 2.2:

The above concepts does not negate the existence of a classical organizational chart, shown in Fig. 2.3 below, which represents the usual reporting relationships and managerial responsibilities. In this environment the reporting manager is an administrative supervisor and performance evaluations come from the team goals.

Project teams are the backbone of the organization. The department should have a specified process for the formation and management of project teams. Proper representation and functioning of project teams is essential for the success of the project to be accomplished. The Process for the development and management of Analytical Project Teams is described in Sect. 2.2.

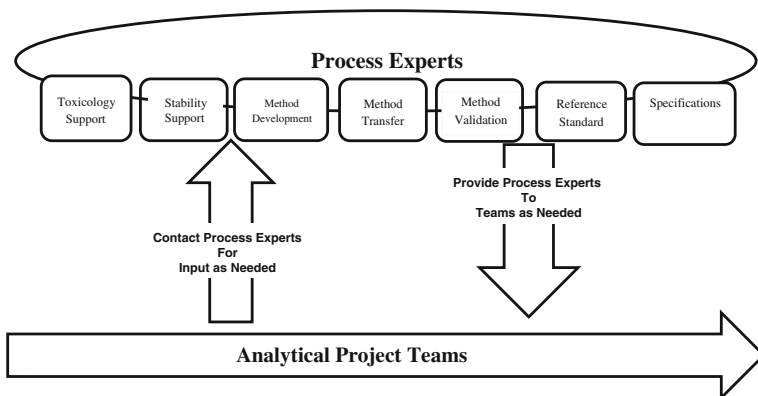
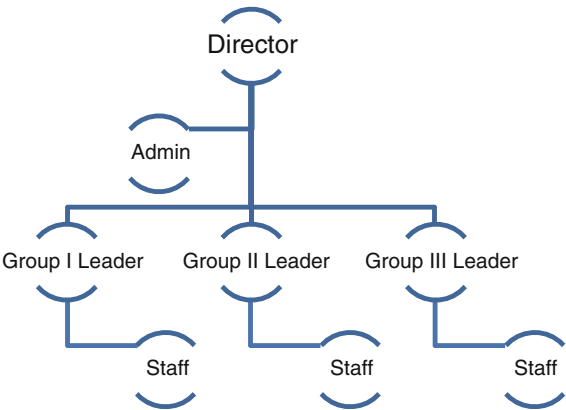


Fig. 2.2 The process experts interaction with the project teams

Fig. 2.3 Classical organizational chart



2.2 Project Teams

2.2.1 Project Team Development and Management

The processes for the development and management of project teams is illustrated in the following Figs. 2.4, 2.5, 2.6, 2.7, 2.8, 2.9.

The strategy document is a detailed description of the project goals and the approach the team will take to achieve these goals. The elements of the strategy document should contain some of the following items:

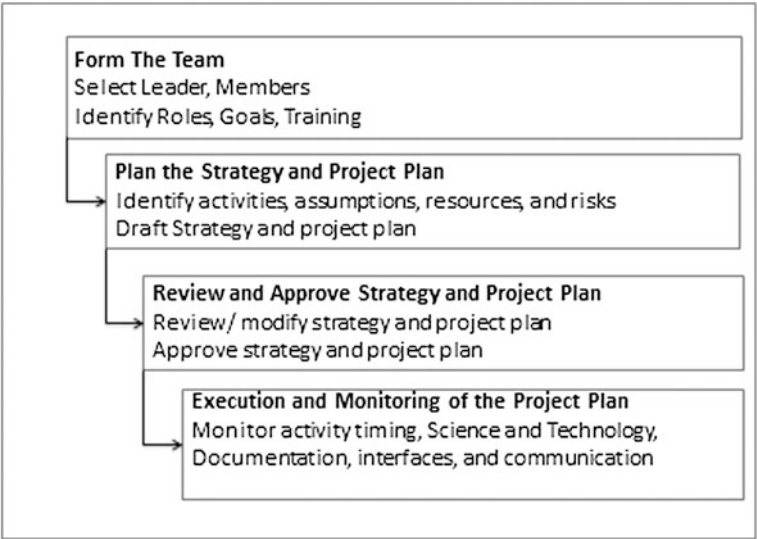


Fig. 2.4 Analytical project teams process outline

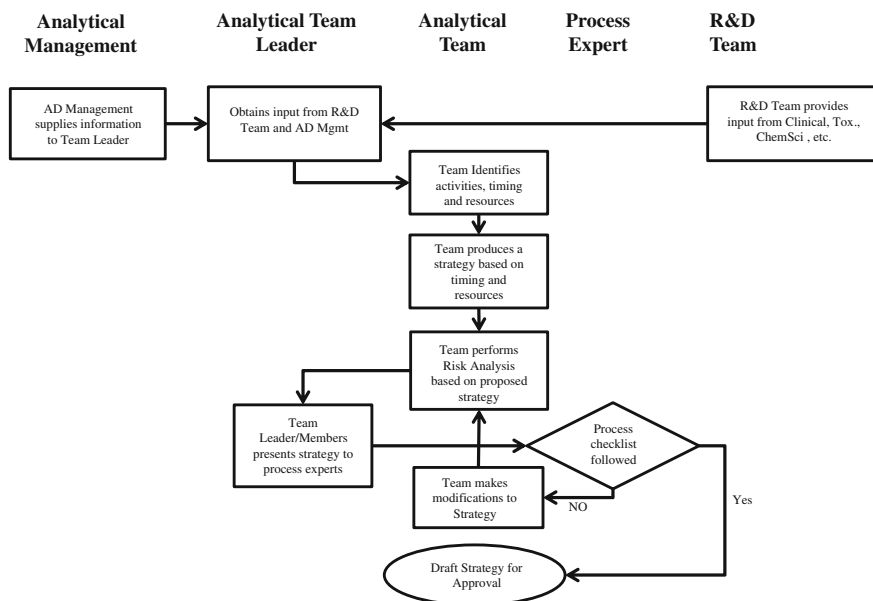


Fig. 2.5 Project strategy development process

1. Summary of the R&D project goals (IND, NDA timing etc.)
2. Chemistry manufacturing schedule
3. Potential/Expected chemistry issues (e.g. solid state, toxic imp)
4. Stability plan (chemical and dosage form)
5. Dosage Form Development (multiple dosage forms)
6. Dosage form manufacturing schedule
7. Additional studies (BA/BE, Tox., etc.)
8. Outsourcing considerations
9. Technology Transfers
10. Specifications setting schedule
11. Resource allocations.

A detailed checklist is available in Appendix I and should be utilized when developing project strategies and plans. An example of a strategy Document is shown in Appendix II.

The low risk plan is a conservative estimation of the plan elements such as, activities, timing, resources, and cost without taking into consideration any of the project goals. This plan is then compared to a plan which is required to meet the project goals and a risk evaluation analysis is performed. The plan is modified until an acceptable balance between risk and project goals is reached. The comparative risk analysis evaluation process will be described later in the chapter.

Once the project plan is approved, it is the responsibility of the team to execute the plan. The process for the execution of the plan is described in Fig. 2.9.

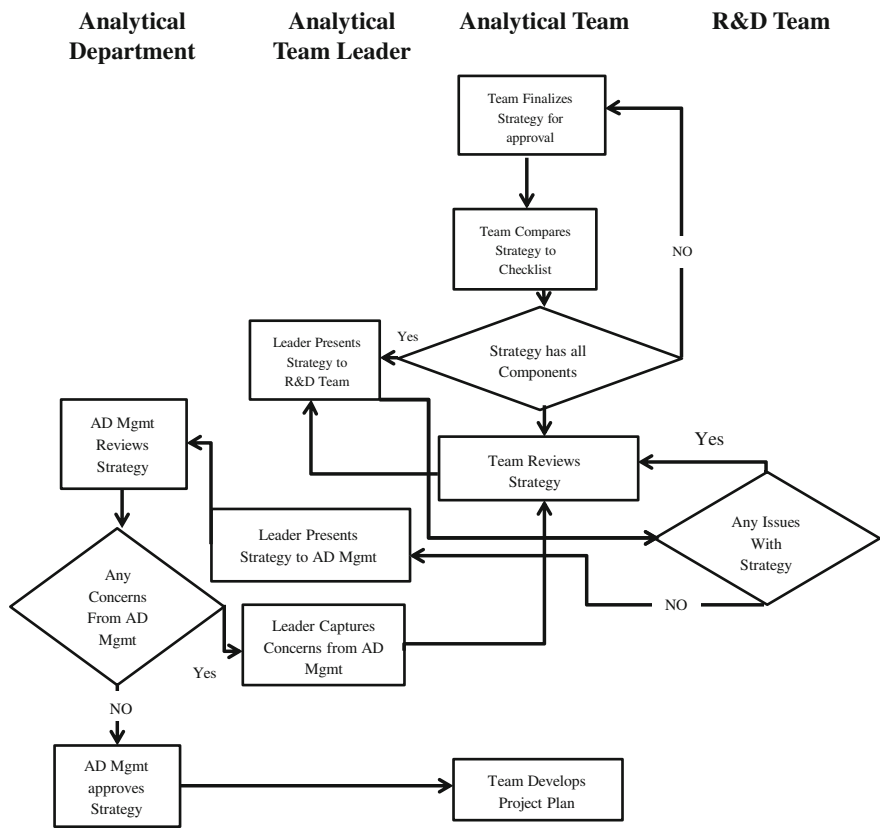


Fig. 2.6 Project strategy approval process

An important part of the execution of the plan is the monitoring of the plan. The monitoring should include items such as: key activities, target start and, actual start and completions dates, deviations from the plan, and reason for any deviations. It is important to capture whether deviations are data driven or due to lack of the team’s performance. Table 2.1 illustrates the monitoring of the plan.

2.2.2 Risk Evaluation

The comparative Risk Evaluation Analysis utilizes weighted activities for each stage of development and a rate factor, which is the probability for the successful completion of the activity in the given time frame. The product of the weighted activity and the rate factor results in a Total Risk Value (X). The Total Risk Value (X) absolute value is of no significance, it is the comparative Risk Value (%R_c) that is

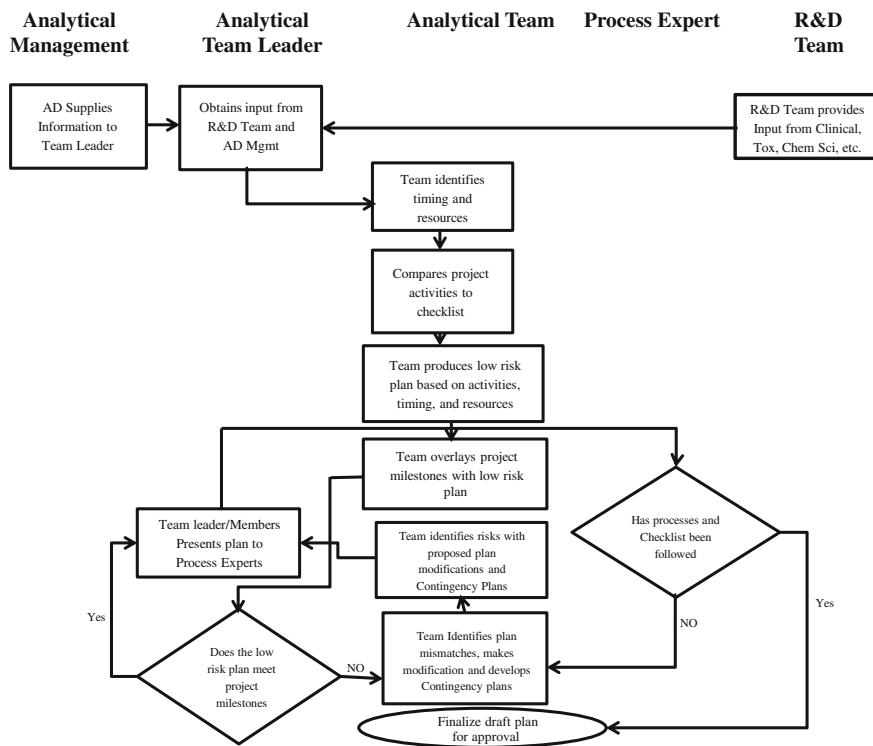


Fig. 2.7 Project plan development process

utilized to evaluate the acceptability of the new plan over the current plan. A detailed description of the Project Risk Assessment process is found in Appendix III.

2.2.3 Project Team Dynamics

There are several team dynamics which should be followed for a team to become a fully functional team [1]. They are:

1. Roles and responsibilities of the team leader and members
2. Utilization of a brainstorming process
3. Rounds of Reasoning
4. Clarifying Questions
5. Highest Level of Authority (HLA)
6. Modes of decision making
7. Use of Consensus
8. Scribe
9. Facilitation
10. Governance.

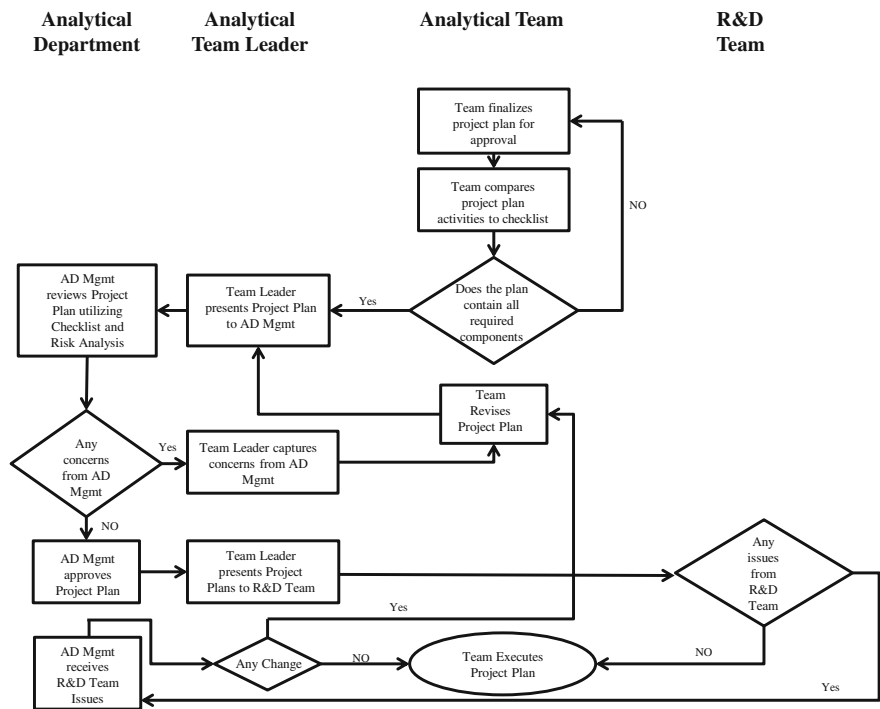


Fig. 2.8 Project plan approval process

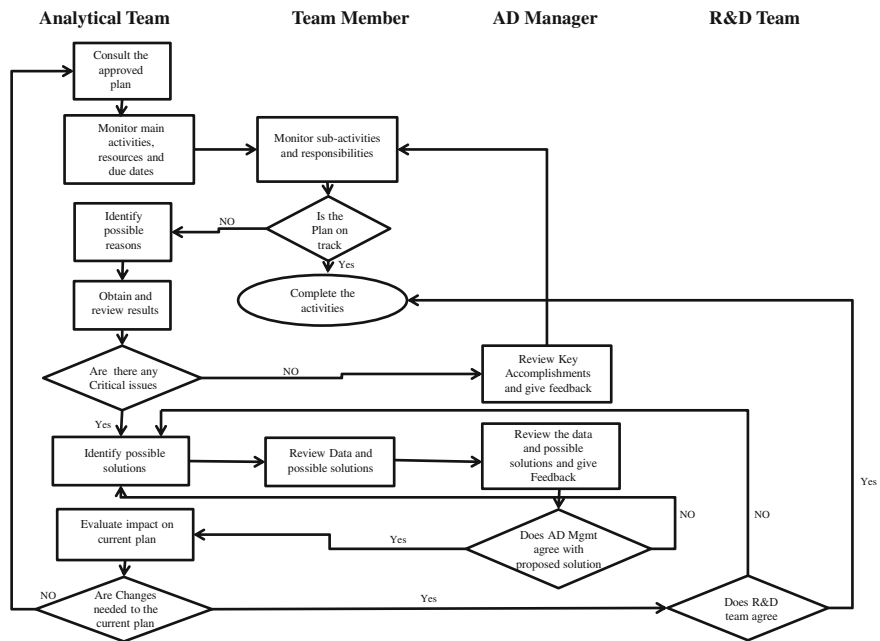


Fig. 2.9 Execution of the plan

2.2.3.1 The Teams Leader Role is as Follows

1. Act as the leader and a communication link with management
2. Set the agenda for each meeting
3. Manages the time resource for each agenda Item
4. Responsible for the minutes for each meeting
5. Is also a member of team as a technical expert in a discipline(s)
6. Is the facilitator of the project review meetings.

2.2.3.2 The Team Member Role is as Follows

1. Is the team technical expert in a discipline(s)
2. Is also an active contributor to the team outside of their expertise
3. May be required to lead sub-teams
4. Will make presentations at the project review meetings
5. Will contribute to consensus or voting decisions
6. Is an effective communicator (written and oral).

2.2.3.3 Brainstorming Process

The Brainstorming process allows each team member to contribute by making suggestions on activities, issues, solutions etc. in an orderly fashion. The process involves going around the table allow each team member to give their suggestions. There is no counter arguments allowed from other team members, only clarifying questions could be asked. The Scribe will capture all of the suggestions on flip charts. After several rounds and there appears to be no further suggestions the team leader will end the brainstorming session and move on to a Rounds of Reasoning.

2.2.3.4 Rounds of Reasoning

Round of Reasoning is a process where each team member is allowed to challenge or support any of the suggestion captured during the brainstorming session. After several rounds a final list of suggestions is comprised and each team member is given 5 votes which they can place next to the suggestions they support. After all the votes are placed the top 5 selected suggestions are chosen and are worked by the team to obtain a final result.

2.2.3.5 Clarifying Question

These are questions which are directed towards asking for a better understanding of the issue. Clarifying questions should not be used to pass judgment or disagreement with the issue.

2.2.3.6 Highest Level of Authority

The HLA is generally part of the management team such as; Director, Associate Director, Section Head, etc.

2.2.3.7 Modes of Decision Making

There are four modes of decision:

1. A decision comes from the HLA and the team implements the decision, there is no discussion or feedback from the team.
2. A decision comes from the HLA and the feedback is requested from the team. The HLA makes the decision without addressing the feedback given by the team.
3. A decision comes from the HLA, there is discussion between the HLA and the team however, the HLA makes the final decision.
4. The HLA gives the team complete empowerment to make the decision and the HLA accepts the decision made by the team.

2.2.3.8 Use of Consensus

The consensus process requires 100 % agreement among the team members; it is not a majority rule scenario like taking a vote. Consensus can still be reached even though members of the team may not fully agree with the decision, but are will to support the team decision. Consensus is generally better than a voting process because you have the agreement that all team members are willing to support the team decision.

2.2.3.9 Scribe

The scribe role is to capture important information on to Flip charts, so the information can be placed into minutes or reports. The flip charts are generally kept as the original reference until the activity is finalized. The scribe role is usually shared among the team member based on a schedule. The scribe is still part of the team and should contribute as a team member while acting as the scribe.

2.2.3.10 Facilitation

The facilitator role is as an overseer of the team process and to help the team to stay on track by making them adhere to the process. The facilitator is not a team member and does not contribute to the agenda. The facilitator has expertise on all team dynamics and total quality management processes.

2.2.3.11 Governance [2]

Governance is the review of the project by the function management. The AD management and the analytical team make a presentation at the function project team meeting. The function management responds to the presentation with questions and concerns, AD management captures the concerns and any unanswered questions and instructs the analytical team to evaluate them against the current team project plans. If revisions to the project plans are required, the analytical team will make the necessary revisions and obtain approval from AD management. The analytical team will then schedule another meeting with the function management. If no revisions to the project plans are required the AD management will prepare a cover letter summarizing the meeting conclusions and attaches it to the finalized presentation which is submitted to the function management.

2.3 Responsibilities

The analytical department responsibilities range from supporting discovery activities, through phase's 1.2, 3 and product registration. These responsibilities are described in the timeline indicated in Fig. 2.10 [3].

2.4 Interactions [3]

The analytical department is a major contributor to a majority of functions within a Pharmaceutical Company. Its contribution is mainly in the form of data that it generates and the technology it developments and validates. Much of the conclusions made for the development of the active pharmaceutical ingredient (API) and the drug product are based on the data generated from the analytical department. The API characterization and justification for the choice of the drug formulation are based on the analytical data from methods which were demonstrated that they are appropriate for their intended use through detailed validation. Specification setting is another major responsibility of the analytical department. A detailed Specification process should be utilized, which will be discussed in a

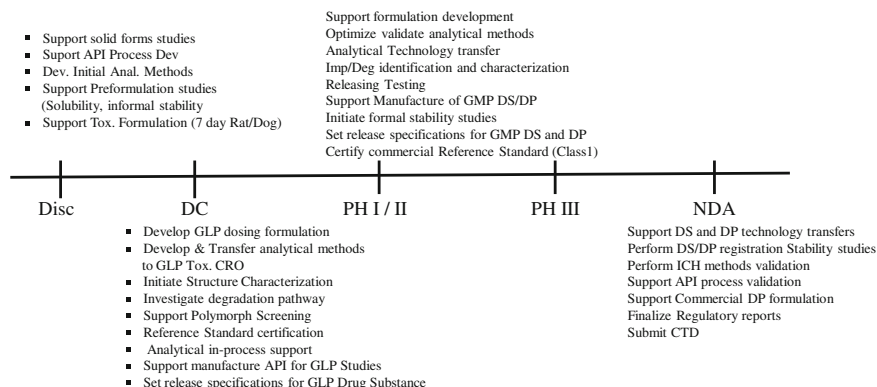


Fig. 2.10 Analytical responsibilities

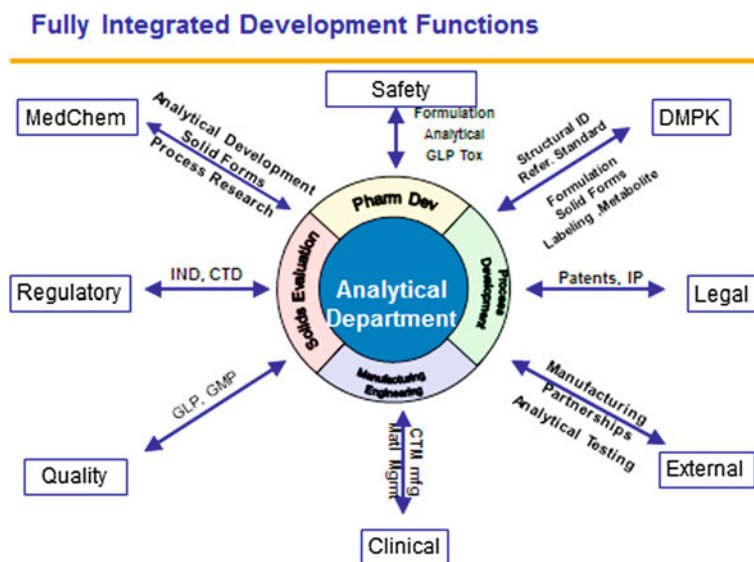


Fig. 2.11 Analytical department interactions

later chapter. Figure 2.11 is a diagram of the interactions of an analytical department within a typical pharmaceutical company.

Other Activities, within the department, which are essential to maintain staff interactions and a free flow of information, are the Staff and Project review meetings. Staff meetings are generally held bimonthly, they are generally administrative in content, an example of a typical staff meeting agenda is shown below Table 2.2.

Table 2.2 Staff meeting agenda

#	Agenda Item	Type	Individual	Minutes
1	Safety			
1.1	Lab inspection	Update	NG	10
2	GMP and laboratory operation			
2.1	GMP compliance, lab operation issues, expired chemicals	Discussion	TC	15
3	Departmental operation			
3.1	Update for board visit	Discussion	ZG	5
4	Instrument and capital			
4.1	2008–2009 capital budget items	Discussion	All	10
5	Vacations and department leave			
5.1		Update	TC	5
6	General off site meetings			
6.1		Update	TC	5
6.2		Discussion	All	10

Table 2.3 Project plan

Item no.	Activity	Start date	Finish date	Total time (days)	Resources	Precursor links
1	Develop method	1/2/12	1/16/12	10	A	
2	Qualify method	1/17/12	1/1/20/12	3	A	
3	Validate method	1/21/12	1/26/12	5	A	1, 2
4	Documentation	1/20/12	2/4/12	15	0.4A, B	3
5	Method transfer	2/5/12	2/25/12	20	A, B	4
6	Release testing	2/26/12	3/6/12	10	A, 0.5B	4
7	Report of analysis	3/7/12	3/10/12	3	0.6 A	6

Project review meeting are generally held monthly and are very technical in nature. There is usually are detailed project plan and the team responds to the progress of each activity, resource issues that need to be addressed, technical difficulties, inclusion and exclusion of items within the plan, and the current risk assessment for the project success. There are several computer software programs available on the market which can support very sophisticated project plans. An example of a typical basic project plan is shown in Table 2.3.

Where each resource is identified by a letter A, B, C, etc. and the fraction before each letter represents the fraction of that resource being utilized for that activity. The precursor links represent which activities are dependent on each other and changes in one impact the other.

2.5 Operating Guidance's

Among the most basic essentials, and a requirement, in any successful GMP Analytical Chemistry Department is the establishment of Standard Operation Procedures (SOP's) and working Guidelines. This is the most efficient way to communicate best practices within the group and establish minimum standard requirements which must be met. It is a requirement and a good practice that personnel are trained on these SOP's and guidance's annually or when changes are made. In addition it is a good practice that analytical personnel are made familiar with the contents of regulatory documents in general, such as the CMC, so that it allows the staff to understand the need for the attention to detail and the stringent documentation requirements placed on them. Owing to the changed scenario in the pharmaceutical manufacturing and control procedures, coupled with the risk based approach to pharmaceutical GMPs adopted by US FDA, it essential for the analytical department SOP's and Guidelines are kept current and meet the same quality standards. The SOP's are given classifications such as, Laboratory Operations, Department Policies, and Management Control. Examples of SOP's under each classification are given below.

2.5.1 *SOP's and Guidelines*

2.5.1.1 Laboratory Operations

- Automated Instrument Implementation and Use
- Rounding Rules
- Decimal Place Reporting for Analytical Data
- Criteria for Identification and Qualification of Impurities
- Qualification of Chromatographic Peaks from Stability Samples as Degradation Product
- Replicate and Composite Size Determination for Dosage Form Assays
- Criteria for Identification and Qualification of Impurities
- Reporting Impurities, Including Degradation Products
- Forced Degradation Studies for Method Development
- Excipient/Raw Material Control/Acceptance Testing
- Analytical Data Review Process
- Equipment Calibration and Maintenance.

2.5.1.2 Department Policies

- Notebook/Data Handling/Creation and Use of Work Sheets
- Analysis Request/Sample Handling/Reports of analysis
- Analytical Method Development

- Analytical Method Document
- Method Validation Packages/Reports
- Performance Characteristics of Method Validation
- System Suitability for Chromatographic Methods
- Retention Sample Policy
- Laboratory Investigation of uncharacteristic analytical results
- Records Retention
- Reference Standard Certification.

2.5.1.3 Management Control

- Specifications Development
- Documents for Submission to Regulatory Agencies
- Method Transfer Process
- Analytical Support of GLP Studies
- Personnel Training and Certification program.

SOP's are written to allow for a clear understanding of the intended procedure but to an extent of detail which will allow for minor variations without being considered non-conformant. However on the other hand Guidelines are considered to be documents associated with the SOP's but the procedure is described in much more detail and allowing for little flexibility without justification. All SOP's and guidelines should be written following a standardized format (template). An example of a template is shown in Fig. 2.12.

2.5.2 Regulatory Guidance's

The history of medicinal product registration, in much of the industrialized world, has followed a similar pattern which could be described as: *Realization, Rationalization and Harmonization*.

- The Realization
 - It was important to have an independent evaluation of medicinal products before they are allowed on the market,
 - In the United States—1930s,
 - In Japan—1950s,
 - In Europe—1960s.
- Rationalization
 - Although different regulatory systems were based on the same fundamental obligations to evaluate the quality, safety and efficacy, it required duplication of many time-consuming and expensive test procedures, in order to market new products, internationally.

<i>Company</i>	Standard Operating Procedure	Document No.	Rev. 1
<i>Name</i>			
Standard Operating Procedures, Title		Effective Date:	

1.Purpose – define the intent of the document.

2.Scope – describe the range of systems or processes the document covers. It may also describe any exceptions.

3.Responsibilities – list the responsibilities of the individuals or departments.

3.1

4.References

4.1 List any government governance document which supports the procedure.

4.2 List any guidance or trade document which supports the procedure, such as ICH, USP/EP, etc.

4.3 List any internal document which supports the procedure.

5.Attachments

5.1 List any attachments at the end of the document

5.2 List any forms associated with the document

6.Definitions – define any acronyms and/or verbiage which may not be understood by those who train on the document.

7.Equipment and Material – list all equipment and material needed to follow the procedure. Be as specific as needed to comply.

8.Procedure – General and specific instructions are written in a chronological order.

9.Revision History- The revision history lists the Document control number, revision number, effective date, description of changes, and the initials of the initiator.

9.1 Reference to another document is **not** an acceptable description of change. The description of change needs to be as concise and complete as reasonably possible.

9.2 Do not delete any of the sections from the template. If any of the above Sections are not required, mark as N/A under section heading.

DCR #	Revision	Effective Date	Description of Change	Initiator Initials
	1		Initial Release	

Fig. 2.12 Standard operating procedure template

- Harmonization

- Harmonization was implemented due to concerns over rising costs of health care and the need to meet the public expectation that there should be a minimum delay in having safe and efficacious new medications available to patients in need.

There are guidance's that should be followed when generating data, and writing justifications, protocols and reports. If not followed, a very strong justification must be submitted to the agency along with comparative data or logic.

- GLP's—21CFR part 58 [4]
 - Governs the conducting of nonclinical laboratory studies that support or are intended to support applications for products regulated by the Food and Drug Administration. Compliance with this regulation is intended to assure the quality and integrity of the safety data.
There are several subparts that control all aspects of the studies performed.
 - Personnel,
 - Facilities (testing and operation),
 - Control Articles,
 - Protocols,
 - Records and Reports.
- GMP's—21CFR part 210 and part 211 [5]
 - The regulations in the parts of these chapters contain the minimum current good manufacturing practice and controls used for:
 - Facilities,
 - Manufacture processing,
 - Packaging,
 - Storage,
 - Distribution.
 - Drug substance and product to meet the requirements for:
 - Safety
 - Identity
 - Strength
 - Purity
 - The failure to comply with any regulations above shall render the drug substance and/or drug product to be non-compliant as well as the person who is responsible for the failure to comply; both could be subject to regulatory action.
- International Conference on Harmonization (ICH) [6]

They consist of Guidelines Q1 to Q10. The ICH Guidelines are complimentary to The GLP's and GMP's; they describe in more detail the activities to be performed and the criteria to be achieved such as

 - Stability (Thermal and Photo)
 - Bracketing and Matrixing designs for stability testing
 - Evaluation of stability data
 - Stability data for Climate Zones III and IV

- Validation of Analytical procedures
 - Attributes
 - Criteria
- Specifications
 - Critical Attributes
 - Justification
- Impurities
 - Control new drug substance and product impurities
 - Definitions (Qualified, Specified, Unspecified)
 - Residual solvents

Class 1, Class 2, Class 3

- Good Manufacturing Practice
 - Quality management
 - Personnel
 - Building and facilities
 - Material Management
 - Laboratory Controls
 - Process Validation Program
 - Cleaning Validation Program
 - Microbiological attributes
- Pharmaceutical Development
 - Components of the Drug Product
 - Manufacturing Process Development
 - Container Closure System
 - Compatibility
- Quality Risk Management
 - Scientifically Based
 - Based on level of risk

The regulatory guidance that the **GMP Analytical Chemistry Department** plays a significant role is the submission of the **Chemistry, Manufacturing and Controls (CMC)**. The Chemistry, Manufacturing and Controls (CMC) is a compilation of information, data, justifications and reports required to adequately characterize drug substance and drug product for acceptance by global regulatory agencies for approval to be commercially available to the public. The generation of information, data, justifications and reports can begin at the discovery stage and continue throughout development process.

The following Fig. 2.13 is an example of the contents for a typical CMC submission.

Table of Contents

3.2.S Drug Substance

- ◆ 3.2.S.1 General Information
 - 3.2.S.1.1 Nomenclature
 - 3.2.S.1.2 Structure
 - 3.2.S.1.3 General Properties
- ◆ 3.2.S.2 Manufacture
- ◆ 3.2.S.3 Characterization
- ◆ 3.2.S.4 Control of Drug Substance
- ◆ 3.2.S.5 Reference Standards or Materials
- ◆ 3.2.S.6 Container Closure System
- ◆ 3.2.S.7 Stability

3.2.P Drug Product

- ◆ 3.2.P.1 Description and Composition of the Drug Product
- ◆ 3.2.P.2 Pharmaceutical Development
- ◆ 3.2.P.3 Manufacture
- ◆ 3.2.P.4 Control of Excipients
- ◆ 3.2.P.5 Control of Drug Product
- ◆ 3.2.P.6 Reference Standards or Materials
- ◆ 3.2.P.7 Container Closure System
- ◆ 3.2.P.8 Stability
- ◆ 3.2.A Appendices

Fig. 2.13 Contents for CMC

The Analytical Department supplies data and technology to the CMC from three major areas.

- Process Chemistry
- Solid Forms
- Pharmaceuticals and Formulation Development.

The support to Process Chemistry involves preforming release testing, impurity identification and characterization, stability and reference standard certification. The support also involves in-process monitoring by the use of Process Analytical

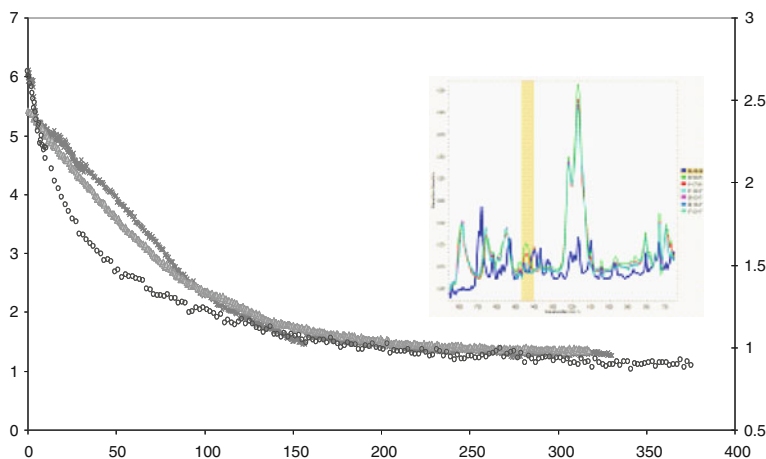


Fig. 2.14 Reaction monitoring

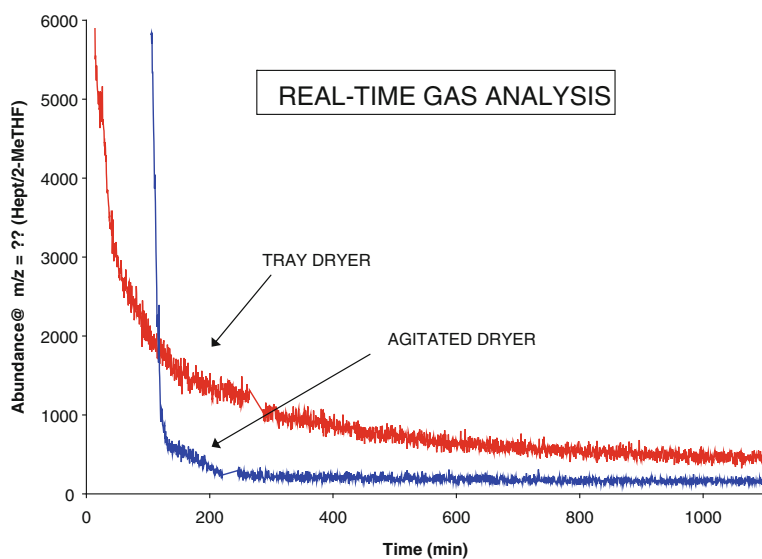


Fig. 2.15 Drying profiles

Technology (PAT). PAT utilizes in line instrumentation to monitor the process in real time and determine the critical process parameters. Examples of in-process support utilizing PAT technology is shown in Figs. 2.14, 2.15, 2.16, 2.17.

The support to solid forms involves the following activities:

1. Crystal and Polymorph Screening
2. Solid State characterization

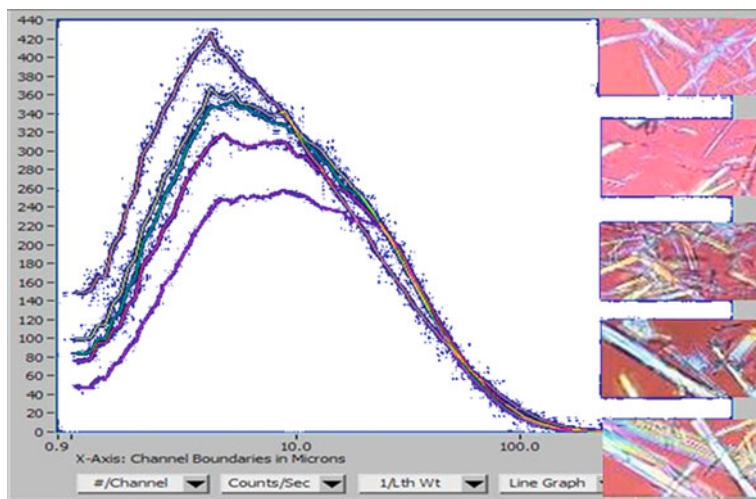


Fig. 2.16 Particle size control

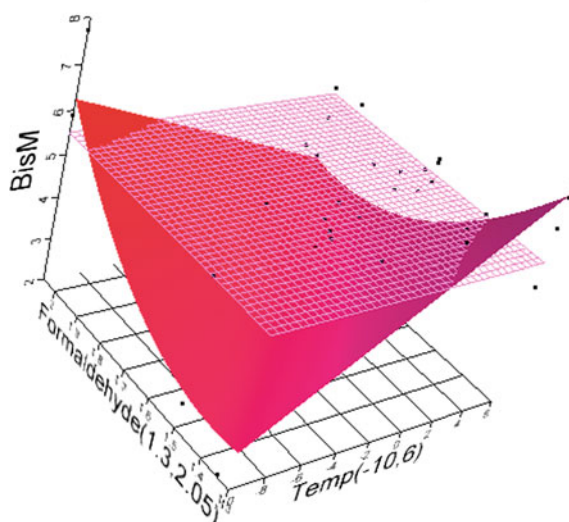


Fig. 2.17 Determination of critical process parameters

3. New Salt selection
4. Generation of intellectual Property.

The support to Pharmaceuticals and Formulation Development is described below:

- Pharmaceuticals
 - Solubility
 - Aqueous
 - pH Dependence
 - Organic
 - Stability
 - Solid State
 - Solution
 - pH Aqueous
 - Intrinsic Dissolution
 - Purity
 - Impurity/Degradation profile
 - Physical characterization
 - Bulk solid properties
- Formulation Development
 - Evaluate Chemical and Aqueous Stability
 - Evaluate Excipient Compatibility
 - Consider Dosage Forms
 - Powder in a Capsule
 - Powder in a Bottle
 - Blended Formulation
 - Evaluate Form Change Issues
 - Consider Wet Granulation process
 - Evaluate Stability in Lipids/Solubility Enhancing Agents
 - Consider Liquid/Semi Solid filled Capsules
 - Consider Amorphous Solid Dispersions
 - Consider Micronized Nano-Crystal Technology.

References

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2. Joiner B (1997) 4th generation management. Rosemount Horizon
3. Pharmaceutical Manufacturers Association (1998) Pharmaceutical management development seminar, Columbia University, Arden House, Harriman, NY
4. GLP's, 21CFR part 58
5. GMP's, 21CFR part 210 and part 211
6. ICH Guidelines, Q1 to Q10



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Department

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