Documentation in pilot plant scale up

1. Scope and boundary limit description
2. Process flow diagram and general arrangements drawing
3. Cost estimate
4. Basic piping and instrumentation diagrams
5. Estimated project timelines
6. Equipment, instrumentation and value list
7. Technical peer review
8. Process simulation

Scope and boundary limit description

- The documentation of a project's scope is called a scope statement, explains the boundaries of the project, establishes responsibilities for each team member and sets up procedure for how completed work will be verified and approved.
- During the project, this documentation helps the project team remains focused and on task.
- The scope statement also provides the team with guidelines for making decisions about change request during the project.
- The boundaries are defined as measureable and audible characteristic and closely linked to project objectives.
- The boundaries of a project are the reasonable limits of project work to determine what is included in the project and what's not.
- They create a holistic project perception, determine limits and exclusion of the project and form the content of project scope in terms of expected results.

Process flow diagram and general arrangement drawings

Process flow diagram is a simplified sketch that uses symbols to identify instruments and vessels and to describe the primary flow path through a unit.

It illustrates the general plant streams major equipments and key control loops.

Benefits of process flow diagram

- The process flow chart providing a visual representation of industrial process equipment is interconnected by a system of pipeline. It has following six benefits
- Gives everyone a clear understanding of the process
- Shows the plant design basis indicating feedstock, product and main stream flow rates and operating condition.
- Help to identify the scope of the process.

- Facilitate teamwork and communication.
- Shows graphically the arrangement of major equipment, process lines and main control loop.
- Improve utilities which are used continuously in the process.
- Technical peer review
- Process simulation

Cost estimate

Process system typically has two types of cost

1. Required to design and built the process.
2. Operating cost which includes everything needed to run the plant on location. Such as raw materials, electricity, water and man power are all examples of typical operating cost.

Pilot plant cost factors

- Application complexity
- Process condition
- Flammables
- Instrumentation
- Flow rate
- Number of pieces of equipment
- Major equipment types
- Materials of construction
- Available utilities
- Site readiness

Basic piping and instrumentation diagram

A piping and instrumentation diagram shows the piping and related components of a physical process flow.

Function and purpose of P & IDs

1. P & IDs are foundation t he maintenance and modification of the process that it graphically represents.
2. At the design stage, the diagram also provides the basis for the development of system control schemes, like hazard and operability study.

Processing facilities is a graphic representation of

- Key piping and instruments details
- Control and shut down schemes
- Safety and regulatory requirements
- Basic startup and operational information

Estimated project timelines

A project timelines give teams an understanding of a project at just a glance, keeping everyone informed and aligned at every stage of project.
The timeline is composed of a series of tasks, each of which has a due date and duration.
The link between these tasks can also be created, helping to reveal dependencies and preempt any potential blockers.
A successful project timeline helps to maintain a productive and engaged team who work together toward a common goal to seize success.
A poor timeline on the other hand, can lead to confusion deadlines, wasted cost and unhappy client.

Equipment instrumentation and value list
Identify clearly the instrumentation in pilot plant they are:

- Differential pressure transmitters
- Vortex formation
- Magnetic flowmeter
- Pressure regulator
- Pressure indicator
- Rotameters
- Stream traps
- Pressure relief values and rupture disks

Technical peer review
Technical peer reviews are a well defined review process for finding and fixing defects.
A technical peer review may also be called an engineering peer review, a product peer review, a peer review inspection or an inspection.
The following peer review work aids are available

- Inspection summary report
- Issue log
- Inspection moderator's checklist
- Inspection lesson learned questionnaire
- Defect checklist for several types of software work products.

Process simulation

- Process simulation is a model based representation of chemical, physical, biological and other technical processes and unit operation is software.
- The goal of a process simulation is to find optimal condition for a process.
- This is essentially an optimization problem which has to be solved in an iterative process.

SCALE UP AND POST APPROVAL CHANGES

- In the process of developing new drug product the batch size used in the earliest human studies.
- The size of the batches is gradually increased (scale-up).
- Approval is taken for particular formulation.

How can we update or change the information in approved application?

Types of change

- Vendor change process
- Component or composition changes
- Source and specification for raw material
- Equipment requires repair, servicing or replacement
- Manufacturing location are changed
- Batch sizes are increased or decreased
- Advancement in technology made that dictates changes to the operation.

These changes are called post approval changes because they effect applications that have already been approved.

SUPAC guidance defines

- Level of change
- Recommended chemistry, manufacturing and control test for each level of change.
- In vitro evaluation test / or in vivo bioequivalence test for each level of change
- Documentation that should support the change.

Level of change

Level of change may impact on formulation quality and performance.

Level 1

Those changes that is unlikely to have any detectable impact on formulation quality and performance.

Level 2

Changes are those that could have significant impact on formulation quality and performance.

Level 3

Changes are likely to have a significant impact on formulation quality and performance.

A) The components or composition changes:

. This section focuses on changes in excipients in the drug product.

. SUPAC-MR - Excipient critical or non-critical to the Modified drug release.

Changes in non-release and release controlling excipients.

. SUPAC-SS - Changes in preservative in semisolid formulations.

. SUPAC-IR Changes for immediate-release solid oral dosage forms.

B) The site changes of manufacture:

- Changes in location of the site of manufacture, packaging operations and/or analytical testing
- laboratory.
- Do not include any scale-up changes, changes in manufacturing (including process and/or equipment), or changes in components or composition.
- Current Good Manufacturing Practice (CGMP) inspection.

Level I Changes -

Classification-Single facility where the same equipment, standard operating procedures (SOP's), environmental conditions (e.g., Temperature and humidity) and controls, and personnel common.
Test Documentation - Application/ compendia requirements in chemistry, dissolution and in vivoBioequivalence - None.
Filing Documentation- Annual report.

Level II Changes -

Classification–Same continuous campus, Common personnel, No other changes.

Test Documentation–

- Application/ compendial requirements
- Notification of Location of newsite
- Updated batch records

SUPAC – MR - Multi-point dissolution profiles(15,30,45,60 and 120 min)USP buffer media at pH 4.5-7.5 forextended release). Three differentMedia (e.g., Water, 0.1N HCl, andUSP buffer media at pH 4.5 and 6.8for delayed release)until 80% ofDrug Released.
Filing Documentation- Annual report.

Level III Changes -

Classification– Different campus, Different personnel.
Test Documentation –

- Application/compendial requirements.
- Notification of Location of new site.
- Updated batch record.
- SUPAC - IR: Multi-point dissolution profile in the application/compendial medium.
- SUPAC - MR: Multi-point dissolution profiles (15, 30, 45, 60 and 120 min) USP buffer media at pH 4.5-7.5 for extended release). Three different Media (e.g., Water, 0.1N HCl, and
- USP buffer media at pH 4.5 and 6.8 for delayed release) until 80 % of Drug Released.
- Filing Documentation- Annual report prior approval of supplement.

C) Changes in Batch Size (Scale-Up/Scale-Down):

Post-approval changes in the size of a batch from the pivotal/pilot scale bio batch material to larger or smaller production batches call for submission of additional information in the application.
. Scale-down below 100,000 dosage units is not covered by this guidance.

Level I Changes -

- Classification- Change in batch size, up to and including a factor of 10 times the size of the
- pilot/biobatch.
- Test Documentation – Updated batch records application/compendial requirements stability.
- Filing Documentation- Annual report (long term stability data).

Level II Changes -

Classification- Changes in batch size beyond a factor of ten times the size of the pilot or biobatch,
No other changes.
Test Documentation –

- Chemistry Documentation Application/ compendial release requirements.
- Notification of change and submission of updated batch records.
- Stability testing: One batch with three months accelerated stability data and one batch on long-term stability.
- Dissolution Documentation-Case B testing.
- In Vivo Bioequivalence - None.
- Filing Documentation- Changes being effected supplement; annual report (long-term stability data).

D) Manufacturing Changes:

Manufacturing changes may affect both equipment used in the manufacturing process and the process itself.

i)Equipment -

Level I Changes:

Classification- Alternate equipment of the same design and principles as automated equipment.
Test Documentation – Updated batch records, Application/compendial requirements and stability.

Filing Documentation- Prior approval supplement with justification for change; annual report (long-term stability data).

Level II Changes:

Classification- Change to equipment of different design and principle.
Test Documentation – Updated batch records, Application/compendial requirements and stability.
SUPAC – IR - Multi-point dissolution profiles in multiple media.
SUPAC – MR - Multi-point dissolution profiles in multiple media.
Filing Documentation- Annual report and changes being Effected Supplement.

ii)Process -

Level I Changes:
Classification- Alternate equipment of the same design and principles as automated equipment.
Test Documentation – Updated batch records, Application/compendial requirements and stability.
Filing Documentation- Annual report.

Level II Changes:

Classification- This category includes process changes including changes such as mixing times and operating speeds outside of application/ validation ranges.
Test Documentation – Updated batch records, Application/compendial requirements and stability.
SUPAC - IR - Multi-point dissolution profile.
SUPAC- MR - Multi-point dissolution profiles in multiple media.
SUPAC – SS - In vitro release test Documentation.
Filing Documentation- Changes being effected supplement; annual report (long term stability data).

Level III Changes:

- Classification- Changes in the type of process used (e.g. wet granulation to direct compression).
- Test Documentation – Updated batch records, Application/compendial requirements, stability, bio-study and IVIVC.
- SUPAC - IR - Multi-point dissolution profile.
- SUPAC- MR - Multi-point dissolution profiles in multiple media.
- Filing Documentation- Prior approval supplement with justification; annual report (long-term stability data).

PLATFORM TECHNOLOGY

A platform is a group of technologies that are based upon which other application, processes or technologies are developed.
A common or standard method, equipment, procedure or work practice that may be applied to the research, development or manufacture of different product.

Platform manufacturing: implementation of standard technologies, system and work practices within manufacturing facilities and their use for manufacturing of different products.

Platform technology approaches and their application

The pharmaceutical industry is continuously increase the efficiency of process development in order to move promising products faster and most cost effectively into clinical studies.
A major intent of approach is to prevent process development and clinical material manufacture becoming bottlenecks in overall clinical development of new products.

Benefits of platform process

- ❖ Reduction of process development effort, time and cost.

- Prior platform data inform risk assessment on new process weak points, and focus development efforts where most needed.
- Consistency in process performance and product quality.
- Simplification in technology transfer activities to production facilities.
- Improved asset utilization: one facility/same equipment for multiple product.
- Document preparation can be simplified e.g.