BIOTECHNOLOGY

GMP requirements for APIs manufactured by cell culture / fermentation

The GMP gradient during development and clinical trials

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Agenda

1. Regulatory Background
2. Phases of Product Development
3. The “GMP Gradient”
4. “Good Project Management” Considerations
5. Milestones and “Milestone Deliverables”

Regulatory Background

GMP regulations apply for all clinical trial material, but during clinical trials the *immediate* regulatory risks of noncompliance to GMP are minimal:

the authorities rarely inspect manufacturers of clinical supplies

but for example:

FDA Compliance Policy Guide 7346.832 / Pre-Approval Inspections:

„Conduct an in depth review of the data, including research and development data...“

Regulatory Background

☛ Therefore **GMP deficiencies in clinical batches**

and failure to document sufficient

information to justify process

decisions are ***„time bombs“***

exploding usually during pre-approval

inspections and leading to delayed approvals

Phases of Product Development

	main activities	GMP re-quirement	amou nt of prod.	time (years)	Cost $
pre-clinical	• **fermentation/purification/analytical methods development** • **functional genomics** • **animal metabolism studies** • **animal toxicology**	none, but need to demonstrate equivalence to later GMP material, GLP required	mg	2-4	varies
phase I	• **Production process implementation / validation of safety-relevant parameters** • **formulation** • **characterization, stability** • **human toxicology**	apply, "GMP - gradient"	g	ca. 1	100.000 - 1 Million

Phases of Product Development

	main activities	GMP re-quirement	amou nt of prod	time (years)	Cost $
phase II	• **Production process optimization and scale-up** • **formulation** • **characterization, stability, validation** • **human toxicology and metabolism studies**	apply, "GMP - gradient"	g	1-2	10 - 100 Mill.
phase III	• **Production process scale-up to commercial size** • **formulation, stability, validation** • **safety and efficacy verification** • **preparation of dossier**	apply	kg	2-4	10 - 500 Mill.
phase IV	• **new indications** • **new formulations; bioequivalency studies** • **continuing quality assurance/control**	apply	kg		

Step-wise Approach to Application of Regulatory Requirements *(GMP-Gradient")*

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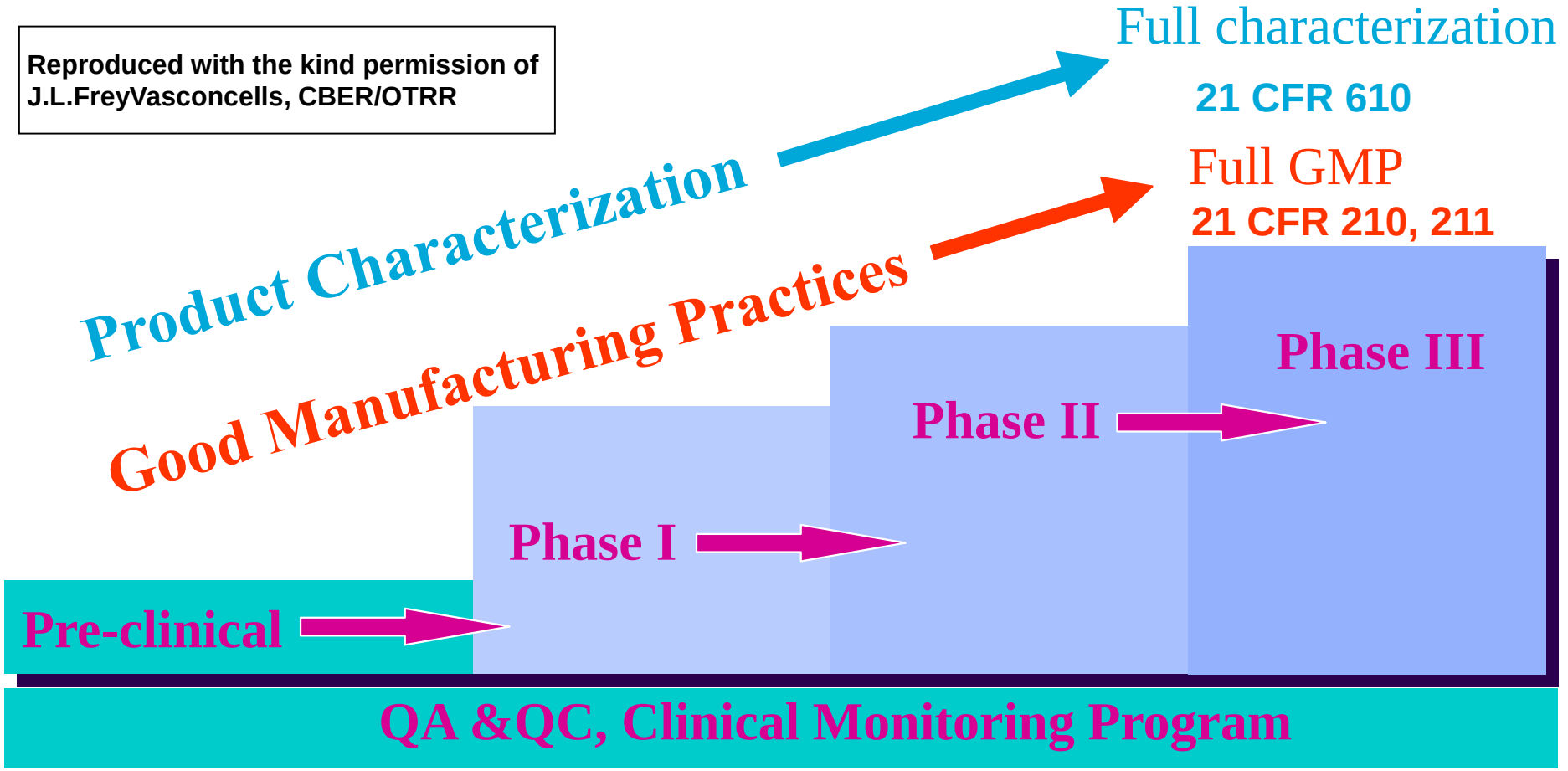


Prior to Phase I : need product safety testing and basic characterization info

The “GMP Gradient”

“Although in each phase of the investigation *sufficient* information should be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available”

(21CFR312.23(a)(7); Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase1 Studies of Drugs, Including Well-Characterized Therapeutic Biotechnology-derived Products**)**

The “GMP Gradient”

"The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages. Once the drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API".

(ICH Q7A Ch.19.11)

The “GMP Gradient”

- examples for cGMPs that develop with clinical studies:

  ↓process validation

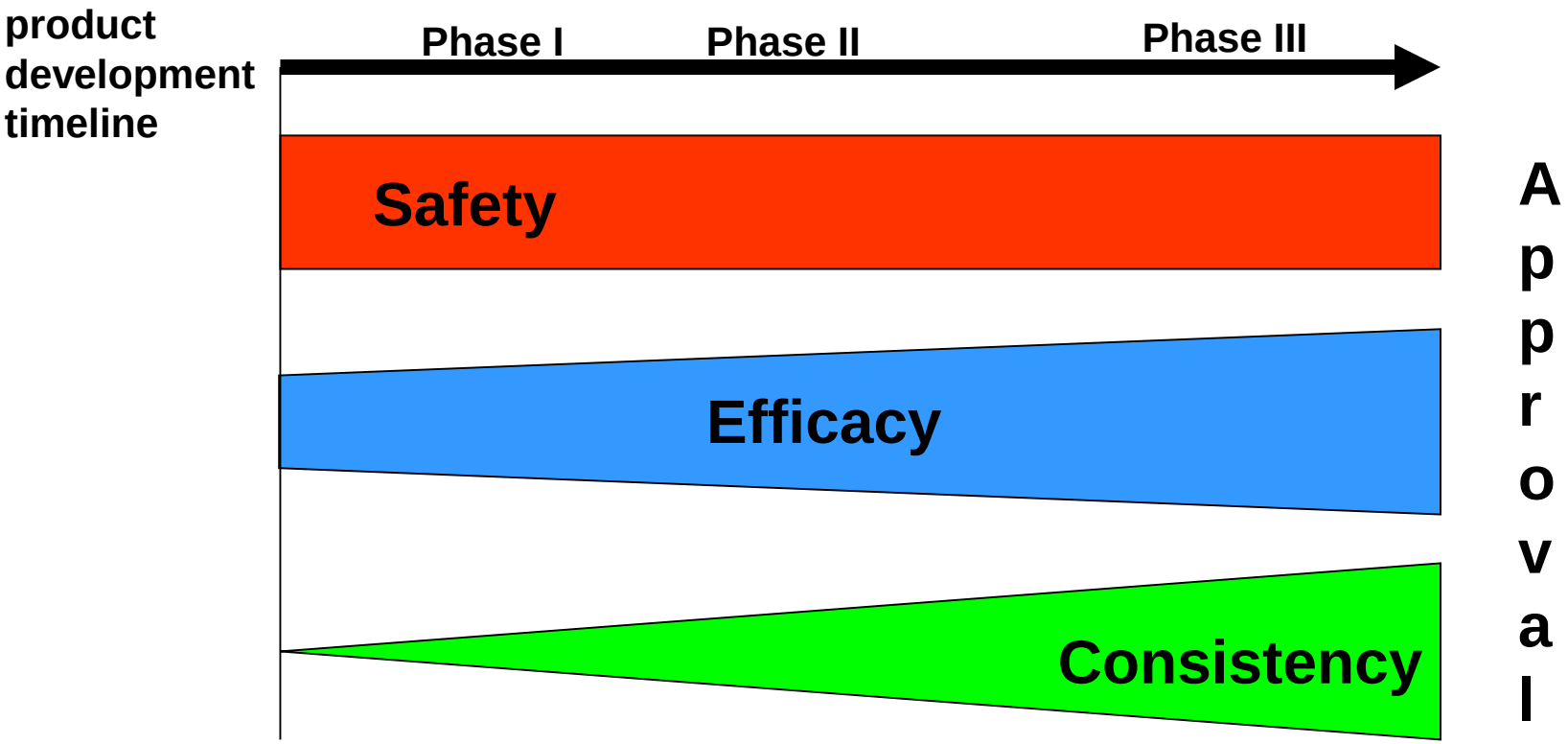
  e.g. manufacturing, cleaning and sterilization

  ↓methods validation

  ↓process controls: in-process testing, specifications

The “GMP Gradient”

- relative priorities during development of a GMP process:



“Good Project Management” Considerations

The complexity of the task can only be handled by a multidisciplinary project team covering at least:

- **↓molecular biology**
- **↓analytical test development**
- **↓fermentation development**
- **↓purification development**
- **↓production**
- **↓QC and QA**
- **↓engineering,**
- **↓IT specialists**
- **↓regulatory affairs**

“Good Project Management” Considerations

The 16 commandments of process development

- ↓ collect and secure data on cell line construction (donor, genetic manipulation etc.) generated during the early research phase
- ↓ avoid use of suspect raw materials (like FCS of doubtful origin, poorly characterised hormones etc.) already during the research phase
- ↓ whenever possible, adapt the cells to serum-free media
- ↓ make sure that the MCB and WCB are of adequate size for long - term production

“Good Project Management” Considerations

The 16 commandments of process development

- ↓ think about validation requirements early in development of manufacturing processes and testing procedures
- ↓ do not narrow specifications too early
- ↓ secure continuous raw material supply
- ↓ keep in mind that the process should be automated later on
- ↓ keep in mind multi - purpose - facility issues
- ↓ remove the most plentiful impurities first
- ↓ remove the easiest - to - remove impurities first.

“Good Project Management” Considerations

The 16 commandments of process development

- ↓ make the most difficult and expensive separations last.
- ↓ select processes that make use of the greatest differences in the properties of the product and its impurities
- ↓ select and sequence processes that exploit different separation driving forces
- ↓ keep in mind waste treatment requirements at production scale
- ↓ Select a reliable CMO and verify its capabilities
- ↓ document, document, document, document, document.....

FDA Attitude:

“we trust in God

but

anyone else needs documentation !

“Good Project Management” Considerations

Most common mistakes during development:

- ↓ project team created too late
- ↓ not all functions involved represented in the project team
- ↓ production, QC, QA and reg. affairs involved too late
- ↓ no clear definition of milestones and milestone deliverables
- ↓ poor documentation of research work, esp. poor documentation of cell line and vector history, gaps
- ↓ no standard format for scientific reports required
- ↓ key GMP responsibilities not addressed in contracts with CMOs

“Good Project Management” Considerations

Most common mistakes during development:

- ↓ use of non- compendial simple raw materials
- ↓ reliance only on the vendor’s certificate of analysis
- ↓ poorly specified components or unnecessarily strict specifications
- ↓ sole - source vendors
- ↓ inadequate hygiene zoning and procedures in production facility
- ↓ no column life span tests
- ↓ no shipping studies
- ↓ lack of identification of “critical” process steps and justification
- ↓ Specifications solely based on process capabilities

“Good Project Management” Considerations

Most common mistakes during development:

- ↓ validation of process steps and analytical methods too late, no “worst case” validation
- ↓ DSP procedures not developed with virus/TSE safety in mind
- ↓ poor change control systems
- ↓ OOS - results ignored
- ↓ raw data for testing of clinical batches discarded
- ↓ over - or underspecified equipment
- ↓ poor process optimization
- ↓ no validation of computer systems (PLC’s, LIMS)
- ↓ multi - purpose facility problems not considered
- ↓ new guidelines ignored

“Good Project Management” Considerations

GPM needs a project manager, who

- ↓ is committed to pursue the company`s interest
- ↓ is accepted as the leader by the other players
- ↓ can easily communicate and motivate people
- ↓ has the adequate scientific background
- ↓ is aware of the project management tools
- ↓ has enough time to do the job
- ↓ can organise the “project controlling”
- ↓ can defend the project and present its progress (“project marketing”)

“Good Project Management” Considerations

GPM requires a project definition, which

- ↓ defines clearly the goals of the project
- ↓ identifies the key players
- ↓ describes the estimated costs and resources needed
- ↓ gives a rough timeline
- ↓ is released by senior management

“Good Project Management” Considerations

GPM is implemented by a detailed project plan, including

- ↓ goals
- ↓ timelines
- ↓ milestones
- ↓ milestone deliverables (product, reports!)
- ↓ splitting into part-projects
- ↓ individual tasks
- ↓ resources

Commercial software can be helpful for project planning

Milestones and “Milestone Deliverables”

Milestone 1: Turnover from research to development

- ↓ basic SOPs available
- ↓ documentation of changes defined
- ↓ preliminary manufacturing and testing instructions documented
- ↓ contract manufacturers carefully selected
- ↓ specifications for finished product and starting / packaging materials as well as utilities (water, nitrogen, air) defined
- ↓ primary seed bank: cell line history documented, tested for absence of mycoplasma or bacteriophages resp.

Milestones and “Milestone Deliverables”

Milestone 1: Turnover from research to development

- ↓ equipment calibration organised
- ↓ product changeover procedures (“visible clean”) in place
- ↓ assay methods for potency, identity, purity, impurities, contaminants and degradation products developed
- ↓ stability indicating methods defined; preliminary stability studies done
- ↓ standard format for scientific reports defined
- ↓ research data reviewed for accuracy and completeness
- ↓ research report summarising the above topics compiled

Milestones and “Milestone Deliverables”

Milestone 2: Turnover from preclinical dev. to Phase I

- ↓ QA-organisation (including self-inspection and training system) in place
- ↓ formal change control system in place
- ↓ contract manufacturers qualified, contract addressing GMP responsibilities available
- ↓ SOP - system in place
- ↓ manufacturing / testing instructions and master batch records formally released
- ↓ specifications for finished product and starting/packaging materials improved / tightened.
- ↓ formal batch record /testing record review and formal lot release by QC in place

Milestones and “Milestone Deliverables”

Milestone 2: Turnover from preclinical dev. to Phase I

- ↓ master cell bank: all safety tests performed
- ↓ reusable materials (UF membranes, chromatography materials) dedicated to single product
- ↓ in process - controls defined
- ↓ critical equipment qualified
- ↓ standard program for calibration/recalibration / preventative maintenance in place
- ↓ clean room / environmental monitoring/ closed systems / hygiene plan operational

Milestone 2: Turnover from preclinical dev. to Phase I

- ↓ cleaning / product changeover procedures: cleaning acc. to standard procedures, then treatment with NaOH; visible clean - criterion
- ↓ critical tests (for potentially toxic starting materials, sterility, retrovirus etc.) validated
- ↓ retrovirus clearance by process validated
- ↓ preliminary shelf life defined based on preliminary stab. studies; further stability testing program defined
- ↓ IND and pre-IND meeting package compiled, IND submitted

Milestone 3: Turnover from Phase I to Phase II

- ↓ specifications for finished product and starting/packaging materials improved / tightened
- ↓ master cell bank formally released
- ↓ clean room / environmental monitoring/ closed systems / hygiene plan improved based on experience during phase I
- ↓ plan for prospective cycle number validation of reusable materials (UF membranes, chromatography materials) fixed

Milestones and “Milestone Deliverables”

Milestone 3: Turnover from Phase I to Phase II

- ↓ cleaning: additionally last rinse - testing (TOC, product-specific test); cleaning validation program defined
- ↓ process validation program defined
- ↓ analytical methods validation program defined
- ↓ scale up - report lab scale - pilot scale available
- ↓ IND updated

Milestones and “Milestone Deliverables”

Milestone 4: Turnover from Phase II to Phase III

- ↓ specifications for finished product and starting/packaging materials at final stage
- ↓ WCB formally released
- ↓ Post - Process - Cell Bank tested
- ↓ validation of utilities (water, air, nitrogen) finished
- ↓ clean room / environmental monitoring/ closed systems / hygiene plan improved based on phase II - data

Milestone 4: Turnover from Phase II to Phase III

- ↓ prospective cycle number validation of reusable materials (UF membranes, chromatography materials) done
- ↓ cleaning: additionally swab testing; cleaning validation program for final scale equipment defined
- ↓ process validation program revised based on phase II - data, adapted to final scale equipment
- ↓ in process - controls tightened based on phase II - data

Milestones and “Milestone Deliverables”

Milestone 4: Turnover from Phase II to Phase III

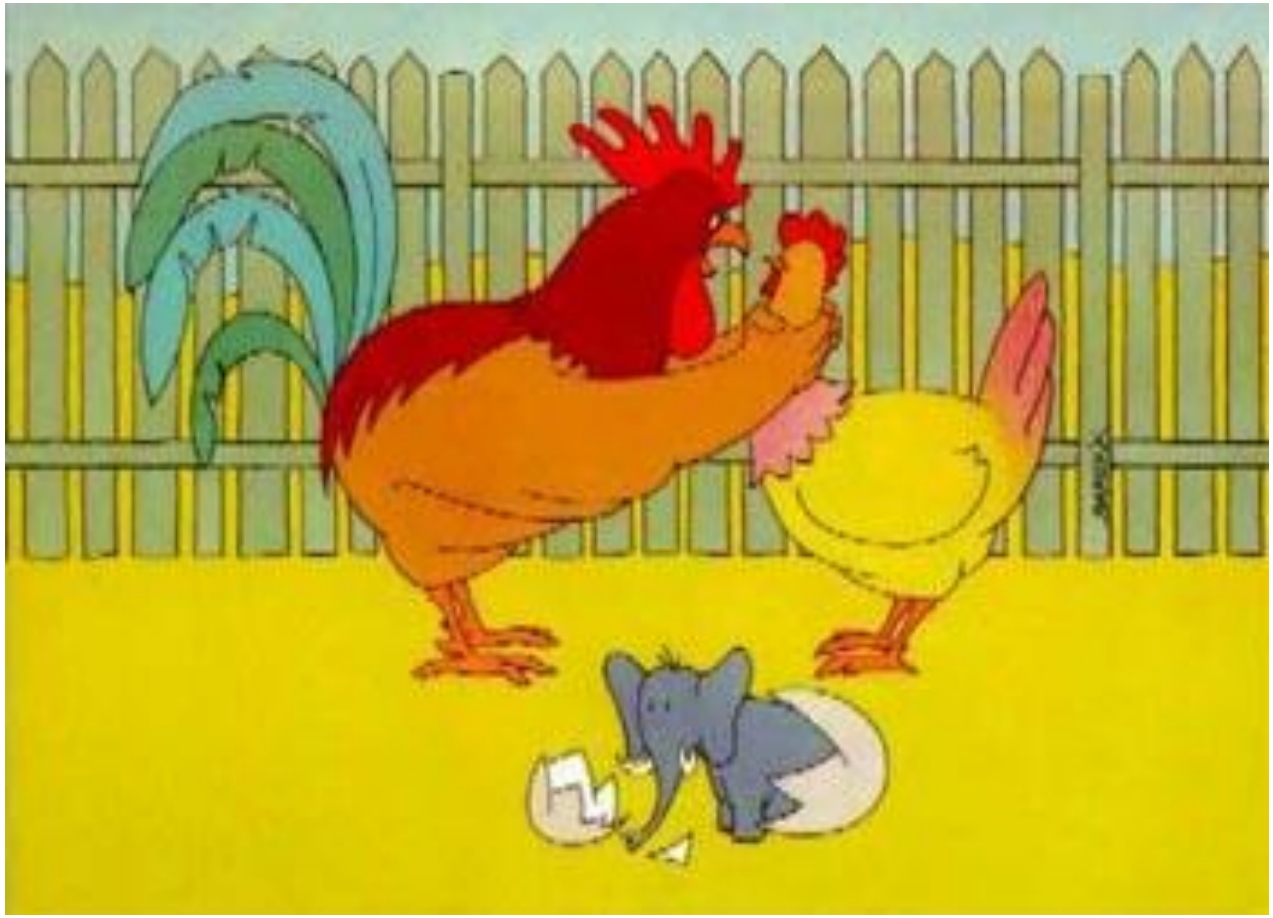
- ↓ analytical methods validation program revised according to experience during phase 2
- ↓ all virus validation reports available, results acceptable
- ↓ stability testing program revised based on results of phase 2 batches
- ↓ IND updated

Milestones and “Milestone Deliverables”

Milestone 5: End of phase III, submission of dossier

- ↓ full genetic characterisation of MCB, WCB and PPCB documented
- ↓ final validation reports / trend analysis data available for process, cleaning, analytical methods, reusable materials, utilities
- ↓ final scale equipment qualification reports available
- ↓ scale up - report pilot to final scale available
- ↓ stability testing report and ongoing program available
- ↓ storage and shipping conditions validated
- ↓ operator training fully documented

More intensely planned projects produce more efficient, less costly, and higher quality products



In biotechnological processing mistakes and deviations during the development phase may be detected only very late and can lead to unexpected product defects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