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GMPs for Early Stage Development Projects

GMPs" should be in place during the later stages of clinical development where the final safety and efficacy of a product are being established.

Below is the proposal for applying GMPs to development projects. The information below is consistent with FDA's proposals on a "graded" approach in developing and building scientific information to support clinical investigations and industry norms for development activities.

Material Controls:

Non-clinical: All materials used for non-clinical safety testing (GLP) must have adequate documentation of the methods of synthesis and must be characterized for identity, strength, purity and composition using scientifically sound methods. No regulations for GLP testing require GMP materials nor are there any specified minimums regarding the level of "validation" required for methods. There is a high probability of "process changes" in the method of synthesis at this stage of development; but maintaining the continuity of impurity profiles is important to be able to reference the data generated in the future. Changes can be made, but a determination will be needed to evaluate if existing data will continue to support the new material or if new studies will be required. Methods are generally expected to be stability-indicating and must provide a means to verify identity, strength, purity and quality. Defining the impurity profile with sufficient sensitivity is necessary to qualify impurity levels in support of future development and registration activities.

> At the IND-enabling-study stages, the key/critical quality attributes will always include purity and impurities.

With respect to specifications, key/critical quality attributes shall be monitored, but there is no regulatory expectation of "limits"; a few exceptions are genotoxic impurities and class I/II solvents. At the IND-enabling-study stages, the key/critical quality attributes will always include purity and impurities (organic, inorganic, residual reagents and solvents, etc.). For injectable products, sterility and bioburden tests are always required. Other attributes that affect bioavailability could be important depending on the dosage form and route of administration. Specifications, per se, are not required for GLP materials, but test articles are expected to be "acceptable" to meet study needs and appropriately characterized. There are no default limits established, so any material that is used in a GLP test would be acceptable. Business risks become the driver, e.g. too pure or too impure could lead to difficulties later in development or to premature demise of the compound.

Phase I/II Clinical: Specifications (tests, test methods and acceptance criteria) are required starting at Phase I although the use of "report results" for the acceptance criteria is acceptable for some determinations, particularly those attributes that will be defined more by process control rather than established as a means of assuring safety.

Key/Critical quality attributes (such as purity/impurity) will require defined specification limits that are supported by toxicological study data.

Key/Critical quality attributes are defined as those attributes that could have adverse impact on safety or efficacy. Key/Critical quality attributes (such as purity/impurity) will require defined specification limits that are supported by toxicological study data. One recommendation would be to have "Control Specifications" and "Characterization Specifications". As more information about the product is known and the manufacturing process is improved, new specifications may be added, specifications may move from one specification list to the other or may be eliminated with appropriate justification. Since IND-enabling toxicology studies will continue to support human dosing, process changes to the API synthesis or formulation changes to the drug product must be evaluated against previous impurity profiles of previous GLP lots. If the change results in a different impurity profile, new toxicology testing might be warranted. So, it is essential that changes be carefully considered before implementation.

Test methods should also have an appropriate level of qualification (validation) during Phase I/II. Minimum standards for method validation and system suitability requirements are attached in Tables II and III. Deviations from these standards should be justified.

Impurity levels at each stage need to be defined, justified and supported by the impurity test method associated with the material. Impurity levels outside of ICH guidelines must include a toxicological justification, as well as appropriate manufacturing controls to limit this impurity or justification as to why manufacturing controls cannot limit the impurity.

Phase III Clinical: In order to advance to Phase III, an investigational product must demonstrate safety and efficacy on a small scale. To support the Phase III program, the materials used for studies should approximate the expected commercial presentation (with allowances for appropriate blinding requirements). This means that the API manufacturing process, solid state properties, dosage form, strengths, manufacturing process, the container-closure system, etc. will be better defined. The proposed site of commercial manufacture may also be selected by this time. Ideally, some Phase III supplies will be produced in the commercial facility. By this stage of the program, several aspects of the product should be controlled in a manner similar to commercial GMP controls. It is still possible that some aspects remain undefined (e.g. optimization controls), but all major aspects (quality controls) should be defined to avoid future delays.

Specifications should be established that are similar to the expected commercial specifications where possible. This means that specifications should be set taking into account the safety limits, the process capabilities and the stability characteristics of the product. This is the appropriate time to evaluate and justify every specification. Sometimes companies inadvertently retain legacy specifications that are left over from early development even though they have become irrelevant and should be removed.

Methods need to be more rigorously validated and should meet ICH standards. Certainly by the time the registration stability studies are initiated, these methods need to be ICH compliant. If the final GMP testing facility is different, appropriate method transfer, revalidation or verification activities shall be carried out and documented appropriately.

Process and analytical change control needs to be strictly enforced at this stage to assure justification of the commercial process is adequate during the peri-approval process.

ICH stability studies will be initiated on the API and drug product. Depending on company's global registration/filing strategy, it is important to consider all required temperature and humidity conditions. Firms must seriously consider method changes in the middle of on-going stability studies. Showing continued correlation of data at any given time point to T0 is important to demonstrate the stability.

Retention samples are required for API and bulk dosage forms for development projects. An amount sufficient to perform the release testing twice (without the sterility and pyrogen testing) is required. This is required for both GLP and GMP

manufacturing, but retention samples do not need to be designated as GLP or GMP; therefore, a single sample per lot is acceptable.

Retention samples are also required for packaged clinical supplies. A common practice is to retain one example of a patient supply per label. Depending on the complexity of the study this could mean, for example, one patient kit per study arm per visit.

There are specific requirements for bioequivalence/bioavailability (BA/BE) studies where retention samples are also kept at the site of the study to assure a completely unbiased conduct. When such a situation is approached, consult with QA and the current regulations to assure that the planned study will meet all requirements.

Facility and Equipment Controls:

Clinical supplies do not have to be manufactured and tested (and often are not) at FDA inspected and approved facilities (but if a facility were to be inspected by the FDA, it should be able to pass the inspection without critical deficiencies). This means that major equipment and supporting utilities need to be maintained in a state of control. Calibration and maintenance programs will need to be in place and documentation must be available to support adequate operation. In some cases, it is feasible to perform the manufacturing at lab scale (although usually not for sterile products) with the use of disposable labware of adequately controlled materials. The IND process allows for flexibility of the production process.

Production and Process Controls:

Non-Clinical: Testing of test articles/materials will need to meet GLP requirements to avoid a GLP Compliance Statement exception in a study report. This includes, but is not limited to, adequate programs to cover training, calibration and maintenance, documentation practices, material controls, Quality Assurance Unit (QAU) review and oversight and data integrity. This may also include computer validation. It is not required nor expected that the release testing of GLP test articles should be done in a GMP lab. Good science and good practices that are defendable are keys.

Phase I/II Clinical: Validation of manufacturing processes is a requirement of the current Good Manufacturing Practice (cGMP) regulations for finished pharmaceuticals and is considered an enforceable element of current good manufacturing practice for active pharmaceutical ingredients (APIs). A validated manufacturing process has a high level of scientific assurance that it will reliably produce acceptable product. The proof of validation is obtained through rational experimental design and the evaluation of data, preferably beginning from the process development phase and continuing through the commercial production phase.

A validated manufacturing process has a high level of scientific assurance that it will reliably produce acceptable product.

Process validation for clinical supplies in Phase I and II requires assuring intra-batch consistency. When producing multiple batches of the same investigational product, it is recommended that internal performance reviews be conducted and documented periodically. It is also recommended that such reviews assess the control and consistency of the production process and overall product quality. Reviews would fall outside of routine production operations and would be conducted to assess procedures, practices, and information including data generated from production and investigational new drug testing. Based on the review, appropriate modifications and corrective actions can be taken to control procedures and production operations. The data generated with each batch can also allow the establishment and/or refinement of acceptance criteria as experience and knowledge permits. This allows the firm to achieve more consistent investigational new drug production.

Activities and decisions will be documented and will be the basis for future change management.

Several elements will need to be considered including, but not limited to:

- Identification and characterization of raw materials
- Calibrated and maintained equipment
- Appropriate methods (validated for stage of development)
- Change management
- Independent QA with approval of
  - Master production and labeling records
  - Production and labeling records
  - Specifications (appropriate to stage of development)
- Cleaning strategy (to avoid cross-contamination)

- Process validation (to assure intra-batch consistency – not batch to batch consistency)
- Bioburden and Sterility Assurance for parenterals (flexible only based on batch sizes allowances)

API and drug product stability need to support the use of clinical supplies for the intended duration of the study. Stability studies that meet full ICH guidelines are not required, but the general scientific principles of the ICH Stability Guidance should be followed. For the reasons of timing and expediency, it is acceptable to refrigerate the product initially. If there are stability issues with the API or dosage form, these should be known by the time the IND is filed. The controls applied should be proportional to the stability of your API/Product. Less stable compounds will require more scrutiny, protection, monitoring and controls.

API and drug product stability need to support the use of clinical supplies for the intended duration of the study.

Phase III Clinical: For Phase III, consistency of material quality of the clinical trial materials (CTM) compared to the eventual marketed product is essential. Process validation for commercial product for the US is not required at pre-NDA stage (although protocols are; however, if speed to launch is important, then early validation would be appropriate. Technology transfer and validation/verification at the final commercial manufacturing site will be required in time to ensure that the associated site/scale/equipment changes have no adverse impact on the quality of the API/drug product.

Defining the final primary container closure is important to study the stability of the dosage form representing final commercial product.

A Change Control process (rather than change management) will need to be initiated subsequent to validation activities (e.g. methods) and manufacture of the registration stability lots.

Records, Documents and Change Control:

Non-clinical: Documentation of the manufacturing activities may be notebook based and does not require any pre-approval from QA to meet compliance requirements.

Forced degradation studies shall be conducted to define the "stability indicating" nature of test methods. Identification of major degradants/impurities should be done to the "best possible" extent. Impurities/degradants having known "structural alerts" with major toxicity potential (e.g. DNA intercalators, aldehydes and alkylating agents like halides) should be monitored closely and controlled. As analytical techniques have improved, low levels of genotoxic impurities have become a major focus. They have to be controlled at very low levels (ppm). Also, leachables and extractables should be kept in mind when developing analytical methods and studying the stability data.

Phase I Clinical: For solid oral products the possibility of lab-based manufacturing operations is possible as long as scientific integrity is maintained and the risk associated with the product is not significantly greater than the risk of the new product itself (e.g. the possibility of cross contamination is significantly minimized). The controls listed above in "Production and Process Controls" section will need to be adjusted to cover such operations. Batch records will be required and QA pre and post approval will be necessary. The batch records at this stage may be constructed in a less prescriptive manner with high level steps. In this case, specific details are recorded during the manufacture to allow reconstruction and evaluation of the manufacturing activities.

Sophisticated dose formulations need not be developed in the early phases as long as the scientific information that is obtained from a particular study design can allow movement to the next step. Phase I supplies are often only API without excipients.

Phase II/III Clinical: Process development activities need to be thoroughly documented at this stage of development. Much of the process control information will be maintained and presented in development reports which need to be available for a Pre-Approval inspection. This will also be the stage where critical process controls will be documented and made available to the commercial manufacturing site through a Technology Transfer process.

Changes to processes and methods used for the clinical Phase III materials will need to be fully documented and justified since they will be a reference point for the commercial processes during a Pre-Approval inspection.

Regulatory Requirements:

Non-Clinical: Information to support Pre-IND briefing documents will follow GLP guidelines listed in Table I. The extent of required documentation will vary and be dependent upon the nature and complexity of the investigational drug.

IND Submission and Phase I through III: Information submitted must demonstrate that all aspects of manufacturing and controls are performed under cGMP as defined in Table I.

The CMC section should discuss the composition, manufacture and control of the API and dosage form (DP) as appropriate for the particular investigations covered in the IND. Sufficient information should be provided to assure the proper identity, quality, purity and strength of the investigational drug. The FDA recognizes that modifications to the method of preparation of the API and DP and changes in the DP itself are likely as the investigation progresses. The emphasis in an initial Phase I submission should generally be placed on the identification and control of the raw materials and the new drug substance.

The amount of information submitted will depend on the scope of the clinical investigation and will vary with each phase and duration of the investigation, the dosage form and the information otherwise available. The sponsor should submit information amendments to supplement the original information submitted as the drug development proceeds and as the scale or production changes from pilot scale production appropriate for the limited initial investigations to the larger scale production needed for expanded clinical trials.

Reflecting the distinctions described above and based on the phase(s) to be studied, the submission is required to contain the following:

(a) API:

- A description of the drug substance, including its physical, chemical or biological characteristics
- Name and address of the API manufacturer
- General method of preparation of API
- Acceptable limits and analytical methods used to assure identity, strength, quality and purity of the API
- Information sufficient to support stability of the API during the toxicological studies and the planned clinical studies
- Brief and general description of the composition, manufacture and control of any placebo used in a controlled clinical trial

NOTE: References to current USP/NF may satisfy relevant requirements

(b) Drug Product:

- List of all components used in the manufacture of the DP (this may include reasonable alternatives for inactive components) including those components intended to appear in the DP and those which may not appear, but which are used in the manufacturing process.
- Where applicable, the quantitative composition of the investigational DP
- Name and address of the DP manufacturer
- Brief general description of the manufacturing and packaging of the DP
- Acceptable limits and analytical methods used to assure identity, strength, quality and purity of the DP
- Information sufficient to assure the stability of the DP over the course of the study

NOTE: References to current USP/NF may satisfy relevant requirements

The amount and level of detail for the information to support the CMC should continue to expand as more information about the DS and DP composition, its methods of manufacture and packaging, analytical methods and specifications and stability data become more defined.

References:

1. INDs for Phase 1 Studies of Drugs & Biotech Products (Nov. 1995); http://www.fda.gov/cder/guidance/phase1.pdf
2. Draft Guidance: INDs--Approaches to Complying with CGMP's for Phase 1 Drugs (12-Jan-06)
3. INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing and Controls Information (May 2003); http://www.fda.gov/cder/guidance/3619fnl.pdf
4. EUGMPs EUDRALEX Volume 4 Annex 13; http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev4.htm

Table I: Pre-IND Briefing Requirements

	Aspect	GLP	Phase I/II	Phase III
Material Controls	Specifications	Limits Not Required; critical quality attributes shall be tracked	Yes, but "Report Results" is OK for some critical quality attributes such as purity/impurities (special impurities such as genotoxic impurities will require NDA level control)	Yes, should approach Commercial
	Method validation	Appropriate to Stage of Development (we must define)	Appropriate to Stage of Development (we must define)	ICH Guidelines
	Stability	Yes, can be concurrent to study. Also consider dosing solutions	Yes, sufficient to cover duration of use of Clinical Trial Materials (CTM) – consider packaging plans. Filing an IND with release data with stability commitment is OK, as long as developmental stability data is available for "representative" API/ product. Less stable APIs/Products will have more requirements	For intended commercial formulations should be ICH. For non-commercial CTMs, need to cover duration
	Raw Materials Control	Document Source and Quality	Document Source and Quality	Qualify Suppliers
	Inventory Management			
	Retention Samples	2x required for all tests for Test Articles and Control Articles	2x required for all tests excluding sterility and endotoxin each for bulk API and Product. Labeled retention of one example of all label configurations. BA/BE 5x	2x required for all tests excluding sterility and endotoxin each for bulk API and product Labeled retention of one example of all label configurations (e.g. 1 pt kit/treatment arm/visit). BA/BE 5x

Table I: Pre-IND Briefing Requirements cont'd

	Aspect	GLP	Phase I/II	Phase III
Facility and Equipment Controls	GMP compliant Facility	Not required	Yes, but not necessarily with an FDA license	Yes, but not necessarily with an FDA license unless validating process for commercial
Production and Process Controls	Process Validation	Not required	Intra-batch consistency and thorough documentation	Intra-batch consistency and thorough documentation, but may be validating commercial process during this timeframe
	Formulation Development	Not generally required except as dictated by API characteristics	Initiated and optimized to address initial commercial expectations	Conducted to enhance knowledge of formulation in support of registration
	Packaging Development	Not generally required	Not required except as primary packaging for parenterals	Finalized to address commercial presentations. Need to coordinate with stability requirements
	QA documentation pre-review	No	Yes	Yes
	QA documentation Post Review	Yes (per GLP)	Yes	Yes
Records and Documents/ Change control	Master Manufacturing Batch Record	Not required	Yes, but may be high level plan (e.g. similar to a protocol)	Yes, should be in a change-managed system
	Batch Documentation	Yes, sufficient to reconstruct the manufacturing process. May be notebook-based	Yes, may be notebook – based for early stages, but compliant with GMP documentation requirements	Yes, should approach form and function of a commercial manufacturing batch record.
	Master Packaging Record	No	Yes, but probably single use for studies and based on clinical protocol	Yes, most likely single use, but can be designed for multi-use based on clinical protocol
	Packaging Batch Record	No	Yes	Yes, may be quite complex depending on complexity of the clinical study (i.e. blinding strategy, arms, visits, locations, IVRS)
	Change process	Change Management	Change Management	Change Management to Change Control

Table I cont'd

	Aspect	GLP	Phase I/II	Phase III
Records and Documents/ Change control	Regulatory Requirements	Information to support Pre-IND Briefing Documents needs to follow GLP guidelines listed in this table. Extent of documentation needed will vary and is dependent upon the nature and complexity of the investigational drug	CMC section should briefly discuss the composition, manufacture and control of the DS and DP as appropriate for the particular investigations covered in the IND The amount of information submitted will vary with each phase and duration of the investigation, the dosage form and the information otherwise available. The sponsor should submit information amendments to supplement the original information as the drug development proceeds.	The sponsor should continue to submit information amendments to supplement the original information as the drug development proceeds and the final composition of DS and DP, as well as their respective manufacture and control processes become more defined.
	Quality Agreements	Not required	Required for EU distribution	Required for intended commercial CMOs and CROs and all EU distribution
	Product Specification File		Required	Required through development

Notes:

1. Phase IV is not included in this table

2. Assumptions for this presentation include:

   a. timelines that would allow the decisions on the commercial presentation and process prior to, or early in Phase III.

   b. Selection of commercial suppliers and CMOs prior to or early in Phase III.

   c. Product characteristics are "standard". The existence of "non-standard" characteristics such as identified sensitivities may require adjusting information and controls forward or back.

Table II. Method Performance, Validation, and Documentation Requirements per Phase of Development – Minimum Standards

	Phase I	Phase II	Phase III
*Registered Starting Materials *Pre-registered starting materials *Isolated intermediates	COA ID test Use test No validation	COA Specificity Use test Linearity LOD/LOQ	Phase II activities + Intermediate precision + Robustness
*In-process controls and *Non-isolated intermediates	Use test Specificity Accuracy	Use test Specificity Accuracy Linearity	Phase II activities
*Raw materials	Use test Specificity	Use test Specificity Accuracy Linearity	Phase II activities + Robustness
*Drug Substance *Drug Product	Specificity Linearity Accuracy + Precision LOD/LOQ	Phase I activities + Intermediate precision	Full ICH (Phase II activities + Reproducibility + Robustness + Specificity*)

* add forced degradation to specificity of Ph III API and drug product

Table III. System Suitability Requirements per Method – Minimum Standards

	# of standard injections pre-run and throughout run	Chromatographic performance (Resolution or tailing factor)	Sensitivity check @ LOQ
*Pre-registered starting materials *Isolated intermediates	5 or 6 + 2 after all samples (RSD NMT 2.0% pre-run and throughout run)	Pre-sample injections, 1 injection	Pre-sample injections, 1 injection
*In-process controls *Non-isolated intermediates	Blank, system suitability solution for retention times,	Pre-sample injection(s); 1 injection	Pre-sample injections; 1 injection
*Raw materials	2 + 1 (no precision check)	Pre-sample injection(s); 1 injection	None required
*Drug Substance *Drug Product *Registered Starting Materials	5 or 6 + 2 after all samples (RSD NMT 2.0% pre-run and throughout run) + sys suit solution	Throughout run, on check/bracketing standards	Pre- and post-sample injections, 1 injection each

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