

Docket 2005N-0285

Comments to Draft Guidance 6164dft
INDs - Approaches to Complying with cGMP During Phase 1

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General comments and assumptions

1. Intended audience is the mainstream pharma and biotech industry and the non-commercial, investigator sponsored IND sponsors. The intention of the guidance was to provide some relief from the "burden" of full cGMP compliance and to enable more compounds to be tested in the clinic earlier. However, most investigators, clinicians and physicians do not read the FR or have a history of being compliant with FDA-issued guidances [due to naivety about what terms mean, what GMPs are in the first place and probably have no appreciation the need for zero-defect exactness in clinical manufacturing activities]
2. Guidance is intended to be consistent with other FDA Guidances such as 1987 Process Validation and FDA Initiatives for the 21st Century
3. This guidance could benefit from noting specific differences between the cGMPs in 21 CFR 211(the 211's) and the Agency expectations for phase 1.
4. This guidance could benefit from harmonization with the EU Annex 13 (GMPs for Investigational Medicinal Products)
5. There is an understanding that clinical trial materials (CTM) involve continual change, are unique in many respects as compared to commercial activities, require alternative approaches to acceptable compliance with minimum good housekeeping and documentation standards and, in many cases, require some additional controls above and beyond minimum cGMP when blinded trials are considered.
6. The guidance could benefit from specific comments concerning several GMP aspects where there are differences between in-patient and outpatient trials and between open-label and blinded studies. An example of the recommended discussion that would make this guidance much more informative is provided for Labels and Labeling.
7. The removal of independent Quality oversight and allowance of the same person conducting production, testing and release of batches is contrary to the basic tenets of Good Manufacturing Practices. See specific suggestions below.

When numbers are used they refer to the line item in the draft guidance.

Good things:

- specific suggested alternatives to compliance as in 183-192 and 245-250. This guidance needs many more examples of acceptable alternative practices, some of which are suggested in these comments. The suggested alternatives can be provided as examples and thus not trigger negative comments of "too prescriptive".
- 322-325 - the wording of the minimum analytical requirements is very clear

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Improvement needed:

-some areas of GMP are not addressed (see my comments on labeling, master production records, etc..)

- 31-33 "...the Agency recommends the approaches outlined in this guidance..." The approaches mentioned are very similar to the wording of the GMPs in 211 and do not provide any guidance on what differences in expectations there are between the 211s and this Guidance

-75: I think the exemption from complying to 21 CFR 211 for most phase 1 trials and "certain exploratory products" could convey the idea that GMPs are not required for phase 1. I know the authors of the guidance didn't mean this, but consider how the naïve sector of the industry will interpret this statement. An improved statement of the scope of this guidance might be "Due to the unique nature of the clinical supply investigational product chain [manufacturing, packaging, labeling, testing, shipment and distribution], alternative compliance practices to those specified in 21 CFR 211 will be required in many cases associated with clinical trial materials (CTM). Some aspects of traditional GMP compliance will require alternative compliance strategies to those normally practiced for commercial, approved products, some will not be able to be adopted or adapted to the CTM chain, and some will require additional controls above those required by 21 CFR 211. In many cases, the "minimum current" GMPs as defined in 211.1 will require additional definition for CTM. This guidance outlines the general approaches which are recommended and in some cases provides examples of acceptable alternative practices."

Examples of these are as follows: alternative compliance strategies will be required for process validation (211.110) [normally conducted on repetitive batches with fixed formulation, process and packaging] as these are inconsistent with CTM which for the most part are manufactured and packaged differently each time. However, processes and process parameters should be evaluated with the intent of appropriately controlling those process parameters that will be determined to be critical as development proceeds. Additional in-process and final product testing is prudent. This approach is consistent with the "instant run" provision of the FDA 1987 Process Validation guidance, and consistent with other FDA Expectations (Quality Systems Approach to Pharmaceutical Good Manufacturing Practice Regulations, September 2004; ICH Q8, Pharmaceutical Development [FDA Guidance 6672dft, February 2005]).

Example of GMP requirements that can not be adapted include the examination of final drug product (211.134 a). In commercial products, solid dosage forms have logos or imprinting and thus the comparison between the product and its label is possible. In early open label trials or blinded trials, the identity of drug products is not easily discernable since actives and placebos are purposefully made to be indistinguishable from one another. One alternative used in the industry is the conduct of a final identity test, where

blinded and unidentified samples are tested and compared to the design specifications that are part of the randomized code for medication allocation.

Examples of situations where additional controls, above the minimum GMP in 211 are warranted:

A) In the manufacturing for a small blinded trial, the batch size could be 1000 vials (or 1000 capsules) of both active and placebo, where only 200 vials (or 200 capsules) of active and placebo are required for packaging and labeling for this specific clinical trial. The balance of 800 vials of active and 800 vials of a look alike placebo (or 800 capsules of active and placebo) need to be kept in a "bulk" container that is labeled to clearly differentiate the two identical products and segregated from one another. "Nude vials" are the terminology for unlabelled product and there is a need for a SOP that describes how these products will be identified and separated so that there is no possibility of cross contamination. Usually the bulk container is sealed with a tamper evident seal and labeled with the contents.

B) labels for clinical trials involving multiple regimens (e.g., active versus placebo or low, medium and high doses of the investigational product for phase 1 ascending dose safety trials) are identical except for a subject number or a medication ID number [product names and lot numbers cannot be used as this information will break the blind]. These almost look-alike labels are easy to mis-use for application to one of multiple look-alike bottles containing look-alike drug products. Common industrial practice is to compare each subset of labels to an approved master label copy and to the randomized code.

C) in early development limited stability information is available and expiry dates can't be easily projected. Expiry dates on investigational labels are not required (211.137 (g)) however the internal knowledge of an appropriate shelf life is required. Continual monitoring of all stability data and frequent reviews of expiry and shelf life dating and extensions of same are approaches to this aspect of CTM.

Specific comments to line number items

1. 32 - for most particular approaches, reiterate what is required by GMP 211 and what is the specific relief or alternative acceptable practice. 169, 218-9, 229-237, 255-271 are listed as requirements for GMP for phase 1 but these appear to be equivalent to the 211's. Improved wording is "The Agency recommends the general approaches outlined and provides examples of acceptable alternate practices".
2. 58 - in early drug development there will be continual changes to every CMC parameter - formulation, composition, method of manufacture, analytical methods, specs, packaging, etc. Not just scale!
3. 76 - add "However, alternative procedures must be in place for each 211 requirement."
4. 108-110 - the CMC information required for phase 1 INDs (in the 1995 FDA Guidance in reference 1) is the tip of an iceberg [the firm has much more source data and background information than is submitted to the IND]. I think the FDA should

- not encourage firms thinking or interpretation that includes concepts similar to "The information needed by the FDA is really minimal; why should I create more". This philosophy is inconsistent with the concepts expressed in ICH Q8 (Pharmaceutical Development) and with concepts of Quality by Design.
5. 159 - should acknowledge that CTM involve unique operations and controls where alternative and different approaches to compliance are required.
 6. 173 - the naïve and MD and PhD clinical investigators will have no way to determine if their alternatives would be acceptable. Thus there is prudence to mentioning suggested alternative acceptable practices in this guidance.
 7. 195 - carefully considered risks should be documented in a written form. As a minimum, the aspects in 198-207 should be addressed.
 8. 210 - the "recommendations" to provide flexibility are too vague. I am an experienced industry professional who has taught courses in GMP for clinical supplies for 20+ years and I cannot understand the flexibility in this guidance. In 229-238, these appear to be identical to the 211 requirements.
 9. 221-222 - Good! Excellent specific suggestion that training include basic 211 GMP adding the concepts of the uniqueness of GMPs for clinical supplies.
 10. 226 - Good written QC plan! But what is a QC plan? This could be improved by requiring each organization to have a written summary of their compliance approaches that differ from the 211's. Here the differences and rationale for them could be summarized as in a Quality Manual.
 11. 245-250 - It is dangerous to allow, even in "limited circumstances", one individual to conduct manufacturing, testing and QA release activities, even with periodic oversight. It is efficient and very acceptable to allow the same individual to formulate a product in R&D and to test it themselves and this could even be possible in clinical phase 1 manufacturing but the QA function (e.g., production record review, 211.192) should always be conducted by a separate and trained individual.
 12. 251 - add "...involved in manufacturing and not just QA".
 13. 258-265 - These appear to be basic statements that are already found in the 211 GMPs, without any clarification as to what differences are acceptable for clinical production. Here, the guidance could benefit from suggested acceptable practices. For example there is no text regarding the level of cleaning verification (not validation) that might be acceptable for multi-use equipment. There have been several excellent articles in the trade literature that discuss cleaning verification for clinical supplies. The Agency could mention these publications as examples of acceptable practice (after reviewing them) or distill their suggestions in this guidance.
 14. 286-287 - As an example for a plastic bottle that is to be used only in one clinical trial for a solid dosage form, acceptable criteria could include material [HDPE confirmed by IR], size [sometimes noted on the bottom of the container or if not, volume to overflow], visual [white, round] with cap to fit. The closure acceptance criteria could include material [polypropylene by IR], features [child resistant or not] and sized to fit the specific bottle.
 15. 297- does this imply that for USP components and excipients other than the API, the manufacturer's C. of A. is sufficient? I agree that for API the manufacturer C of A plus an identity test by the dosage form manufacturer is prudent.

16. 305 - add "Formal QA reviewed and approved Master Production Records and authenticated copies of Batch Production Records as specified in 211.186 and 211.188 are optional".
17. 310-311 - add "Due to the frequent changes to every CMC parameter during early development, a simple but effective change control system is required. This procedure should be in writing. In the case where a smaller firm elects to use multiple CMC contractors (e.g., API manufacturing, clinical manufacturing and packaging, analytical laboratory), the sponsor should maintain their own internal change control system."
18. 330-332 - while all relevant acceptance criteria may not be definitively known in early development, the tests to develop this database (see line 67) are known. Consider strengthening this section by adding "The establishment of target ranges, wider than normal specifications or in the cases where there is no or limited historical data, 'report results' can be acceptable. This information will be reviewed in the CMC section of the IND".
19. 339 - Too much room for interpretation [most people will assume a bulk sample is ok]. For clinical supplies, retain samples are kept not only to conduct confirmatory analytical testing but also to confirm the identity of exactly what was used in the clinic [should spurious clinical results be obtained]. I would explain that a representative sample would be the actual bottles or vials of the investigational product. In the case of an open label, in-patient trial using a bulk dispensing bottle, a partially filled bottle [amount = 2X for analytical testing] could be acceptable. In the case of a blinded trial or outpatient study, the retain sample should be representative of what was dispensed to the subject. This should be consistent with the retain sample requirements in the EU Annex 13, # 36-37.
20. 347-349 - This section recommends concurrent stability on the actual investigational product. It would be helpful to add "Stability studies on feasibility, R&D, laboratory or prototypes batches, which were produced as part of formulation development can be used to determine appropriate storage conditions and project shelf life (or use dates). All investigational products used in actual clinical studies must meet all acceptance criteria through the date of last administration". Note that this is usually referred to as LPO (last patient out).
21. 353-356 - Add "Labeling and storage operations should be controlled to prevent any possibility of mix-ups especially with blinded trials". Please add some examples of acceptable "controls". Add the required elements needed on investigational labels, which is provided as Appendix 1 to my comments.
22. 367 - Are there any recordkeeping requirements defined in 211 that are not required for clinical phase 1 trial manufacturing?
23. 369-375 - Make this consistent with 211.192 and EU Annex 13 # 9 (Product Specification File). Add bullets for specifications and analytical methods for components, packaging materials, bulk and packaged product; manufacturing methods; in-process testing; approved label copy; clinical protocols and any randomization; technical agreements with contractors; stability data on prototype and investigational batches; storage and shipment conditions
24. 398-406 - Are the segregation requirements any different here than those in line 253? Are the requirements for equipment calibration, maintenance and cleaning (404-405)

any different than those in 263-265? Does the Agency intend for the reader to assume that screening and microdose studies require less control since the risk to the limited # subjects, limited duration and/or reduced dose is less?

25. 412-413 - This sentence makes no sense.
26. 509-545 - It would be helpful to differentiate between these recommendations and the expectations in 211. Was it a purposeful omission or an oversight to not mention media fills?

Appendix 1

The following are suggested topics to be covered by the FDA Guidance concerning labels and labeling.

Controls

In contrast to commercial labels and labeling [where there are large runs, identical labels which are identified as to product contents by name and lot number], clinical labeling involve very limited numbers of labels where each label may be distinct except for subject number [or medication ID number] and where each label is associated with a specific but unidentified treatment or medication regimen. In the case of blinded trials, comparison between each separate label type and the master approved label text should also include comparison between the labels and the randomization code.

In blinded trials, there should be a 200% (2-person) reconcillation of each type of label

In blinded trials, there can be a multiple-panel label where a separate tear-off panel is used for the clinical study case report form. This panel may also contain emergency unblinding information.

Label text should contain the following elements:

	Open label		Blinded trial	
	In-patient	Out-patient	In-patient	Out-patient
Sponsor's contact name	x		x	
Sponsor's name and phone number		x		x
Investigator's name	o	o	o	o
Dosage form	x	x	x	x
Quantity of dosage units	x	x	x	x
Route of administration	(1)	(1)	(1)	(1)
Name of drug and lot number	x	x		
Code to identify contents (2)			x	x
Clinical protocol #	x	x	x	x
Subject ID number (or medication ID #)	x (3)	x	x	x
Directions for use (4)	x	x	x	x
Caution statement (312.6 (a))	x	x	x	x
Storage conditions	x	x	x	x
Keep out of reach of children statement		x		x

o = optional

(1) = only if parenteral

(2) = packaging code traceable back to manufacturing records and to randomization code

(3) = may be pre-printed on the label or filled in at the clinical site

(4) = subject directions for use may be provided for on a separate leaflet



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