Novartis Pharmaceuticals Corporation Comments on the Draft FDA Guidance Drug Product CMC Information; Docket No. 02D-0526

General Comments

This draft Drug Product Guidance represents a comprehensive rewrite of the 1987 NDA Drug Product Guideline and as such warrants a critical review. Critical review is hampered by several factors, including:

1. The open status of several significant draft documents such as the 1997 draft Stability Guidance
2. The harmonization efforts of CDER and CBER requirements in one DP Guidance
3. The introduction of additional regulatory content requirements through the CTD format changes and ICH references
4. The lack of a current Drug Substance baseline due to the planned revision of the Drug Substance and BACPAC II Guidances under development.

The logical flow of regulatory requirements and scientific criteria beginning with drug substance starting materials and culminating with the final drug product would result in a more unified NDA Guidance set for submission and review purposes. Changing DP requirements before establishing new DS requirements may require amendment of the proposed DP Guidance.

Revision in multiple areas concurrently, although ambitious, may result in unintended contradictory regulatory requirements, with respect to:

- GMP review and revision
- Finalization of planned or open draft FDA Guidances
- Ongoing harmonization efforts
- Electronic submissions standards, and maintenance of electronic dossiers as submissions are updated.

Guidance reference [CTD section]	Line number	Major Comments	Rationale
General		Overall, this seems to increase filing information requirements for NDAs and ANDAs while the CTD structure was meant only as a formatting tool and was not intended to identify additional requirements above and beyond those currently required for drugs. Instances throughout the document identify requirements not previously listed in regulations or current guidances for drugs. Cross-reference to other Guidance documents is very useful! However, the reference to Guidances that remain in the draft or development stage increases the difficulty in reviewing this draft.	This Guidance is intended to be applicable to NDAs and ANDAs. In cases where specific sections would not be required for an ANDA, or would require amplification for a biological, it should be stated as such in that section
General		This document places a great focus on development activities and the need for comparative historical data to support and justify the information in the "for market" application for the intended commercial product. For examples, please see: lines 495-505; lines 580-587; lines 777-780; lines 1317-1326; lines 1469-1472; lines 1573-1593.	These requests for historical information are excessive. Novartis believes much of this information would have been exchanged with the Agency during product development (for example at end-of-Phase meetings), rather than at the time of the original NDA, and is therefore redundant. This information should be consolidated in the Development Pharmaceutics part of the application, and its purpose and use in Application review of the historical information clarified for both industry and FDA staff.
General		This draft cites the GMPs on a regular basis. This is not appropriate. These citations are most prominent in the analytical sections, in which acceptance of results on protocol are discussed. These lines should be removed from the Guidance as being under GMP regulations: Lines 1022-1025; Lines 1035-1038; Line 1089; Lines 1607-1609; Lines 1817-1819.	GMP requirements are covered in separate regulations. Although we are aware of recent FDA initiatives in updating GMPs, it may be premature to integrate specific GMP requirements into the Drug Product dossier requirements prior to the completion of these ongoing initiatives.
IV.C [P.2.3]	580 - 588	The guidance is very specific on what information should be in the equipment comparison table; however, this	This section is an example of information considered excessive for conventional dosage forms.

		amount of detail is typically not required. Change to: **For equipment of different operating design or principle,** *a table should be provided that compares the equipment used to produce clinical batches that support efficacy or bioequivalence and primary stability batches to the equipment proposed for production batches.* *The table should identify (1) the identity (e.g., batch number) and use of the batches produced using the specified equipment (e.g., bioequivalence study batch # 1234), and (4) any significant equipment differences (e.g., different design, operating principle, size).* **Please provide a representative table of equipment similar to that provided in the SUPAC Equipment Addendum**	We also suggest that the agency and industry develop standardized terms for operating equipment, including those for transdermal and other unconventional products, to make the comparison process more consistent and meaningful. Equipment comparisons should be based on existing SUPAC Guidances, where possible.
V.C. **[P.3.3]**	790-796	Change to: • *each manufacturing step, with identification of the* **critical process controls** *and any manufacturing step where, once the step is completed, the material might be held for a period of time (i.e. noncontinuous process) before the next processing step is performed* • *the material being processed* • **critical in-process material tests** *and the points at which they are conducted* • *the type of equipment used (equipment* **vendor model and** *model number is not needed)*	For clarification purposes, it is recommended to revise "critical steps" to "critical process controls" in the first bullet and "critical process controls" to critical in-process material tests" in the third bullet. It is also recommended to reduce the level of equipment detail. The section should be revised **from**: • each manufacturing step with identification of the critical steps and any manufacturing step where, once the step is completed, the material might be held for a period of time (i.e. noncontinuous process) before the next processing step is performed. • the material being processed • critical process controls and the points at which they are conducted

			• the type of equipment used (equipment model number is not needed)
V.C.2 **[P.3.3]**	824-826	BSE statement currently required only for biologics? Please clarify the extent of effort to be expended concerning ruminant-derived materials "**used or manipulated**" at a facility, with respect to pharmaceutical materials. The cited 9CFR94.11 concerns importation of meat and animal products from specified regions.	Regulatory requirement clarification
	849-852	Add word "critical": *Steps in the process should have the appropriate process controls identified. Associated numeric values can be presented as an expected range. All* **critical** *process controls, should be included in the description of the manufacturing process (MPR or narrative).*	"All process controls" are considered too inclusive. Frequently, there are processing controls that have no effect on the quality attributes of the product. These controls may be in place to monitor process yields or efficiencies. These may be added or deleted during routine Production and should not require regulatory action to change.
V.E. **[P.3.5]**	956-958	Please provide examples of where validation documentation is "appropriate" for submission as this information is not typically submitted to the FDA, with the exception of sterilization validation.	It should be made clear that for US submissions the only process validation data needed is for sterile drug products. Further, the level of documentation typically provided in non-US applications is much less than that typically provided in the US for sterile product validation. Clarification of the expected level of detail in light of the CTD harmonization efforts is requested. Process validation is the responsibility of the field inspectors for all other types of dosage forms.
VI.A **[P.4.1]**	1022	We request that the agency clarify the impact the following statement has on reduced testing: *In addition to listing all the tests for an excipient, the specification should identify the tests that the drug product manufacturer will routinely perform and the test results that will be accepted from the excipient manufacturer's certificate of analysis (CofA).*	Does this approach indicate that a supplement will be required if the reduced testing arrangements stated in the NDA are subsequently changed? As a GMP issue, it may be appropriate to remove this point from the draft Guidance (see General point 3).

	1024-1026	Specifications – ID Testing	A CMC guidance should not be citing the GMPs
	1034	Full monograph testing need not be performed **in house** by the sponsor on every batch. Acceptance of data from the vendor can be done if the vendor's data has been confirmed to be comparable to the data generated internally.	Established as part of vendor certification requirements.
VI.C. **[P.4.3]**	1062	Change to: *Analytical procedures for excipients should be validated **as appropriate**.*	We prefer not to state **all** analytical procedures. For example, compendial methods are well characterized and thus need not be validated additionally.
VI.D. **[P.4.4]**	1089	*A certificate of analysis (COA) from the manufacturer and the test results for the same batch from the drug product manufacturer should be provided for the components described in P.4. The information should be for the materials used to produce the batch described in the executed production record (R.1.P)*	The comparative analytical information request need not be submitted in the NDA and the statement should be removed from the draft Guidance. This is part of the qualification process for suppliers (GMP process which should be held internally). Alternatively, Results of tests on the components of EPRs will be included in section R.1.P, as stated in the draft guidance.
VI.F. **[P.4.6]**	Section	Unable to comment as Guidance unavailable	
VII.A. **[P.5.1].**	1174 (Table 3)	Release Specifications should not be included. We trust that IPCs such as "core weight" was provided for example purposes only, and not as an indicator that tablet weight should be part of product release testing.	A true "regulatory" specification is a "control" (stability) specification. Non-functional tests such as dosage unit weight are of limited value as accept/reject criteria; tests such as assay or dissolution provide more useful data. Further, the IPC example again brings up the question if the testing needs to be carried out in the Quality Unit.
	1176	PQIT Testing—why not use the ICH Q6A term "periodic" or "skip" testing, instead of introducing another term?	All testing which is critical to product quality should be listed in the filed control procedure and specifications. Discussions concerning product failure investigations (GMP) are not appropriate for this document. Sponsors should have the option of including periodic

			frequency testing in the filed control procedure and specifications, or, in a separate document. Consistency of terminology with ICH would be helpful to reduce potential confusion.
VII.D.1. **[P.5.4]**	1311 (section); 1317-1326	Batch Analysis – History *A summary of any change in the analytical procedures should be provided if the analytical procedure (1) change over the course of generating the batch analysis data and/or (2) are different from the analytical procedure included in P.52.*	**Batch Analysis Reports** (DELETE THIS SECTION – We fail to see the value of including such extensive information in the NDA since this would have already been included in IND amendments. (Only information required to support justification of the proposed NDA specification is relevant). We feel that this is also redundant as the historical information about the analytical procedures is captured in the stability section (X.C.). We feel that the requirement of a summary of changes is unduly burdensome. If the principle of the assay changes (titration versus HPLC) then this should be included, but minor changes (mobile phase and chromatographic conditions) need not be reported.
VII.E.1 **[P.5.5]**	1344, 1399	*All expected drug product impurities (e.g., degradation products of the active ingredient, residual solvents, enantiomeric impurities, excipient degradants leachables from the container closure system) should be listed in this section of the application whether or not the impurities are included in the drug product specification.*	This implies the potential need for analytical methods that are stability indicating for selected excipients. Under what circumstances are these excipient-related impurities quantified and qualified?
X.C **[P.8.3]**	1607-1609	Stability data to support holding in-process materials for longer than 30 days is not usually provided in the NDA. The data is available internally as per GMPs.	Reference to GMPs

Guidance reference	**Line reference**	**Minor Comments**	**Rationale**

General		Define the terms "critical process" or "critical step" and "PQIT" in the glossary. Use the ICH Q6A term instead of introducing a new acronym (PQIT). Discuss the concept of PQIT's in a separate document that addresses both pre- and post-approval concerns	Clarity of concepts
III.C **[P.1]**	265 269	Change to: *In some instances, the composition of distinct subformulations (e.g., cores, coating) of the drug product **may be** listed separately in the composition statement.* *In these cases, the composition of the immediate release and extended release portions of the drug product **may be** listed separately.*	These changes are suggested to provide flexibility for the presentation. In some instances it may be more illustrative to include both subformulations in the same table. This should be left to the discretion of the applicant in particular if drug substance is not portioned between the parts of the subformulation.
	304, (footnote 10)	Efforts to accept compendia in addition to USP/NF (for example, EP or JP) should be accelerated to provide global consistency.	Global consistency
IV.A.2 **[P.2.1.2]**	451-454	Change to: *An applicant **may wish** to discuss the use of noncompendial–non-novel excipients with the appropriate review division prior to submitting its application to ascertain the level of information that would be warranted to support the use of the excipient.*	Define non-novel (e.g. used in EU, listed in Inactive Ingredient Guide, etc.) at this point in Guidance
V.A. **[P.3.1]**	692	Building #s	Building numbers need not be registered (with the exception of sterile products)
	695-697; 710 (with respect to PAI)	Clarify: *Addresses for foreign sites should be provided in comparable detail, and the name, address, and phone number of the U.S. agent for each foreign drug*	Format (placement in CTD Module 1?) and regulatory requirement question to clarify the number of individuals the FDA would like named in the Application, and whether a change in Agent would necessitate an update

		establishment, as required under 21 CFR 207.40(c), should be included. US agents--The reference to 21 CFR 207.40(c) is for registering drug establishments. The FDA needs a contact or responsible person at the site in question for the purposes of scheduling an inspection as noted on line 710.	to the NDA.
V.C. **[P.3.3]**	832	It appears redundant to the sterile validation information already required for inclusion in the "US Regional" part of a CTD.	Clarification of format for US CTD.
VI **[P.4]**	1003	Please clarify why the "patch" would be different from the drug product.	
VII.E.1 **[P.5.5]**	1344	What is the intention of including excipient degradants as a miscellaneous drug product impurity? How should it be quantified?	
IX **[P.7.]**	1536	Secondary Packaging	Information on non-functional secondary packaging should not be needed in the file