

# GlaxoWellcome

November 22, 2000

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm 1061  
Rockville, MD 20852

**Re: Draft Guidance for Industry: Analytical Procedures and Methods Validation  
Documentation; Notice of Availability Appearing in the Federal Register for  
August 30, 2000, (65 FR 52776) (Docket # 00D1424)**

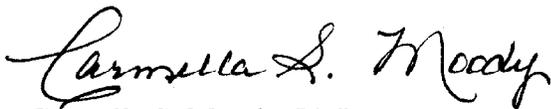
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Dear Sir or Madam,

Enclosed please find comments from Glaxo Wellcome Inc. on the Draft Guidance for Industry: Analytical Procedures and Methods Validation (Docket # 00D1424). These comments are provided to assist the FDA in the further development of this draft guidance. The format for these comments is in a tabular format to aid in review. The first column of the table provides the line number reference for the Draft Guidance, the second column provides Glaxo Wellcome's comments and the third column provides a recommended action to be implemented in the guidance to address the specific comments. We hope this format is helpful in review.

Glaxo Wellcome appreciates the opportunity to provide feedback and suggestions regarding this guidance. If there are any questions or comments, please feel free to contact me by telephone at (919) 483-5754 or by fax at (919) 483-5381.

Sincerely,



Carmella S. Moody, Ph.D.  
US CMC Submissions, World Wide Regulatory Affairs  
Glaxo Wellcome Research and Development

00D-1424

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**COMBINED GLAXO WELLCOME INC. COMMENTS FOR  
FDA DRAFT GUIDANCE FOR INDUSTRY: ANALYTICAL PROCEDURES AND METHODS VALIDATION  
AUGUST 2000**

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<b>Line Number</b>	<b>Comment</b>	<b>Proposed Action</b>
<b>General</b>	<p>The guidance states that "the recommendations apply to drug substances and drug products covered in new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), product license applications (PLAs), and supplements to these applications." While we appreciate that the scope of the guidance is of necessity very broad, the BLA/PLA specific guidance is very minimal.</p>	<p>It would be appreciated if further guidance on potency assay validation requirements could be included in this document.</p>
<b>General</b>	<p>It is indicated that this guidance is to provide further information/clarification relative to ICH guidance documents (ICH Q2A and Q2B, and ICH Q3A) but some information that is presented in the ICH guidance documents is restated here. This restatement of information can lead to confusion over specific terms being used differently from one document to another.</p> <p>Examples:</p> <p>513 – 520</p> <p>551 – 579</p> <p>1000-1001</p>	<p>To avoid confusion, it is suggested that information that is duplicated or restated in this document relative to ICH guidance documents, be stated in the exact terms and using the same terminology as used in the ICH document or preferably, it is suggested that this duplicated information be left out of this guidance to allow readers to focus on the new guidance information. ICH guidance information should be referenced only (as appropriate).</p>

Line Number	Comment	Proposed Action
<p><b>General</b></p>	<p>Throughout the guidance, there are notations indicating that “raw data” and “raw data outputs” are required. However, a clear definition of “raw data” is not provided. If raw data can be assumed to be the electronic signal from an instrument, then this information is available during a Pre-Approval Inspection and should be reviewed at that time.</p> <p>Examples:</p> <p>Line 461, Line 483, Line 499 Line 605 Line 683-684</p>	<p>It is suggested that the term raw data and raw data output be replaced with the word “response” and a clear definition of response is provided in the glossary. Alternatively, the term could be replaced with ‘legible reproductions of representative chromatograms and instrumental recordings’ as per the original 1987 guidance.</p> <p>Response encompasses electronic signal, integrated area, UV absorbance or any instrument output, but it can also mean a chromatogram or an appropriate derivation from raw data such as a calculated drug concentration. It should be left to the company to define what specific information is most appropriate to show control of an analytical procedure and a process with additional data being available for review during a PAI.</p>
<p><b>General</b></p>	<p>Throughout the guidance, it is requested that raw data be included in sample calculations. It is suggested that if a clear equation is provided, with clearly defined variables, providing an example calculation using raw data would provide little if any further information to the chemistry reviewer or an analyst.</p>	<p>Change the notations about “sample calculations performed using raw data” to complete equations with clearly identified variables”</p>
<p><b>General</b></p>	<p>Throughout the guidance, it is suggested that certain information and discussions (most specifically in Section VII.2) should be included in the methods validation section. In many cases, this information is more appropriate for inclusion in other sections of a marketing application.</p>	<p>Clarification is requested whether the Agency is requesting that this information should be specifically included in the Methods Validation sections instead of in other more relevant sections with appropriate cross referencing to the Methods Validation information.</p>
<p><b>General</b></p>	<p>The terms “stress samples”, “samples at the end of life” and “accelerated stress condition samples” may have different meanings in different companies.</p>	<p>It is requested that the terms “stress samples”, “samples at the end of life” and “accelerated stress condition samples” be included in the glossary with appropriate definitions</p>

Line Number	Comment	Proposed Action
44 & 361	The guideline states that validated analytical procedures should be used to analyse "raw materials, intermediates, excipients, container closure components and other material used in the production of drug substances and drug products" but the guideline does not address the validation information appropriate for these components. This comment could lead to confusion that the same stringent approach to validation defined in this guidance should be applied to the validation of these components/materials.	<p>Since specific guidance is not given, it is suggested that the sentence beginning on line 44 and ending on Line 47 should read as follows to avoid confusion:</p> <p>This guidance does not address the submission of analytical procedures and validation data for raw materials, intermediates, excipients, container closure components, and other materials used in the production of drug substances and drug products.</p>
91	The term "acceptance testing" may be interpreted differently between companies and between the US and Non-US Regulatory Agencies.	It would be appreciated if the FDA definition of acceptance testing would be included in the glossary.
120-129	It is appreciated that a clear definition of stability indicating assay and occasions of use has been provided	None
139-140	For biological reference standards, due to the complexity of the molecules and/or mixture of molecules, it may not be possible to fully characterise. For biologicals 'characterise as fully as practical' would be more appropriate.	It is suggested that a sentence be added to the end of the paragraph indicating that biological reference standards should be characterized as fully as practical with guidance from the appropriate review division.
139-140	Reference standards may be prepared by a company as long as appropriate purification and characterization is completed.	Please add additional clarification to the paragraph that reference standards can be internally generated.
142	Clarify that working standards can be qualified against these internal reference standards <u>or</u> fully characterised/tested for suitability as a working standard	<p>The suggested rewording of this sentence is:</p> <p>"A <i>working standard</i> (i.e., in-house or secondary standard) is a standard that is used instead of the reference standard. A working standard is qualified against a reference standard or fully characterized/tested for suitability as a working standard."</p>

Line Number	Comment	Proposed Action
147-148	The sentence beginning on line 147 indicates that a "Certificate of Analysis (COA)" is required for reference standards from non-official sources....". It may be a company's practice, to include complete batch analysis data for the reference standard characterization instead of an officially signed Certificate of Analysis.	Please amend this text to clarify that alternatively batch analysis data from the complete characterization of the reference standard can be provided in the submission.
156	The caveat "that can be obtained by reasonable effort" is appreciated.	None
159	It is appreciated and understood that procedures "more extensive than" those used to control the identity...potency of the drug substance or the drug product are required" for characterization of the reference standard, however, the term "different from" implies that assays that are also used for the Regulatory Specification are not appropriate for use in characterization of the reference standard.	It would be appreciated if the term "different from" could be defined clearly or deleted.
160-162	The statement "should not rely solely on comparison testing to a previously designated reference standard" lacks clarity.	Please provide further clarification as to what additional testing, other than "comparison testing to a previously designated reference standard" would be required to characterize a reference standard.
187	The term "physical form" could be confused with meaning a characteristic such as polymorphic form instead of a descriptive organoleptic characterization.	It is suggested that the term "physical form" be changed to a term such as "physical state".

Line Number	Comment	Proposed Action
192-193	It is a standard GW practice to include a complete description of the methods used to characterise non-compendial excipients and inactive ingredients, in-process controls, Regulatory Specifications and stability parameters such that FDA Laboratories can duplicate the methods for validation testing. However, it has not been a general practice to include specific information on characterization methods such as NMR, MS etc. that are used to further characterise reference standards.	Please provide further clarification regarding what is meant by a "detailed description of analytical procedures" relative to characterisation of reference standards.
205-206	It is indicated in line 205-206 that "specific recommendations for validation of biological and immunochemical test are not contained in this guidance document", however with the advent of "Well-Characterized Biological products, information on basic validation parameters for procedures such as ELISA or Particle Infectivity assays should be possible and would be much appreciated.	It is requested that further guidance on basic validation parameters of the most frequently used biological and immunochemical tests, i.e. ELISA assays, particle infectivity assays etc., be provided.
253	The requirement to describe the number of replicate analyses per sample would preclude the ability to make changes dependent on method and/or process capability without the submission of a supplement to the regulatory application. These details, however, would be available for review during a PAI inspection.	It is suggested that the sentence beginning on line 253 be modified to read:  The <b>minimum</b> number of samples (e.g. vials, tablets) selected, how they are used (i.e., as individual composite samples), and the <b>minimum</b> number of replicate analyses per sample should be described.
318	The requirement to specify the number of significant figures to be reported is implied in the specification and should make it unnecessary to include information on the number of significant figures in a method description.	It is suggested that the phrase on line 318 "including the specific number of significant figures to be reported" be deleted.
332-333	The Quantitation Limit of a method can be below the Quantitation Treshold (ICH Q3A and Q3B term) which is the level specified in the ICH guide that all impurities above this value should be included in the total impurities summation. This statement is therefore, not in agreement with the ICH guidance Q3A and Q3B.	It is suggested that in line 333, the term QL be changed to Quantitation Threshold.

Line Number	Comment	Proposed Action
337	The clarification that process impurities may be excluded from drug product analysis is appreciated.	None
337-339	Rather than state that drug substance process impurities may be excluded from reporting if an acceptable rationale is provided, why not state that drug substance process impurities may be excluded from reporting if it can be demonstrated that these compounds are not also degradation products.	<p>It is suggested that the statement in ICH Q3B:</p> <p>“Impurities present in the new drug substance need not be monitored or specified in drug products unless they are also degradation products.”</p> <p>be substituted for the sentence beginning on line 337 and ending on line 339.</p>
433-436	During robustness testing, only significant effects caused by varying analytical parameters (i.e. parameters that would result in differences in quality control data) need to be discussed or submitted. Additionally, robustness data are taken into consideration when defining system suitability criteria. Provision of instrument output in all cases where an effect is observed would result in inclusion of considerable documentation in the application that are more appropriately reviewed during Pre-Approval Inspections.	<p>The suggested text for the sentence beginning on line 434 is as follows:</p> <p>Such testing should be performed during development of the analytical procedure, and data <b>relative to quality control parameters</b> should be discussed and/or submitted.</p> <p>It is suggested that the sentence beginning on line 436, read as follows:</p> <p>“In cases where an effect is observed, representative instrument output (e.g., chromatograms) should be submitted”</p> <p>be deleted or rephrased to read:</p> <p>“In cases where a significant effect is observed, the effect should be described and supported by summary data, as appropriate”.</p>

Line Number	Comment	Proposed Action
441-448	<p>It is indicated that stressed samples ("products of acid and base hydrolysis...") should be used to demonstrate specificity of the assay. It is noted that stressed samples can contain degradation products that are not observed in formal stability studies used to define expiration periods. Stressed samples of drug substances and products are appropriate for use in method development but not necessarily for method validation. For method validation use of samples at end-of-life (stored at registered storage condition) or samples stored under accelerated conditions for the maximum period defined in the NDA stability protocol are often more appropriate. The comment, therefore, is that the use of stressed samples, as defined above, should not be mandated. Flexibility should be added to allow use of these other types of samples for method validation as described above.</p>	<p>Reword as follows:</p> <p>"Degradation information obtained from <i>stress studies</i> (e.g., Products of acid and base hydrolysis, thermal degradation, photolysis, oxidation) for the drug substance and for the active ingredient in the drug product <b>may</b> be provided to demonstrate the specificity of the assay and analytical procedures for impurities. The stress studies <b>may</b> demonstrate that impurities and degradation products from the active ingredient and drug product excipients at <b>expiry</b> do not interfere with the quantitation of the active ingredient. <b>Ideally, the stability indicating nature of the analytical method can be established by demonstration of peak purity of the active ingredients in product stability samples at expiry or stored under accelerated conditions (e.g. 40°C/75% relative humidity for 6 month; ICH light storage conditions, etc.). Accelerated testing and stress studies are described in various FDA guidance relating to the stability of drug products (see references)."</b></p>
466	<p>The example proposed is one of several ways in which assurances that the impurity profile is adequately characterised may be obtained. The actual approach taken should be scientifically valid and developed on a case by case basis but should not have to be included in the submission but be available during a PAI.</p>	<p>It is suggested that the sentence beginning on line 465 be changed to read as follows:</p> <p>"Additional information should be <b>generated</b> to confirm that the impurity profile is adequately characterized."</p> <p>Additionally, the sentence beginning on line 466 should be deleted or examples of other appropriate methods such as diode array, LC/MS etc. should be included.</p>
473	<p>The paragraph beginning on this line is potentially confusing. How do we know if response factors are or are not <b>close</b>. Guidance should be given on the meaning of close.</p>	<p>It is suggested that the sentence beginning on Line 483 be revised to read:</p> <p>"In cases where the response factors are not close (<b>i.e. 0.8-1.2</b>), this practice may still be acceptable...being overestimated."</p>

Line Number	Comment	Proposed Action
482	The term "complete" could be interpreted to mean all potential impurities, however, the profiles that are most relevant for inclusion are chromatograms that show the typical peaks that are most likely to be seen on a routine basis in samples over time.	It is suggested that the term "complete" in the sentence beginning on line 482 be replaced with "typical or representative."
493-494 509-510	Lines 493-494, and 509-510 state that manufacturing date and date of analysis should be provided. This information (as related to method validation) is not usually presented in an NDA but is available during a PAI inspection. As long as there is a clear documentation trail that is available to link specific information to the original data during the PAI, this information should not be necessary in a submission.	It is suggested that manufacturing date and date of analysis be deleted from the sentence beginning on line 493 and the sentence beginning on line 509.
506	Release testing may encompass more testing than is appropriate for use in monitoring the stability of a drug substance or a drug product. Additionally, release testing is not always the Time Zero point for stability studies.	It is suggested that the sentence beginning on Line 506 be written as follows:  "At a minimum, the submission should include instrument outputs <b>from appropriate stability indicating assays</b> for <b>the initial stability time point</b> and the latest available time point for a <b>representative</b> batch."
549-550	This sentence does not provide an all-inclusive list of analytical procedures that may be used for Identification and does not include any qualifying terms that would indicate other methods are also possible.	It is suggested that the sentence beginning on Line 549 be modified as follows:  "Identification analytical procedures may include tests such as IR, differential scanning calorimetry (DSC), X-ray diffraction (XRD), UV, HPLC retention time, <b>NMR, Raman etc., as appropriate.</b> "
583 - 591	Flexibility should be allowed to include a justification for not performing method validation in the NDA where relevant.	It is suggested that the line beginning on Line 586 be modified as follows:  Information on the specificity, intermediate precision, and stability of the sample solution should be included, <b>where appropriate.</b>

Line Number	Comment	Proposed Action
599	The use of statistical analysis method examples should include examples of programs allowed in Europe, (e.g. ANOVA ).	It is suggested that the sentence beginning on line 599 be modified as follows:  "Statistical analysis (e.g. linear regression analysis, relative standard deviation, <b>ANOVA, etc.</b> ) of methods...to demonstrate the validity of the method."
594-608	It should be recognised that the intention of method validation is to scope the range of conditions suitable for use. As such, the statistical procedures for the analysis of the validation data may not always be fully definable prior to the start of a validation study. The statistical analysis method to be used may need to be augmented or changed based on the results of the validation. As long as there is clear justification for the statistical analysis or lack of statistical analysis, flexibility should be allowed for identifying the statistical procedure used for analysis.	It is suggested that the sentence beginning on line 600 be modified as follows:  "If used, the statistical procedures proposed for the analysis ...prior to the start of any validation study."
610	The section title "Comparative Studies" can be interpreted to have different meanings. This section specifically addresses assay precision.	It is suggested that the title to the section be changed to "Precision" to correlate with the term used in ICH guidance documents.
618	It is not always practical or necessary to statistically analyze all comparative data.	It is suggested that the sentence beginning on line 618 should be modified as follows:  "Comparative results should be statistically analyzed, <b>as appropriate</b> , and discussed and any bias explained."
666	The content of the method validation package is almost identical to the main CMC section of an NDA, excluding the stability section.	It is proposed that a submission be simplified by providing an extra copy of the CMC volume and a "Methods Validation Package" that consists of the list of samples to be submitted and associated material safety data documentation.

Line Number	Comment	Proposed Action
700 - 706	A Material Safety Data Sheet is not necessarily a global term.	<p>It is suggested that the sentence beginning on line 702 be modified as follows:</p> <p>The applicant should include material safety data sheets (MSDSs) <b>or the equivalent</b>, for all samples standards, and reagents (21 CFR 1910.1200(g)."</p>
714	<p>The sentence beginning on line 713 indicates that "representative samples of the product must be submitted". This sentence indicates that only the finished dosage form is required for submission without corresponding reference samples etc.</p>	<p>It is suggested that the sentence beginning on line 713 be modified as follows:</p> <p>"For BLAs and PLAs, representative samples of the product <b>and corresponding reference samples, etc.</b>, must be submitted..."</p>
737	The term "several" can be interpreted to mean numbers greater than one, whereas, generally data from 3 batches is required in actual practice.	<p>It is requested that the sentence beginning on line 737 be modified as follows:</p> <p>"For biological products, samples from several (<b>e.g. 3 batches</b>) consecutively manufactured batches should be submitted.</p>
778	The sentence beginning on line 778 uses the term validated instead of re-validated. Validated is incorrect because validation has already been completed at the time of the submission	<p>It is suggested that the sentence beginning on Line 778 be modified as follows:</p> <p>"The review chemist, in co-ordination with the appropriate FDA laboratories, will decide which analytical procedure are to be <b>revalidated</b>."</p>

Line Number	Comment	Proposed Action
823-832	The information that should be included is information that is critical to performance and reproducibility of the assay. It is suggested that Frit size (line 823) and Filter type (line 824) shape and pore diameter (line 829) is information that is not routinely necessary for performance of an assay.	Delete line 823 (Frit Size) and line 824 (filter type) and include an additional bullet as follows: <ul style="list-style-type: none"> <li>• <b>Any critical column parameters</b></li> </ul> Revise line 829 as follows: <ul style="list-style-type: none"> <li>• <b>Particle type: (e.g. shape, etc.)</b></li> </ul> Add to line 832: <ul style="list-style-type: none"> <li>• <b>Recommended pH range for column use, if appropriate.</b></li> </ul>
849	This guideline should allow the option to determine RSD from a reported average using injections from beginning and end and optionally middle of the run—not just at the beginning of the run without the need to provide justification or for it to be valid only if the assay has a lengthy run time.	It is suggested the sentence beginning on line 849 be modified deleting the phrase: “for assays with lengthy run times or as otherwise justified by the applicant” and changed to read: <b>“However, the reported average may be taken from injections at the beginning and end of the run, or at the beginning, middle and, end of the run.”</b>
862	In many instances different numbers of samples may need to be analyzed and defining specific sequences may lead to compliance difficulties. It may be more appropriate to specify the maximum number of samples between standard injections and critical injection sequences only.	It is suggested the sentence beginning on line 862 be modified as follows: “The sequence of injection of blanks, system suitability standards, other standards and samples should be defined, <b>where appropriate.</b> ”

Line Number	Comment	Proposed Action
867	Only parameters, critical for the preparation and ultimate performance of the mobile phase in the method should need to be defined in the submission.	<p>It is suggested that the sentence beginning on line 866 be modified as follows:</p> <p><b>“Complete details should be provided for the preparation of the mobile phase, including the order of addition of the reagents and the methods of degassing and filtration, if critical to the performance of the method.”</b></p>
925	Minor interference could be acceptable if accuracy is not significantly impacted for a validated method.	<p>It is suggested that the sentence beginning on line 925 be modified as follows:</p> <p>Validation criteria should include specificity (demonstrating no <b>significant</b> interference of placebo)....</p>
973	Optical rotation is an indication of the composition of optically active species in a mixture, not necessarily stereochemical purity.	<p>It is suggested that the sentence beginning on line 973 be modified as follows:</p> <p><b>“Optical rotation is used for the measurement of stereochemical composition”.</b></p>
988	Braces are used instead of brackets around M when it is first used in the equation.	<p>Change: e.e. = 100% * {[M]} - ... to e.e. = 100% * <b>[M]</b> - ...</p> <p>Brackets [] should be used to denote concentration, not braces {}.</p>
1044	An extensive discussion of the reasons for selecting the dissolution medium is most appropriate for inclusion in the method description, not in the methods validation section.	<p>It is suggested that the sentence on line 1044 be modified as follows:</p> <p><b>“A brief discussion of the reasons for selecting the medium, if not included in other sections of the application.”</b></p>
1093	Demonstration of the equivalence of a manual procedure should only be required if a method is new and not yet considered to be “state of the art”.	<p>It is suggested that the sentence beginning on line 1093 be modified as follows:</p> <p><b>“To avoid this delay, applicants should ensure that the automated procedures can be performed manually, whenever possible.”</b></p>

Line Number	Comment	Proposed Action
1108	The reference for "stress studies" is incorrect in the text.	Stress studies Section VII.A.2.c should read Stress studies Section VII.A.2.b
1109	The reference for "Instrument output/raw data for impurities" is incorrect in the text.	Instrument output/raw data for impurities Section VII.A.2.b should read Instrument output/raw data for impurities Section VII.A.2.c
1117	ATTACHMENT A, reads "Representative instrument output and raw data for initial and oldest sample of a batch"	Please revise as follows:  "Representative instrument output and raw data for initial and <b>stressed samples</b> of a batch" to be consistent with the content and instructions in referenced section (Section VII, A.2.b).
Glossary	The GLOSSARY contains a definition for Working Standard but not for Reference Standard.	For completeness, please add a definition for Reference Standard in the glossary.

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