

Global Partner for GMP and RA Issues

**Dornaper Str. 16-18, Haus 1
D 42327 WUPPERTAL,
Germany**

INTERACTIVE
Consulting Associates GmbH

Tel: + 49 (0) 2058-98 17 90 • Fax: + 49 (0) 2058-98 19 09 E-mail: norman.frnklin@wtal.de

Interactive Consulting Ass. GmbH, Dornaper Str.16-18, 42327 Wuppertal

Dockets Management Branch, (HFA 305)
Food and Drug Administration,
5630 Fishers Lane, Rm 1061
ROCKVILLE, MD 20852
USA.

July 14, 2004

Re Docket No 2003D – 0571: DRAFT GUIDANCE for Industry on DRUG
SUBSTANCE CHEMISTRY – Manufacturing and Control Information,
Lines 1290 to 1664 and 1990 to 2254.

Dear Sir/Madam,

As pointed out in my letter of July 4, 2004 an opportunity is being taken to submit comments and suggestions on Docket 2003D-0571 Draft Guidance for Industry on Drug Substance Chemistry by the founder of the above international GMP consulting company who was a member of the ICH Q7a Expert Working Group. Comments are now being submitted on the remaining part of the document (**Lines 1290 to 1664 and Lines 1990 to 2254**) and **it is REQUESTED that they are included in the COMMENT REVIEW PROCESS.**

It is appreciated that considerable efforts have been taken by the CMC CC (probably over a number of years) to provide "Guidance" to the industry on the amount of information required to be submitted in an Application. However as was said earlier it is regretted that these efforts **appear to disregard both the current FDA risk-based approach** to the approval of new drug substances and drug products **as well as the basic ICH Agreement** between the three Regions – USA, Europe and Japan.

Although some doubts may have been expressed that, because ICH Q 7 covers GMP this document does not need to be considered by an Applicant . The agency itself has however given cross references to ICH Q 7a, and therefore apparently accepts the binding nature of this ICH document. This author has cited ICH Q 7a when appropriate.

Summarising up to this point: the ICH Q7a document is part of the internationally accepted ICH documents and cannot be dismissed purely because it PRIMARILY (but not only!!) covers GMP.

2003D-0571

C29

BASIC COMMENT on Docket 2003D-071

This Docket should be considerably revised to bring it into line with the RISK-BASED APPROACH of the FDA and ICH Documents

In an attachment to this basis position, comments are made on the individual subtitles of Docket No 2003D – 0571: DRAFT GUIDANCE for Industry on DRUG SUBSTANCE CHEMISTRY – Manufacturing and Control Information, all of which support the contention that this Docket 2003D-0571 should be considerably revised.

Regrettably before the deadline of July 6 NOT ALL THE SECTIONS could be covered by this author and thus the author is submitting now comments on Lines 1290 to 1664 and Lines 1990 to 2254 in the hope that by granting an extension to the submission date (it is NOT 180 days) these later comments will also be considered.

The author believes that the regulatory authorities and the industry are best served in an open dialogue, (as happened in the Q7a Expert Working Group) and would suggest that in view of the IMPORTANCE of FOREIGN APIs to the US patient, (generic drugs) this dialogue should also include foreign representatives – possibly from the CTD – Q Expert Working Group – who could explain in greater detail what the group agreed up and was signed.

Yours faithfully



Norman C. Franklin

Founder – Interactive Consulting Associates

Attachment 1: Detailed Comment on **Lines 1290 to 1664 and Lines 1990 to 2254** of Docket No 2003D – 0571: DRAFT GUIDANCE for Industry on DRUG SUBSTANCE CHEMISTRY – Manufacturing and Control Information

Attachment 2. Statement on Education, Training and Experience of the author according to ICH Q 7a § 3.3 Consultant.

GUIDANCE for INDUSTRY

Drug Substance

Chemistry, Manufacturing and Controls Information

COMMENTS on the DRAFT GUIDANCE

– Lines 1290 to 1664 and Lines 1990 to 2254

Introduction

These **further** comments **from Line 1290 onwards** have also been prepared by Dr. Norman C. Franklin, an international consultant in GMP and previously Team Leader of the European Industry Team in the ICH Q 7a EWG on GMP for APIs. (See **Appendix 1**, which is now included with these final comments, for the qualification of the author as per ICH Q 7a § 3.)

General Observations

The general observations accompanying the comments on Lines 1 to 1284 are also valid for these remaining lines, in particular however the authors have in some cases gone beyond the CTD-Q or other ICH requirements and included wording, which if followed would result in TWO CTD-Q, one the regions Europe and Japan, and the other for the region USA. This was obviously not the purpose of the CTD-Q and the fact that the representatives of the three regions reached agreement on the contents of the CTD-Q should be respected: The temptation to include requirements going beyond the CTD-Q (or other ICH documents) should be resisted.

This above statement is particularly true when DETAILS are required in certain parts of the submission. The sole basis for judging whether the information IS REALLY NECESSARY is use the yard stick of “is it ESSENTIAL to have this piece of information to assess the identity, quality and purity of the drug substance or is there other information available in the application which can be used in its place. The comments below will therefore be guided by the following principles (a) is this a requirement of CTD-Q, (b) do other ICH (in particular ICH Q 7a) document have these requirements (c) is it **essential** to have this amount of detail. If any one of these three conditions are not met suggestions will be made to change the wording of the draft guidance to fulfil these principles. Such suggested changes in wording will be highlighted in **BOLD PRINTING**.

Lines 1290 and 1308

COMMENT: It is difficult to understand how these two lines are compatible. Line 1290 requires “ A justification for the proposed drug substance specification whilst line 1308 says “The inclusion of a test in a drug substance specification **need NOT be justified**” Although these lines 1290 to 1308 are BASED ON the corresponding ICH Q 6 A wording nevertheless the “word-smithing” carried out has sometimes resulted in the advice being LESS CLEAR than in the original ICH Q 6 A document. For example the inclusion of the wording “toxicology data (Line 1293) gives the impression that toxicology data ITSELF should be included in the relevant justification.

ICH Q 6a however says “**Test data** for drug substances **USED** in toxicology and clinical studies”

In addition the draft document **DOES NOT INCLUDE** the advice that “Approaches other than those set forth in this guide may be applicable and acceptable”. This advice could be very useful if the proposed specification needs to take account of other factors not listed in Lines 1291 to 1298, (e.g. variations due to climatic conditions and harvest time of semi-synthetic drug substances derived from plants. The impression is unfortunately given that a “universal world-wide applicability” in the “Justification of Specifications” (as anticipated in CTD Q § 3.2S. 4.5) is being replaced with TWO DIFFERENT JUSTIFICATIONS the USA-FDA requirement and the EU/JAPANESE requirement. This impression could disappear if the wording of ICH Q 6 a (§3.1.2) was included here as a replacement for lines 1290 to 1377

██████████: **Replace** the wording of lines 1290 (starting with) “Justification for the proposed drug substance specification to line 1377 ” with the corresponding **wording from ICH Q 6a § 3.1.2**

Line 1314 to 1333

COMMENT: In concept of a “sunset test protocol” (although difficult to explain to our Indian clients) is a useful concept permitting IN ADVANCE the concept of deleting certain tests when sufficient test data has been required. It could be useful to define “A Sunset Test Protocol” in the Glossary.

██████████: **Add** a definition of “Sunset test protocol” to the glossary of terms, (**new Lines 2240a.onwards**)

Line 1335 to 1345

By splitting up the original ICH Q 6 A guidance into THREE SECTIONS (Justification of Specification, Tests, and Acceptance criteria) the agency is not only making life more difficult for the applicant than it need be, it is also **ignoring the ICH Q 6 A definition of a “SPECIFICATION”** (see FR Vol. 65,, No 251 pages 83044 and 83051) which is “ A list of tests, REFERENCES to ANALYTICALPROCEDURES and appropriate **ACCEPTANCE CRITERIA** that are NUMERICAL LIMITS, **RANGES** ... for the tests described. Thus the section E “Justification of Specification” should therefore also cover “Justification of Acceptance Criteria”. If the agency had more closely followed the ICH Q 6 A Guide THESE THREE SECTIONS could have been dealt with AS ONE SECTION, and thus avoiding the duplication of wording found in Lines 1290 thro 1345

In addition the draft document does **NOT INCLUDE** certain **ADVICE from ICH Q 6 A WHICH IS VERY USEFUL**, namely “At the time of filing it is unlikely that sufficient data will be available to assess process consistency. Therefore **it is considered INAPPROPRIATE to establish acceptance criteria which TIGHTLY encompass the batch data** at time of filing.” This is **██████████** which was accepted by the Q 6 A Expert Working Group and this **SHOULD NOT BE ELIMINATED** when transferring from ICH to FDA wording.

The discussion on the **Lines 1335 to 1345** could have been shortened if the ICH Q 6A definition of Acceptance Criteria (FR Vol. 65, No 251, pages 83050, § 4) had been included in this document.

In **line 1341** the ICH Q 6 word “**range**” has been **UNNECESSARILY** been replaced by “allowance”. The ICH Q 6 A approach, to point out that the “**RANGE**” i.e. difference between Upper and lower limits for any test” (and the word used in Federal Register Vol. 65, No 251 page 893044 and 83051), should take into account the (often unknown) variability in the manufacturing process and the analytical test procedures, is very important.

Another comment is that the Draft Docket does not include the **IMPORTANT ICH Q 6A CONCEPT** of “Upper confidence limits of three times the Standards Deviation of the Data”. This **AGREED** statistical approach **should not be eliminated** by the **Lines 1344 and 1345**, (“Furthermore any statistical approaches that are used to establish acceptance criteria should be described”)

: In lines 1306 to 1345 delete TESTS and ACCEPTANCE CRITERIA as separate sections and **REPLACE WITH ICH Q 6 A § 3.2 UNIVERSAL TESTS / CRITERIA**

If this radical, (but effective) solution finds insufficient support in the Review committee **AT LEAST**

In **line 1341 replace** “allowance” with the word “**range**”

In **lines 1343 to 1345 replace** “Furthermore any statistical approaches that are used to establish the acceptance criteria should be described” with the words “**The range for any acceptance criteria should usually be calculated by determining the mean of the test value for the batches being considered and setting the Range as the difference between the Upper and Lower confidence limits, these having been calculated by adding three times the standard deviation to the mean for the Upper confidence limit and subtracting three times the standard deviation from the mean for the Lower confidence limit. Alternative statistical approaches may be used if these are explained and justified.**”

Add a definition of Acceptance Criteria to the Glossary of term, (see **new lines 2108 a and 2108 b**)

Lines 1347 to 1366

COMMENT: Even if the “radical solution” proposed above for Lines 1306 to 1345 are accepted this should **NOT** result in the withdrawal of lines 1347 to 1366. The approach here to initially work with “**INTERIM** Acceptance criteria is useful, and could reduce the number of supplementary applications once it is determined that the (sometimes) too narrow ranges included in a submission result in a high number of rejected batches. Thus precautions taken in advance to deal with this situation are welcome.

Keep the wording of lines 1347 to 1366 (provided the “references” are limited to “the assigned MF number and the name of the holder”)

Lines 1368 to 1377

COMMENT: Bearing mind the comments on lines 1343 to 1345 above, the draft docket should also include in line 1377 the reference to ICH Q 6 a (as this gives in "Decision trees" 1 to 7 the methodology for determining Acceptance criteria not only for impurities but other properties). This cross reference will confirm the Agency's acceptance of the ICH Q 6A approach

: Add to lines 1377 the words "ICH Q 6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances"

Lines 1384 to 1389

COMMENT: The "guidance" given here is **not found in ICH Q 3A or 6A** and quite rightly so. The impression is given that non-stability indicating methods are inferior to stability indicating methods without considering **WHY EACH HAS ITS' PLACE**. In many cases, once the overall stability of a drug substance has been determined, and it has been shown that the material is extremely stable, **there is no reason for continuing to use a "stability-indicating" method** particularly if this is expensive or time consuming, e.g. a time-consuming HPLC assay as opposed to a quick and simple UV assay. This concept has also been approved in **ICH Q 2B, I, Introduction 1st Paragraph. Lines 5 to 7** which say "In some cases (e.g. the demonstration of SPECIFICITY) the overall capabilities of **A NUMBER of analytical procedures IN COMBINATION** may be investigated in order to ensure the quality of the drug substance". This concept has been in use for many years, e.g. for the release of B-lactam antibiotics. The wording should be changed to make it clear that under certain circumstances a non-stability-indicating method is quite acceptable for routine release testing.

: Replace the words in lines 1385 to 1389 "justification should be provided for the use of a non-stability indicating assay procedure (upto) quantitatively monitoring impurities including degradants" with the words. **"In some circumstances a non-stability indicating assay procedure can be appropriate. If such assay procedures are used a brief explanation of the advantages these procedures should be described"**

Lines 1393 to 1402

COMMENT: The guidance given in ICH Q 7 a Chapter 11 General Controls, the **LAST THRE PARAGRAPHS have not been adequately considered** in these lines 1395 to 1402 (

These lines 1395 to 1403 have been re-written completely to take account of the ICH Q 7 A principles.

[REDACTED]: Replace the wording on lines 1393 to 1402 with the following:

line 1393 **VII PRIMARY and SECONDARY (or WORKING) REFERENCE**
line 1394 **STANDARDS or MATERIALS**
line 1395
line 1396 **Information on the primary reference standards used in the analysis of**
line 1397 **the drug substance should include whether this was obtained from an**
line 1398 **official source or is an “in-house primary reference standard. If the**
line 1399 **primary reference standard is not from an official source the results of**
line 1400 **the analytical tests used to confirm its suitability as a primary**
line 1401 **reference standard should be submitted. Secondary (or working)**
line 1402 **references standards used for the routine batch by batch testing of the**
line 1402 a **drug substance need not be from an official source but the suitability**
line 1402 b **of such secondary reference standards should have confirmed by**
line 1402 c **comparing these against the primary reference standard. A list of**
line 1402 d **other reference standards used for impurities and intermediates**
line 1402 e **should be included in S 5**

Lines 1407 to 1418

COMMENT: The guidance given here is almost identical to that given in ICH M 4 CTD – Q, which is as it should be.

Lines 1482 to 1483

COMMENT: There is no requirement in the CTD-Q document to submit stability data to support holding times during manufacture. **THIS IS A GMP ISSUE**, and was covered in ICH Q 7a in § 8.2 Time limits.

[REDACTED]: Delete the wording on lines 1482 and 1483 because although this is included in the section “Supporting Studies” and is prefaced with the word “can”, nevertheless the impression is given that such studies “should” be submitted.

Lines 1490 to 1495

COMMENT: There is no requirement in the CTD-Q document to submit the results of Stress testing. This is tool used by manufacturers to determine WHERE degradation products might show up in some chromatographic system and NOT to check the “stability” of the product. In particular where the degradation route has been well described, e.g. for older and well-know drug substance NO stress testing will have been carried out.

[REDACTED]: Delete the wording on lines 1488 to 1495 and IF NECESSARY suggest that Section C Validation of Analytical Procedures (Lines 1223 to 1235 be supplemented with the words: “If **stress studies** were carried out to assist in proving the suitability of the analytical procedures these tests should be briefly described in this section”

ADDITIONAL COMMENT: By suggesting that “Stress testing be covered in the Section on Analytical Validation” it is clear that **NO SUCH DATA would BE REQUIRED** if the Applicant is using already validated methods, and would only be required IF the analytical methods being used were NOT IN ANY OFFICIAL published procedure e.g. in a compendium.

Lines 1510 to 1516

COMMENT: It is welcomed that generally speak it is NOT NECESSARY to provide information on Facilities and Equipment OVER AND ABOVE that required in certain sections of the application. These are GMP issues and can not be easily judged at an office desk but must be seen in the factory environment, e.g. an open centrifuge may be perfectly acceptable to separate off a stable intermediate but would be unsuitable if the factory was located close to a coal coking plant (as the author has seen). **KEEP THIS STATEMENT** in lines 1512 to 1516

Lines 1520 to 1528

COMMENT: The issue raised here is a GMP issue: **avoidance of cross contamination**, and it is not warranted to specifically high-light this risk of cross contamination from TSE or viral adventitious agents whilst neglecting other risks, e.g. the manufacture of β -lactams in the same fermenters as might be used for **non**- β -lactam antibiotics. The risk of serious patient side effects – anapheletic shock with *exitus* is so high that ICH Q7a specifically rejected this multipurpose use – which was not the case with possible TSA agents, etc. **This is a GMP issue** and not relevant to a filing application.

[REDACTED]: **Delete** the wording on lines 1520 to 1528

Lines 1530 to 1547

COMMENT: It can be also argued that the requirements outlined in this section are **ALSO GMP ISSUES** and therefore should be the subject of official inspections **[REDACTED]**

[REDACTED]: **Delete** the wording on lines 1530 to 1547

Lines 1553 to 1617

COMMENT: **NO Comments are being submitted on this section as the author has insufficient experience in this field to provide useful and scientifically sound suggestions for improvements.**

Lines 1628 to 1631

COMMENT: It is welcomed that the agency has recognised that an executed production record, EVEN IF TRANSLATED INTO ENGLISH, is of little value for a process which may need to be scaled up after approval. Executed production records are GMP documents and there is no reason at all for purely selecting these for submission, (perhaps much more important would be a SOP on Cleaning of Equipment in a multi-purpoe plant - but then this will need to be re-written as soon as a change in batch size is made! It is good that this requirement has been dropped **KEEP THIS STATEMENT in lines 1628 to 1631**

Lines 1633 to 1642

COMMENT: An explanation of a “Comparability Protocol could be useful, however it is not understood why it is necessary to add this to **this** document. No positive or negative comments will be made on these lines.

Lines 1663 to 1664

COMMENT: It is welcomed that the agency has recognised the submission of monographs from official compendia only contributes to the profits of the paper-making industry!!. Modern communication tools now make it easy to check the contents of a NON-USA Compendium **KEEP THIS STATEMENT** in lines 1663 and 1664

Further comments on lines 1669 to 1971 ATTACHMENT 1 were submitted in a separate document under the name of this authors

Lines 1976 to 1979

COMMENT: It is welcomed that the agency has recognised that one cannot go infinitely back down the chain which lead to the new drug substance. Thus the statement that it is not necessary to report to the agency post-approval changes to starting materials is sensible. **KEEP THIS STATEMENT** in lines 1663 and 1664

Lines 1979 to 1982

COMMENT: It was hoped that it would not be necessary to include this wording but that it could be replaced by the requirement that the Agency only need to be informed if tests are deleted. However should the starting material manufacturer for example start using benzene in a Friedels-Craft reaction, then it is not appropriate for the drug substance manufacturer to add a test for this solvent to the specification, but also file this new specification under “Changes being effected”. One therefore has no choice but to retain this paragraph even if no test is deleted but a new test is added. **It is NECESSARY to KEEP THIS STATEMENT** in lines 1979 to 1982

Lines 1984 to 1988

COMMENT: This advice should be deleted, as **it is a GMP issue**. ICH Q 7a quite adequately covered the need to the manufacturer maintaining close contact with the supplier in Chapter 7 Material management, making sure the Specification for a raw material is appropriate, (Chapter 11) and also including such changes in the Change Control system, Chapter 13. Thus these lines should be deleted

: Delete the wording on lines 1984 to 1988

Lines 1994 to 2020

COMMENT: This advice is necessary, (but perhaps in less detail). It is appreciated that in the case of starting materials from biological sources it is not always possible to draw up a specification for such starting materials which ALONE would uniquely confirm that it is the material required. Thus as required in the following sections, starting at Line 2022, it will be necessary to provide more detailed information as to the source of the starting material. NEVERTHELESS this section.(lines 1994 to 2020) should be rechecked once the ATTACHMENT 1 (lines 1667 to 1973 have been re-written.

: Review lines 1994 to 2020 once lines 1667 to 1971 have been revised to ensure the two sections are in agreement

Lines 2038 and 2039

COMMENT: This requirement may be impossible to follow. Even if the source of the biological material is exactly known, to give a list of pesticides or herbicides which MIGHT have been used there would mean listing EVERY PESTICIDE approved in the country (IF THERE IS SUCH AN APPROVAL SCHEME !!). This is however a total negation of the RISK ASSESSMENT approach of the agency. The limits for pesticide residues are given based on the risk to the consumer who may **ingest the biological material DIRECTLY**: However this is not relevant in this case as the biological mater will be further treated, e.g. solvent extraction, heating, chromatography, etc. before the drug substance is obtained. Thus it is **highly unlikely** that ANY pesticide residue will pass through to the drug substance.

Also if this requirement is compared with the information required on a chemical starting material **it is not necessary to test for residues of every chemical used in the synthesis of a chemical stating material** (e.g. potassium cyanide used in the Bucherer - Berg reaction to produce hydantoin as an intermediate).

: Delete this requirement in Lines 2038 and 2039 as being IMPRACTICAL to FULFILL.

Lines 2040 and 2041

COMMENT: This requirement may be possible to follow, but will bring very little useful knowledge. In countries like China such companies **ARE THOSE HOLDING an EXPORT LICENCE**, which has no relationship to their ability to control the material they are exporting (see the export of “Synthetic glycerine” from China to Rotterdam which later caused the deaths of over 200 children in Haiti in 1995-996 –FDA investigation by David Pulham). The source of any starting material is a GMP ISSUE, and to have to add this to an application will mean that the application will need to be ammended if the supplier changes. THIS IS NOT in compliance with the FDA Risk-based approach.

: Delete this requirement in Lines 2041 and 2041 as contributing nothing to the ASSESSMENT of the application as it is a GMP requirement.

Line 2048

COMMENT: This requirement may be impossible to follow. Even if the case of a well-known source of the animal starting material (e.g. beef bulls and cows) a list of know pathogens associated with the species would be a full veterinary text book, (and even then my exclude diseases transmitted by ticks or insect bites) The same arguments as used in Lines 2038 and 2039 are as valid here. This requirement is a total negation of the RISK ASSESSMENT approach of the agency. Even if the biological source material is beef lungs (for Aprotinin) it is impossible to know whether any of the lungs of the animals used (and contained in the 50 Kg bags of deep frozen lungs) are infected with specific pathogens. It is **part of the MANUFACTURING PROCESS** to ensure that these are not carried through to the final drug substance, (and the fact that this is possible is shown by the fact that the Aprotinin drug substance is just then diluted and aseptically filled to give a product used in open heart surgery). This requirement should be deleted as being IMPRACTICABLE.

: Delete this requirement in Line 2048 as contributing nothing to the ASSESSMENT of the application and is impracticable.

Lines 2052 and 2053

COMMENT: Following the arguments used in lines 2040 and 2041 above, this requirement **MAY be possible to follow**, but will bring very little useful knowledge. As already stated, in countries like China such companies **ARE THOSE HOLDING an EXPORT LICENCE**, which has no relationship to their ability to control the material they are exporting (see export of Cysteine obtained from chicken feathers, whereby the chicken feather can have come from ANYWHERE in the COUNTRY including those areas which had outbreaks of fowl pest in 2003)

: Delete the “definition” of **Postsynthesis materials** completely, as discussed in the comments to lines 839 to 854

Lines 2192 and 2193

COMMENT: Following the comments on Lines 2184 to 2191 and the request to delete these lines, then as a consequence of this the lines 2192 and 2193 should also be deleted

: Delete the “definition” of **Postsynthesis Material Tests** completely, as discussed in the comments to lines 839 to 854

Lines 2195 to 2200

COMMENT: The concept of testing during a process and using the results of testing (previously known as “In-Process tests (see FR Vol. 65, No. 251, Pages 83051), is covered by **TOO MANY DEFINITIONS** in the Glossary. Preferably keep the definition given in lines 2151 to 2153, and delete lines 2195 to 2201, or take the definition from FR Vol. 65, No 251, pages 83051 as given below, BUT DON'T COMPLICATE THAT MATTER by having too many definitions for the same activity.

: Delete the “definition” of **Process controls and Process Tests** completely and replace IF NECESSARY with

In-process tests: Tests that may be performed during the manufacture of a drug substance or drug product rather than as part of the formal battery of tests conducted prior to release. (The essential objective of such in-process tests is to monitor and assess the performance of the process).

Lines 2207 to 2209

COMMENT: The definition of Residual Solvents given here is that taken from ICH Q 3 C which was drawn up before ICH Q 7a had provided the definition for a Starting Material (i.e. API Starting material). Thus the possibility that residual solvents may also arise from the API Starting materials was not considered in ICH Q 3 a. The definition here however should be extended beyond that given in ICH Q 3 a to include the possibility that a residual solvent in the API Starting material MAY BE carried over to the Drug substance itself.

: Add the to the definition of **Residual solvent** the following text:

“**Residual solvents** may also arise from the organic volatile solvents used in the manufacture of the drug substance starting material and also are not removed by practical manufacturing techniques”

██████████ **Replace** the definition of **Residual solvent** with the the following text:

Residual solvent: Organic volatile chemicals that were present in the drug substance starting materials or are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products, that are not completely removed by practical manufacturing techniques.

Lines 2228 to 2232

COMMENT: The definition used here is limits the word “Specification” solely to the Quality standards provided in an application. (It is for this reason that many development companies still say **THEY HAVE NO SPECIFICATIONS** because the are not upto the point of making a “submission”). As this Draft Guidance is giving guidance on the application of the Common Technical Document, this definition should be replaced by that given in FR, Vol. 65, No 251, page 83051, which is that given in the Common Technical Document.

██████████: **Replace** the “definition” of **Specifications** in lines 2228 to 2232 with the wording as given in Federal Register Vol. 65, No 251, page 83051 namely:.

Specifications A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use.

Lines 2234 to 2239

COMMENT: Regrettably the definition used here is NOT THAT GIVEN in ICH Q7a although in other places in this Draft Guidance the definitions as given in ICH Q 7a (e.g. “Intermediate” or “Validation”) are taken from this ICH Q7a document. This should also be the same for Starting Material.

██████████: **Replace** the “definition” of **Starting Material** in lines 2234 to 2239 with the wording as given in ICH Q 7a and supplement this definition with a **NOTE** on biological sources.

Starting Material: A raw material, intermediate, or a drug substance that is used in the production of a drug substance and that is incorporated as significant structural fragment into the structure of the drug substance. A starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. Stating materials are normally of defined chemical properties and structure.

NOTE Starting materials for drug substances obtained from biological sources should refer to the (1) cells, (2) plants, or parts of the plants, macroscopic fungi or algae or (3) the animal tissues, organs or body fluids which from which the drug substance is derived.

Lines 2240a. NEW onwards

COMMENT: As discussed in the comments made on lines 1314 to 1343 the idea of) submitting IN ADVANCE the concept of deleting certain tests when sufficient test data has been required is welcomed. However the Glossary of terms should be extended to define what is a “Sunset Test Protocol”

_____: **Add** the following definition of **Sunset Test Protocol** in lines 2240a to 2240c as below namely:

Sunset Test Protocol: A proposal by an applicant to delete certain tests from a specification after it has been reasonably well demonstrated that the test is not critical for evaluating the identity, quality or purity of the drug substance or drug product.

Lines 2241 to 2243

COMMENT: Regrettably a “Synthesis branch” appears to be limited to an intermediate “that is to be **COVALENTLY** joined” to another intermediate etc. This definition would there **EXCLUDE** those synthesis branches where the joining occurs through the formation of a salt. An example of this is the manufacture of “Injectable aspirin” in which the final synthetic step is the formation of the L lysine **salt** which itself has been synthesis along a “synthetic branch”.

_____: **Replace** the “definition” of **Synthesis branch** in lines 2241 to 2243 with the wording given below, namely:

Synthetic Branch: A part of a synthesis which is separate from the main synthetic route and which, when joined with the main synthetic route, gives an intermediate suitable for further processing to an drug substance or gives the drug substance itself.

Lines 2245 and 2246

COMMENT: This very much more general definition, (in place of specific definitions such as “Post synthesis material”) is to be welcomed as it can be used in several situations and it indicates that the material being discussed may have the correct structure but is not yet suitable for use in the manufacturer of a drug product. This definition can therefore cover the crude drug substance on a centrifuge before it is washed and dried up to a crystalline drug substance of very low solubility which needs to be micronized in order to provide the bio-availability spectrum required. **KEEP the WORDING of LINES 2245 and 2246**

Lines 2251 to 2253

COMMENT: The acceptance of this definition provided by ICH Q 7a is highly welcomed. Considerable word was put into Chapter 12 on “Validation” and it is highly doubted if a clearer guidance can be found as to what validation is, and that there is a need to fix the **ACCEPTANCE CRITERIA** in advance. bio-availability spectrum required. **KEEP the WORDING of LINES 2251 to 2253**

Global Partner for GMP and RA Issues

Dornaper Str. 16-18, Haus 1
D 42327 WUPPERTAL, Germany

INTERACTIVE
Consulting Associates GmbH

Tel: + 49 (0) 2058-98 17 90 • Fax: + 49 (0) 2058-98 19 09 E-mail: norman.frnklin@wtal.de

Dr. Norman C. Franklin

Summary of Education, Experience and Representation

EDUCATION:

From 1957 to 1963 **B.Sc. and Ph.D** in Chemistry at the University of Nottingham
From 1963 to 1966. **Post-Doctoral Fellowship** in Pharmaceutical Chemistry,
University of Tübingen, Germany, with research into the **use of**
NMR in stereochemical analysis of pharmaceuticals

EXPERIENCE:

From 1998 to present **FOUNDER of Interactive Consulting Associates and Independent consultant** to the pharmaceutical and chemical industry in GMP and specifically Quality Management Systems for Active Pharmaceutical Ingredients and their Intermediates.

From 1992 to 1997 **Head of Corporate GMP and Documentation** in the Tech Ops. Dept. of **Pharma Division** of Bayer AG in Leverkusen, Germany,

From 1989 to 1992 **Head of Quality Assurance of the Self Medication Division** of Bayer AG in Leverkusen, Germany, responsible for the establishment and auditing of quality assurance systems in factories of this division throughout the world.

From 1987 to 1989 **Head of Quality Assurance of the Agrochemical Division** of Bayer AG in Leverkusen, Germany, responsible for the control and release of raw materials and active ingredients for pesticides

From 1984 to 1987 **Head of Quality Assurance of the Diagnostic Division** of Bayer at Elkhart in the USA, responsible for the control and release of solid and liquid diagnostic products

From 1975 to 1984 **Head of Audits and Quality Systems of the Pharmaceutical Division** of Bayer AG, Leverkusen

Responsible for organising and conducting Foreign Audits of all Bayer pharmaceutical manufacturing plants and **auditing Bayer AG active ingredient and drug product plants** in Germany

From 1972 to 1975 **Head of Quality Control Laboratories for Penicillin Analysis of the Pharmaceutical Division** of Bayer AG Leverkusen, responsible for the control and release of penicillin starting materials, intermediates and drug substances from Bayer AG

Global Partner for GMP and RA Issues

Dornaper Str. 16-18, Haus 1
D 42327 WUPPERTAL, Germany

INTERACTIVE
Consulting Associates GmbH

Tel: + 49 (0) 2058-98 17 90 • Fax: + 49 (0) 2058-98 19 09 E-mail: norman.frnklin@wtal.de

From 1966 to 1971 **Lab Manager for Spectroscopic Methods, and later Lab Manager for Formulation Development** at Lilly Research Laboratories, Windlesham, England

REPRESENTATION:

- From 1998 till April 1999 **TOPIC LEADER** for EFPIA, (the European Federation of Pharmaceutical Industries and Associations) on the **ICH Q 7 Expert Working Group (EWG)** on **GMPs for Active Pharmaceutical Ingredients (APIs)**
- From 1995 to 1998 Member of the EFPIA "**Mutual Recognition Committee** on the Mutual Recognition Agreement of GMP Inspections between the EU and the FDA
- From 1995 to 1996 **Chairman of the EFPIA / CEFIC Working Group** on the joint EFPIA / CEFIC Guidelines on GMP for Active Ingredient
- From 1993 to 1997 Founding member of the German VFA (Association of Research based Pharmaceutical Manufacturers) **GMP / QA Group** GMP or the PIC Guidelines.
- From 1993 to 1996 Representative of the German pharmaceutical industry on the **International Standards (ISO) Committee** on the Aseptic Manufacture of Healthcare products, ISO Standard 13408.
- From 1982 to 1983 Representative of the German chemical and pharmaceutical industry at the **OECD** in Paris on the introduction of **GLP in the toxicological testing of chemicals and pharmaceuticals.**

MAJOR LECTURES:

- In September 2003 In **Dublin (Ireland)** at the ICPMA Bi-Annual Conference on APIs, (alongside several FDA representatives) on "Retrospective Qualification and Validation"
- In Barcelona 2002 Plenary lecture in **Barcelona (Spain)** at the 4th CEFIC international GMP conference on "The ghost of Barr"
- In September 2000 In **Hamburg (Germany)** at the CEFIC international GMP conference on "Retrospective Qualification and Validation"
- In September 1999 In **Brussels (Belgien)** at the CEFIC international GMP conference on "European Council Directive 75/319 Current situation"
- In November 1998 In **Baltimore (USA)** at the 4th DIA Conference on Bulk Pharmaceutical Drug Substances (APIs) as expert in the Panel Discussion on the ICH GMP G M P Guide for Active Pharmaceutical Ingredients

Global Partner for GMP and RA Issues

Dornaper Str. 16-18, Haus 1
D 42327 WUPPERTAL, Germany

INTERACTIVE
Consulting Associates GmbH

Tel: + 49 (0) 2058-98 17 90 • Fax: + 49 (0) 2058-98 19 09 E-mail: norman.fmklin@wtal.de

- In March 1998 In **New York (USA)** at the Annual Meeting of the National Association of Pharmaceutical Manufacturers on
"European Industries Views on the Future Direction of GMPs for Active Pharmaceutical Ingredients"
- In February 1998 In **London (UK)** at the IBC international conference on Process Development and Validation on
"Simplifying the Documentation of Process Development and Validation"
- In August 1997 In **Karachi (Pakistan)** at the DIA Conference on Focus on Pharmaceuticals, National and International Issues for the Pakistan Health Board and the Pakistan pharmaceutical industry on "GMP Risks associated with the Manufacture of Finished Pharmaceuticals".
- In June 1997 In **Naantali, (Finland)**, at the annual PIC / PIC-S Conference of inspectors on "Cleaning Procedures for Active Ingredients (and their Validation)".
- In November 1996 In **Philadelphia (USA)**, at the 3rd DIA Conference on Bulk Pharmaceutical Drug Substances (APIs) on
"EFPIA / CEFIC Good Manufacturing Practices for Active Ingredient Manufacturers"
- In September 1996 In **Canberra (Australia)**, at the at the annual PIC / PIC-S Conference of inspectors on
"The EFPIA / CEFIC Good Manufacturing Practices for Active Ingredient Manufacturers".