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

July 4, 2004

**Re** Docket No 2003D – 0571: DRAFT GUIDANCE for Industry on DRUG  
SUBSTANCE CHEMISTRY – Manufacturing and Control Information  
**ATTACHMENT 1: Starting Materials for Synthetic Drug Substance**

Dear Sir/Madam,

An opportunity is being taken to submit **SEPARATE** comments and suggestions on **ATTACHMENT 1: Starting Materials** for Synthetic Drug Substance to Docket 2003D-0571 Draft Guidance for Industry on Drug Substance Chemistry by the founder of the above international GMP consulting company who was a **member of the ICH Q7a Expert Working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**.

It may not be so well known outside ICH circles that the Quality Expert Working Group working on the Common Technical Document (CTD M4 - Q) **ASSIGNED to the ICH Q7a Expert Working Group** at the ICH Meeting in Tokyo in August 1998 **the task of defining an API Starting material and providing advice to the industry on what criteria should be used in choosing an API Starting Material**. This assignment was given further to **THE AUTHOR** of these comments **WHO WAS** at that time the **TOPIC LEADER** of the **EUROPEAN INDUSTRY** in the Q7a Expert Working Group. (This assignment resulted in Chuck Hoiberg later referring to the undersigned as "Mr. Starting Material", - as can be seen from the attached photograph of the undersigned explaining a "API Starting Material" at he ICH meeting in Tokyo in August 1998). Thus the credentials of the author of these comments are not only well established, but also as a consultant to the **intermediate** and **active** pharmaceutical ingredient industry – (hence the company name **INTERACTIVE**) he is representing not a single drug substance API manufacturer but over forty different companies world wide.

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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 choice of a suitable point to start the description of the a synthetic process and it is also appreciated that there is a crying need to revise the 1987 CMC guidelines. However 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 in some quarters it has been argued that Q7a covers only GMP this view is contrary to the decision of the ICH Tokyo meeting and contrary to the basic ICH Agreement. Thus any "Guidance" issued in any of the three regions needs to take account of ICH documents already approved, - just as Q7a cross-referenced existing ICH documents and did NOT write their own version of how to do analytical validation or to carry out stability studies.

**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.

**BASIC COMMENT on ATTACHMENT 1 to Docket 2003D-071**

**This Attachment should be withdrawn by the Agency** as it is NOT IN COMPLIANCE with international guidance previously agreed upon by the Agency.

In an attachment to this basis position, comments are made on the individual sub-titles of Attachment 1 all of which support the contention that **Attachment 1 to 2003D-0571 should not revised but should be WITHDRAWN.**

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 – if necessary under the ICH umbrella.

Yours faithfully



Norman C. Franklin  
Founder – Interactive Consulting Associates

**Appendix:** Supplementary Detailed Comment

**Photo** Norman Franklin explaining the concept of API Starting Material at the ICH meeting in Tokyo, August 1998

## APPENDIX

to comments and suggestions by INTERACTIVE CONSULTING Associates on  
**ATTACHMENT 1: Starting Materials** for Synthetic Drug Substance to Docket 2003D

**Line 1669/70: A statement on what is a starting material**

This statement is **contrary** to the DEFINITION of and API Starting Material given in ICH Q 7a because **it omits the words “SIGNIFICANT STRUCTURAL FRAGMENT”**. In the plenary discussion at the ICH Tokyo meeting in August 1998 it was pointed out that even simple molecules “contribute” to the structure of a drug substance, (the example being given by this author when the photograph was taken was how m-chloroaniline “contributed” to the structure of the anti-malarial drug “Chloroquin”). Thus the additional wording SIGNIFICANT STRUCTURAL FRAGMENT was added to the definition of an API SM.

**Conclusion:** This **ATTACHMENT 1:** to Docket 2003D –0571 should keep the same definition of an API SM as was given in ICH Q7a

**Line 1683/85: A drug substance is not an appropriate candidate as an API SM**

This statement is contrary not only to the EMEA view of what is an API SM, but also **contrary to the view the agency has taken in the past**. Whether this is essential or not **depends not on a rule like this** but **on scientific judgement**. In the case of Ampicillin it is acceptable to use CRUDE Pencillin G as the starting material because it is possible to purify the Ampicillin itself; in the case of Mezlocillin one needs to use pure Ampicillin as the starting material because of the difficulty of purifying the Mezlocillin formed after the condensation reaction

**Conclusion:** This **ATTACHMENT 1:** to Docket 2003D –0571 should keep to the same policy as previously used by the agency, (i.e. use scientific judgement)

**Lines 1696 and onwards: API Starting Materials – with or without a Significant Pharmaceutical Use.**

In the discussion in the Expert Working Group of ICH Q 7a (Q7a – EWG) the idea of **“Commercial Availability” was rejected** as a criterion for designating a substance as an API starting material (API-SM) because *inter alia* it was felt that many commercially available substances were insufficiently described and generally had uses far removed from the pharmaceutical market. The view was that the industry might be lulled into a false sense of security if the API SMs were selected on this principle and not on the principle of having been **PROVEN to be SUITABLE FOR USE**.

**APPENDIX (Continued)**

**Conclusion:** Significant or Non-significant pharmaceutical market for the API SM should NOT BE a selection criteria, of much more importance was that they should have defined chemical properties (which might also cover “stability”) and structure.

**Line 1740 and onwards: Propinquity**

It is highly regretted that this word has been introduced into the discussion AS IT HAS NEVER BEEN USED BY the FDA before NOR IS IT UNDERSTOOD by the non-native English speaking world. The Agency SHOULD HAVE KEPT to the old principle of “number of reaction steps”.

In the discussion in the Expert Working Group of ICH Q 7a (Q7a – EWG) on whether a MINIMUM NUMBER of reaction steps (Line 1743) should be conducted under GMP **this was rejected** as a criterion for designating a point at which GMP activities should start because *inter alia* it was felt that in some cases **JUST ONE REACTION STEP** could be sufficient to give a reproducibly PURE and SAFE API, (e.g. Aspirin is synthesised in just ONE REACTION STEP from a solution of salicylic acid in a suitable solvent). In other cases, **ALTHOUGH THERE IS ONLY ONE REACTION STEP**, the crude material needs to be recrystallised 3 times in order to reduce a reactant – hydrazine – below an acceptable level. Again the view was taken that the industry might be lulled into a false sense of security if a minimum number of reaction steps were prescribed

**Conclusion:** Propinquity (the number of reaction steps) should NOT BE a selection criteria, of much more importance is whether the reaction(s), (bearing in mind the defined quality of the API SMs), are capable of REPRODUCIBLY giving an API of the quality defined in the specification.

**Lines 1743 and onwards: Intermediates need to be isolated and purified.**

It is highly regretted that the suggestion is made that intermediates need to be isolated and purified before proceeding to the final reaction step.

The Q7a – EWG rejected the idea of specifying that an intermediate needed to be “an ISOLATED and PURIFIED material”. On the contrary it said “**Intermediates may or may not be isolated**”. An attempt to specify that intermediates “should be isolated and purified” would be contrary to the agreement reached in Q7a.

**Conclusion:** Isolation and purification of intermediates should NOT BE a selection criteria. Of much more importance is whether the reaction(s), bearing in mind the that the intermediates may not (or CANNOT) be isolated, are capable of REPRODUCIBLY giving and an API of the quality defined in the specification.

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**Lines 1745/46: Changes in the Manufacturing Steps of the Starting Material**

The Q7a – EWG was well aware of this potential risk and therefore introduced in § 7 Materials Management a section on General Controls – which includes not only the need to purchase SMs against a specification but also the need to EVALUATE the suppliers of critical starting materials and follow the “Change Control Procedure” when changing the source. The Q7a – EWG felt that by following these TIGHT GMP principles it should be possible to reduce the risk of new impurities being carried through to the API. This, coupled with the need to “compare the impurity profile of the API with the profile in the regulatory submission” (ICH Q 7a Chapter 11, Section 11.2 – 3<sup>rd</sup>. Paragraph) was thought to be sufficient to reduce the risk of new impurities being found in the API.

**Conclusion** The need to have “several reactions steps” to decrease the risk of impurity carry over WAS NOT ACCEPTED BY Q7a EWG and should NOT BE a selection criteria.

**Lines 1748/57: The risk of impurities being carried over decreases with the number of Manufacturing Steps – A reaction followed by multiple purification should be counted as a single reaction step.**

Unfortunately the concept that an increasing number of reaction steps results in a decrease in the risk of impurities being carried over coupled with the statement multiple PURIFICATION STEPS should be considered as ONE reaction step is **SCIENTIFICALLY UNSOUND!**

Every chemical reaction produces more or less the desired substances ( C )

i.e.  $A + B \rightleftharpoons C + D$

However no matter how hard we try, at the end of the reaction we may have produced our required C but **this is contaminated with A, B and D**. If we now take C and do not purify this we will, in the next reaction to give us F

i.e.  $C + E \rightleftharpoons F + G (+ A + B + D + \text{residues of C and/or E})$

have our desired product **but now contaminated with A, B, D and G and residues of unreacted C or E**. Even this simple example shows how the number of impurities **RISES** with a increasing number of REACTION STEPS and it is only when the manufacturer introduces PURIFICATION STEPS at appropriate points in manufacturing chain does he (or she) finish up with an API meeting the proposed specification. Simply put: three purification steps are to be preferred to one reaction step when we need to reduce the amount of impurities.

**Conclusion** Not only should this statements about “increasing number of reactions steps” be deleted here, **it should not be included in any replacement guidance**. In countries where process development is almost negligible (e.g. Mainland China where usually the original patented process is followed), this statement will definitely lead to a ~~raise sense of security – as been found by this author when auditing in China.~~

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**Line 1768: An API SM should be “isolated and purified”**

It was previously mentioned that although the Q7a EWG accepted that “isolated and purified” starting materials MAY reduce the risk of carry over of degradants and/or other impurities into the API **THIS IS NOT THE ONLY WAY OF DOING THIS**. The Q7a – EWG therefore rejected the idea of specifying that an starting material needed to be “an **ISOLATED and PURIFIED** substance” and **DID NOT INCLUDE THESE REQUIREMENTS in their DEFINITION of an API Starting Material** - and quite rightly so – as the example of Aspirin shows daily.

**Conclusion** The need to have an API SM as an “isolated and purified substance” **WAS NOT ACCEPTED BY THE Q7a EWG** and thus suggestions that this should be a criteria is **CONTRARY** to the **APPROVAL** given to ICH Q7a by the agency.

**Line 1775: Carry over of Impurities.**

The concepts advanced here are **NOT IN COMPLIANCE** with the concepts for impurities described in **ICH Q 3 A** where **IT IS ACCEPTED that IMPURITIES from API SMs may be the SOURCE of SIGNIFICANT LEVELS of IMPURITIES in the drug substance.** There is no **demand** in Q 3 A to reduce the levels of the impurities in the API SM so these are no higher than 0.1 in the drug substance **This ICH Q 3 A approach is correct.** Solely because we are capable now-a-days of routinely detecting and quantifying impurities down to levels of 100 ppm or less is not **in itself** a reason for banning such impurities. This concept is now well recognised when establishing the residues of pesticides in foodstuffs (where the daily intake could be 100 to 200 times higher than in drug products). The criteria for “levels of impurities” as defined in ICH Q 3a is **NOT “SIGNIFICANT LEVELS” ALONE** but whether the level of impurities “produces toxic or pharmacological effects.”

**Conclusion** The need to eliminate *per se* the quantity of impurities in an API SM if this results in any of these impurities appearing at a “significant level” (i.e. above 0.1 %) in the drug substance is **CONTRARY** to the **APPROVAL** given to ICH Q3 A by the agency and thus should **NOT BE** a selection criteria for an API SM.

**Line 1799: Complexity of Structure**

The suggestion in the rest of this paragraph, (**LINES 1801 to 1818**) is that the API SM **ITSELF** should be readily distinguishable from its potential isomers etc. However this **SHOULD NOT BE A COMPULSORY SELECTION CRITERIA**. The manufacturer may consciously decide to use an isomeric mixture as an API SM rather than a pure isomeric substance because the subsequent reactions are so selective for **ONE ISOMER** that other isomers are eliminated in the course of the production. He may even decide to conduct **ALL THE REACTIONS** with an isomeric mixture and then finally eliminated the unwanted isomers **to give the pure isomer at the last step.**

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The synthesis of Cerivastatin is a classical example of such a procedure, the required isomer being present in the penultimate step to approx. 80%. However the final step eliminates all the unwanted isomers and the API itself is obtained in over 98% optical purity.

**Conclusion** The need to have an API SM as a substance “readily distinguishable from potential isomers etc.” was not even debated by the Q7a EWG as it was clearly left to the manufacturer to decide what were **APPROPRIATE ACCEPTANCE CRITERIA for and API SM (ICH Q 7a Section 11.1 General Controls**: “All specifications ..... should be **SCIENTIFICALLY SOUND AND APPROPRIATE**”). The agency should eliminate any need to have an API SM substance “readily distinguishable from potential isomers etc”.

**Lines 1807 to 1809: A proposed API SM should possess only a limited number of functional groups etc.**

The suggestion in these lines is that one need to go back to “simple chemical molecules” This concept was, quite rightly, **REJECTED BY Q7a EWG** (The famous statement being made during the discussions: “There is no need to go back to Earth, Fire and Water!!”) This rejection found its place in the definition of an API SM as a material that is incorporated “**AS A SIGNIFICANT STRUCTURAL FRAGMENT** into the structure of the API”. With this wording the EWG **REJECTED THE NEED** for an API SM to be a “simple molecular entity” The number of functional groups **SHOULD NOT BE A COMPULSORY SELECTION CRITERIA**. The manufacturer may consciously decide to use a starting material where he has confirmed that the required functional groups are present rather than go back in the synthesis to where some of these are introduced **AND THEM ELIMINATED THOSE HE DOES NOT WANT**

**Conclusion** Simplicity of structure should **NOT BE A CRITICERIA** for choice of an API SM as this is not only contrary to the definition of an API SM in ICH Q 7a but also neglects the advances made in modern analytical chemistry to confirm a structure of a material. The agency should eliminate any need to limit the number of functional groups or structural features.

**Lines 1815 to 1818: If advanced techniques suitable for complex structures (<sup>1</sup>H-NMR, <sup>13</sup>C-NMR Mass spectrometry etc) are needed then the chemical is not an appropriate candidate as an API SM**

It is highly regrettable that techniques such as <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, Mass spectrometry etc. are given as “advanced techniques”. **<sup>1</sup>H-NMR was in use over 40 years ago**, (this author used this technique in 1965 to distinguish between the four isomers of menthol – see the Proceedings of the International FIP Congress in Prague 1965!!) There is not the slightest reason why one should not use **ALL THE POWERS OF ANALYTICAL CHEMISTRY** to distinguish between possible isomers of starting materials if this is appropriate.

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This one of the main reasons why the original FDA Guide of 1987 is NO LONGER APPROPRIATE because it relied almost entirely on “commercial availability” as the criteria for selection of an API because, even at that time, doubts were still present as to the specificity of instrumental analysis in determining the structure of a starting material

**Conclusion** The time has now come to recognise that instrumental analysis is almost an essential tool in structure confirmation. **NO LIMITATIONS** should be placed on the analytical techniques which may be used to confirm the structure of an API SM **IRRESPECTIVE of HOW COMPLEX THIS IS**. This change of policy would then be in line with the decisions taken by ICH Q 7a EWG:

**Lines 1821 to 1971: Documentation**

No individual comments on these lines will be provided THIS WHOLE SECTION NEEDS TO BE RE-WRITTEN in the light of the comments made on the lines 1669 to 1818

**Conclusion** The agency should completely re-write the section of the documentation to be provided in S 2.3. The suggested information that the applicant should provide is in many instances contrary to the international agreements concluded in ICH Q 3A, ICH Q 7a and ICH M 4 Q and there is NO hope that purely addressing one or two paragraphs will eliminate this lack of compliance, this section **NEEDS a COMPLETE REWRITE.**

## Expert Working Group ICH Q 7a



## Explaining the Philosophy behind “Significant Structural Fragment” of an API Starting Material

