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

July 6, 2004

Re Docket No 2003D – 0571: DRAFT GUIDANCE for Industry on DRUG
SUBSTANCE CHEMISTRY – Manufacturing and Control Information

Dear Sir/Madam,

An opportunity is being taken to submit comments and suggestions on Docket 2003D-0571 Draft Guidance for Industry on Drug Substance Chemistry by the founder of the above international GMP consulting company who was a **member of the ICH Q7a Expert Working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

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 certain tasks including that 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 was taken into account when writing the comments and suggestions included as an Attachment to this letter.

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 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.

Also some doubts have been expressed that because ICH Q 7 covers GMP this document does not need to be considered by an Applicant. 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 **all** 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.

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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 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 sub-titles 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 considerably revised.**

Regrettably before the deadline of July 6 NOT ALL THE SECTIONS could be covered by this author and thus the intention of the author is to submit within the next couple of weeks comments on lines 1314 to 1665 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

A handwritten signature in black ink, appearing to read "N. C. Franklin". The signature is written in a cursive style and is positioned above a horizontal line.

Norman C. Franklin
Founder – Interactive Consulting Associates

Attachment: Detailed Comment on Lines 1 to 1308 of Docket No 2003D – 0571: DRAFT GUIDANCE for Industry on DRUG SUBSTANCE CHEMISTRY – Manufacturing and Control Information

GUIDANCE for INDUSTRY

Drug Substance

Chemistry, Manufacturing and Controls Information

COMMENTS on the DRAFT GUIDANCE

Introduction

These comments have 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** for the qualification of the author as per ICH Q 7a § 3.)

General Observations

In general the authors of this Draft Guidance have very successfully taken the Common Technical Document – Quality (CTD-Q) and explained in a lucid manner what the applicant should submit to the Agency in order to meet the CTD-Q requirements. Unfortunately 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. It is obviously neither of interest to the agency nor to the industry if such details have to be continuously updated to cope with local environmental or safety regulations, not to mention the need to remain competitive. Thus although the “natural curiosity of a reviewing chemist” often leads to detailed requirements, this trend should be resisted, and 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**.

As this guidance is not specifically limited to new drug substances which would be the subject of a NDA many of the requirements are either impossible to fulfil, e.g. the full development history or are inappropriate, e.g. several spectroscopic identity test for drug substance which are already in a pharmacopoeia. The comments here will relate primarily to NEW DRUG SUBSTANCES although it will be pointed out where the Guidance is inappropriate for grandfather” drug substances.

Line 34

COMMENT: In the Guidance Document here (and at other places) the words “Drug Substance” are used.

Although this is the traditional name used by the FDA for the substance impacting the pharmacological activity to the drug product, this could be the opportunity to change this name to bring it into line with ICH Q 7a nomenclature because this document will in the future be used by an international audience.

[REDACTED]: Replace the words “Drug substance(s)” here (and at all other places with “API(s)” and add the definition of API given in ICH Q 7a to the Glossary
(However the words “Drug substance(s)” will be used in this commentary purely to make it easier for the USA reader to follow the comments).

Lines 50 and 51

COMMENT: The words “a highly purified and well characterised intermediate derived from plants or animals” are used.

Although this may be ONE of the ways of confirming the correct structure of drug substance, in many cases the production of the drug substance follows from a less well characterised and certainly NOT a HIGHLY PURIFIED intermediate. The purification is often the major part of the production process and the correct structure of the final drug substance is confirmed by several physical techniques.

[REDACTED]: Delete the words “**highly purified and well characterised**” before the word intermediate”

COMMENT: The words “**intermediate** derived from plants or animals” are used.

It is contended the following ICH Q 7a the word “API Starting material should be used here as it was set down in the Table in Section 1.3 of the ICH Q 7a document. (Although the biological source of the API starting material may need to be named in the application, this is insufficient reason for defining that materials derived from such a source is AN INTERMEDIATE

[REDACTED]: Replace the word “**intermediate**” with “API starting material”

Lines 52 to 54

COMMENT: It is difficult to understand why the “chemical modification of an intermediate produced by conventional fermentation” falls under this guidance but the “chemical modification of a starting material produced by conventional fermentation” would NOT fall under this guide.

As many amino acids are produced by conventional fermentation this would mean that any drug substance made from these would not fall under this guide. This surely cannot have been the intention of the agency..

[REDACTED]: On line 53 replace the words “of an intermediate” with the words “**of a starting material and/or an intermediate** ”

Line 67

COMMENT: Drug substance produced by conventional fermentation are NOT COVERED by this Guidance (e.g. Penicillin G) whereas a semi-synthetic drug produced by modification of a product produced by fermentation (e.g. Ampicillin) ARE INCLUDED.

The logic of this argument is hard to follow particularly as ICH Q 7a in Chapter 18 came to a different conclusion.. Essentially it is said there that “Certain APIs of low molecular weight such as antibiotics, amino acids, vitamins and carbohydrates can **also** be produced by rDNA technology and the level of control for these types of APIs is similar to that used for “classical” fermentation” Thus **irrespective of what technology is used** the resulting crude drug substance has to be purified before it may be used. This only difference is the way purification is carried out (e.g. of Penicillin G as opposed to the purification of Ampicillin). In the first case this is carried out by PHYSICAL MEANS, (e.g. chromatography) whereas in the second case it is carried out by CHEMICAL MEANS. Both are however acceptable methods of purification. Thus drug substances produced by convention fermentation **as well as r DNA technology** should be included in the guidance if the resulting drug substance is of low molecular weight.

[REDACTED]: **Delete** the Lines 66 to 68.

Insert between Lines 54 and 56 a **[REDACTED]**: **“Low molecular weight drug substances derived directly from or manufacturing operations involving fermentation (conventional fermentation or using rDNA technology or tissue or cell culture.)”**

Line 73

COMMENT: The wording “as scientifically appropriate” **is highly welcomed**. As in the ICH Q 7a GMP Guide it is recognised that not all situations can be covered in a guidance document and therefore it is necessary for the applicant to think what is “Scientifically appropriate”

Keep this wording

Lines 79 and 80

COMMENT: The explanation of the use of the word “SHOULD” is necessary because this word is used in a different meaning in the ICH Q 7a Guide.

[REDACTED]: **Add** to Line 80 the words **“This use of the word “should” in this guidance is NOT the SAME as the use in ICH documents.**

Lines 129 and 130

COMMENT: The wording “should be presented separately in the application (which) means one complete S section for one drug substance followed by an other complete S section for additional dug substances.” places a burden upon the applicant to duplicate information which may already be in the one section.

However in the light of present-day word processors, which can easily duplicate information on the click of a button, this burden is tolerable, as it simplifies a review. An exception can be made here.

Keep this wording Lines 154 and 155

COMMENT: The wording “This guidance references ICH guidance documents cited in CTD-Q and FDAs guidance on general technical topics” is welcomed as it recognises the fact that, as a signatory to the ICH agreement, documents which have been approved by FDA representatives in the EWGs are in fact binding on other part of the agency.

Keep this wording

Lines 194 to 197

COMMENT: The wording “each reference to information submitted in another application must identify where the information can be found in the referenced application” places an impossible burden upon the applicant and in many cases the referenced information is confidential and the applicant will not know where it is to be found.

SEE ALSO The comments on lines 216 to 218

[REDACTED]: Delete “where the information can be found in”

Line 210

COMMENT: The wording “The CMC information in a Type II MF can be organised in CTD-Q format” is welcomed because it leaves it up to the MF holder to decide if or when the CTD-Q format should be used. There is NO COMPULSION to re-write the MF in CTD-Q format if the MF is being revised. Keep this wording

Lines 216 to 218

COMMENT: The wording “should be identified by name, reference number, volume and page number of the MF and date of submission” may assist the reviewing chemist in locating the referenced information more quickly but the wording in this form places a burden upon the applicant which cannot be met.

The whole purpose of submitting a MF is to give confidential information to the FDA which is NOT AVAILABLE to the applicant.

The applicant can however only give the information required by the wording of lines 216 to 218 if he/she has a copy of the MF. As such information is in fact confidential the applicant will not know by volume and page WHERE it is to be found.

SEE ALSO Similar comments were made on lines 194 to 197

[REDACTED]: Replace “name, reference number, volume and page number of the MF and date of submission” with the text: “**the assigned MF number and the name of the MF holder**” so that the sentence on

[REDACTED] “The incorporated material should be identified by **the assigned MF number and the name of the MF holder**”

Line 239

COMMENT: The wording “In general a MF can be referenced for the information recommended in Section 2.2 through 2.6” is a sensible comment PROVIDED the reference is limited to the assigned MF number and the name of the MF holder (as discussed in the comment on lines 216 to 218).

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

Line 246

COMMENT: The wording “However the information should be augmented by the applicant as appropriate” could lead to some discussion (The ICH Q 7a EWG was criticised for using the words “when appropriate too often!) The change in wording may eliminate further discussion.

[REDACTED]: Replace the words “as appropriate” with the text: “**when the applicant carries out, or has carried out, steps to change or measure the physical properties of the drug substance**”

Line 281

COMMENT: The wording “A methods validation package should be included in the application” might leads to some misunderstanding in those parts of the world where the native language is not English (an also even in English-speaking countries!). It should be made clear that this requirement **does NOT APPLY to production methods** by making the change in the text as given below:

[REDACTED]: Replace the words “A methods validation package” with the text: “**The analytical methods validation package**”

[REDACTED] “ **The analytical methods validation package should be included in the application (R.3.S).**”

Line 287

COMMENT: The wording “Type II MFs for drug substance intermediates can also be submitted in CTD-Q format” is welcomed because it leaves it up to the MF holder to decide if or when the CTD-Q format should be used. There in NO COMPULSION to re-write the MF in CTD-Q format if the MF is being revised.

Keep this wording

Line 336

COMMENT: The wording “A **list** should be provided of the general physicochemical properties of the drug substance” might leads to some misunderstanding in those parts of the world where the native language is not English. It should be made clear that this requirement does NOT mean that these physicochemical properties **should always be tested in every batch** of material, but only be tested if they are included in the drug substance specification as discussed under Control of the Drug Substance (Lines 254 to 261).

[REDACTED]: **Add** to Line 360 the words “**If any of these general physiochemical properties of the drug substance are tested batch-for-batch as part of the “Release testing” of a batch, these properties should included in the Drug Substance Specification (see line 1080), otherwise it is not necessary to routinely test these properties.**

Line 383 and 384

COMMENT: The wording “Building numbers or other specific information should be provided for multiply facility campuses” is **NOT a requirement of CTD-Q** (See 3.2 S 2.1) and is **an unnecessary burden** both for the industry and the authorities. This will lead to either every building on the campus **which might possibly be used** either during small scale production or after process scale up being listed (and the reviewing chemist has no opportunity of checking – even during the inspection –if this is correct), or the authorities will be overloaded with small and insignificant statements such as “We are now using Building 23 to conduct the hydrogenation in Step 4 of the synthesis”.

Bearing in mind the efforts put into BACPAC 1 to reduce insignificant reporting and the trend to use “risk analysis” to determine whether there is a significant patient risk it is proposed that the wording of lines 383 to 386 be deleted.

[REDACTED]: **Delete** the words “ **Building numbers or other specific information should be provided for multiply facility campuses”**

Lines 392 and 393

COMMENT: The wording “Facilities should be ready for inspection when the application is submitted to the FDA” is **contrary to the wording of ICH Q 7a.**

ICH q 7a § 12.43 states that “Process validation should be completed **before commercial distribution** of the final drug product manufactured from that API” This wording was chosen by the EWG to indicate that process validation did **NOT NEED to** (and if fact probably **should not**) **BE COMPLETED** before submission of the an application. This is because such process validation may need to be repeated if, in the course of the review of the application, changes to the final product specification are requested and agreed upon. This could then invalidate the data collected during the process validation activities and under such circumstances the process validation would have to be repeated. For this reason, in order to conserve resources, the ICH Q 7a EWG moved the process validation activities **RIGHT TO THE END** of the development activities, **AFTER THE SUBMISSION.** As this is the case, **WHEN the FACILITIES are LOCATED ABROAD they would NOT BE READY for the INSPECTION.** It should be left to the application, in discussion with the Compliance Branch to decide **when the facilities are ready for inspection.** **This is thus a GMP issue** and should be deleted from this draft guidance.

[REDACTED]: **Delete** the words “ **Facilities should be ready for inspection when the application is submitted to the FDA”** ”

Lines 392 to 498

GENERAL COMMENT on these lines: There is unfortunately a clear indication in this part of the Draft that firstly the requirements **go well beyond those agreed upon in the Common Technical Document – Quality** and secondly REQUIRE the SAME INFORMATION to be SUBMITTED in DUPLICATE. This is a waste of resources both those of the applicant and the FDA reviewers themselves. The following comments are to designed to eliminate this.

Lines 414 to 417

COMMENT CTD – Q Section 3.2 S 2.2 requires a flow diagram that includes molecular formulae, weights yield ranges etc. **There is NO REQUIREMENT** to identify the “those steps that are critical” in the flow sheet. This is only required in the “sequential process narrative”

[REDACTED]: Delete the words “**with identification of those steps that are critical**”

Lines 420 to 422, 504 and 541

COMMENT In the CTD – Q Section 3.2 S 2.2 **there is NO MENTION** of the term “post-synthesis materials” in the flow sheet. This term has been added in the FDA Draft Guidance although it occurs no where in the CTD-Q document and is in fact just another word for “drug substance” and only complicates the process description without adding anything of significant importance to the process flow sheet. (See comments on lines 839 to 850):

[REDACTED]: Delete the words “**post synthesis materials**”

NOTE : This also applies to the use of this term in *inter alia* 772 to 777.

Line 423

COMMENT In the CTD – Q Section 3.2 S 2.2 the term “weights” are included but this **does NOT MEAN** “molecular weights” but the actual weights of the materials which would be used in a typical batch. The term “molecular weights” has been added in the FDA Draft Guidance although **it occurs no where in the CTD-Q document.** the molecular formulae is sufficient in a flow sheet

[REDACTED]: Delete the words “**and molecular weight**”

Line 426

COMMENT In the CTD – Q Section 3.2 S 2.2 **there is NO MENTION** of the term “critical process controls and the points where they are conducted” in the flow sheet. This is only required in the “sequential process narrative”

[REDACTED]: Delete the words “**Critical process controls and the points where they are conducted.**”

Lines 428 to 430

COMMENT In the CTD – Q Section 3.2 S 2.2 **there is NO REQUIREMENT** to indicate in the flow sheet whether the intermediates are used in situ or isolated before being used further and even in the process description this is not specifically requested, (although it will probably be apparent from the description of the process whether the intermediates are isolated or not)

The term “Final intermediate” has traditionally been used by the FDA but this term was NOT INCORPORATED INTO the CTD-Q. It should therefore no longer be used in this guidance document.

[REDACTED]: Delete the words “**An indication of whether intermediates are used in situ or isolated before being used in the next reaction step and which intermediates are considered the final intermediates.**”

Line 431

COMMENT In the CTD – Q Section 3.2 S 2.2 **there is NO MENTION** of the need to give the “yield at each reaction step” because a yield can only be determined if the material is isolated. Where a reaction step results in an “in situ intermediate” any determine of “yield” would involve either determining the concentration of the intermediate in the solution or the isolation of the intermediate in order to weigh it. Even then **the number obtained would have negligible scientific value** because unless the material was dried the weight would be the combined weights of the isolated product, the residual solvent and any impurities isolated at the same time.

[REDACTED]: Replace the words “Expected yield (percent) for each reaction step” with the words “**Expected yields ranges when materials with a determined assay are isolated**”

Lines 433 and 434

COMMENT Although CTD – Q Section 3.2 S 2.2 requires that molecular formulae, and chemical structure of starting materials be included in the flow diagram, in certain cases the molecular weight of the starting materials are unknown as are the chemical structures. In such case it is appropriate to give the trade or proprietary name of the reagent, etc., e.g. Celite. This then not only specifies a reagent with a particular quality but also reduces the tendency to replace such specific reagents with a “generic” equivalent e.g. “diatomaceous earth” (which probably will not be such an effective column packing material..

[REDACTED]: Replace the words “should not be identified using only trade (i.e. proprietary) names” with the words “**may also be identified using trade names.**”

Line 443

COMMENT Although CTD – Q Section 3.2 S 2.2 requires that the process controls be included in the narrative description of the manufacturing process it does not include the numerical ranges and limits in this section 32. S 2. 2 but requires these to be included in 3.2 S 2.4. In the “Question and Answer” document on CTD-Q it is also stated that “All process controls should be **IDENTIFIED** in 3.2 S 2.2 nevertheless “the acceptance criteria” (i.e. numerical ranges and limits) should be presented in 3.2 S 2.4.

[REDACTED]: Delete the words “**and the associated numeric ranges, limits or acceptance criteria**”.

Line 446

COMMENT CTD – Q Section 3.2 S 2.2 requires that a NARRATIVE of the manufacturing process be included. According to a member of the Expert Wording Group this wording was very carefully chosen and agreed upon to make it clear that all the details of the manufacturing process were NOT required. This principle is not being followed in Line 446 which should be the case.

[REDACTED]: Replace the word “The detailed description” with the words “**The sequential narrative**”.

Line 449

COMMENT The wording “A detailed description of each manufacturing step” is not in compliance with CTD – Q Section 3.2 S 2.2, (see reasoning above). CTD – Q Section 3.2 S 2.2 however requires that the “operating conditions (e.g. temperature, pressure, pH, time) be included in the narrative of the manufacturing process and this should also be the requirement in this Guidance. However it must be remembered that NO MANUFACTURING PROCESS ever uses a temperature, a pressure, a pH, or a time and therefore in the guidance document all of these operating conditions should given AS A RANGE. (This is because ICH Q 7 a would require an GMP investigation into the “deviation” if this number was not maintained. (It is however part of process development **to DETERMINE the RANGES** within which the process can be successfully operated, and if these ranges are maintained, then this is not a deviation under ICH Q 7a).

[REDACTED]: Replace the words “A detailed description of each manufacturing step” with the words “**The ranges of the operating conditions, (e.g. temperature ranges, pressure ranges, pH ranges, time ranges)**”.and move this line to **Line 455 a**

Lines 450 to 453

COMMENT Although CTD – Q Section 3.2 S 2.2 does not require in the NARRATIVE of the manufacturing process that the names of the starting materials, intermediates solvent and reagents, etc., be given this is nevertheless advisable.

However in certain cases the chemical or biological names may not be or are too unspecific, (See comment on Lines 433 and 434) thus trade or proprietary names should also be allowed.

In the same sections the word “quantities is used. Unlike drug product manufacture very frequently the quantities are specified within a range (e.g. Silica gel 200 – 250 Kg to give a column height of a minimum of 2 m). This industrial practice should be reflected in the wording of the guide

[REDACTED]

Replace the words “with chemical or biological names and quantities specified” with the words “**with chemical, biological or when appropriate trade names and quantities required. A range in the quantities may be specified**”.

Line 454

COMMENT Although CTD – Q Section 3.2 S 2.2 requires that the equipment and the critical steps be identified in the NARRATIVE part of the manufacturing process, there is **no requirement** to state the materials of construction. This is a GMP requirement and is dealt with in Chapter 5, second paragraph (called § 5.11 in the ICH Q 7a document). This requirement has been a traditional part of GMP since 1978 and it should be left there and not added to the process description. For these and other scientific reasons the requirement to give “materials of construction - being a valuable part of the process “know-how” - should be deleted.

[REDACTED]: Delete the words “including materials of construction when critical”.

Line 458

COMMENT CTD – Q Section 3.2 S 2.2 requires that critical process controls are covered in 2.4 and not 2.2.

[REDACTED]: Delete the word “with critical process controls highlighted”.

Line 459

COMMENT In the “Questions and Answers” Guide to CTD – Q it is stated that “analytical procedures and acceptance criteria should be presented in 2.4 and not 2.2.

[REDACTED]: Delete the word “Types of analytical procedure (e.g. HPLC) for each process test”.

Lines 462 to 465

COMMENT CTD – Q Section 3.2 S 2.2 does not require ANY INFORMATION on the recycling of materials. Such manufacturing steps also are NOT REPROCESSING as defined in ICH Q 7a and there do not need to be mentioned under “Reprocessing”. If however mother liquors are returned to the process this should be mentioned under Lines 452 and 453 and the corresponding process controls mentioned under Lines 457 and 458

[REDACTED]: Delete the word “Identification of manufacturing steps that involve recycling of filtrates (mother liquors) to recover reactants, intermediates or drug substances including for the purpose of producing or isolating additional crystals (e.g. second crops) and the process controls on such operations (see Section IV B .3.c).”.

[REDACTED]: “Where a manufacturing step involves the use of filtrates (mother liquors) such operations should also be included here.

[REDACTED]: “If process controls are carried out on filtrates (mother liquors) these should also be included here. (see Section IV B. 3.c).”.

Line 466

COMMENT CTD – Q Section 3.2 S 2.2 does not require ANY INFORMATION on the recovery of solvents as **this is a GMP issue**. At the ICH Tokyo Japan Meeting in August 1998 this topic was assigned to the ICH Q 7a EWG and was subsequently covered there in Chapter 14.4

[REDACTED]: **Delete** the word “**Identification of manufacturing steps that use recovered solvents or auxiliary materials**”.

Line 473

COMMENT Unfortunately there still exists the **mistaken belief** that a determination of yield at each manufacturing step is a critical measure of quality and maintenance of a reproducible process. That this is not the case is seen daily in batch records of API manufacture where yields are only determined within wide ranges, (e.g. “A fraction of 250 – 400 litres can be expected from the column”) The measurement of the yield of a product is only carried out when an intermediate is isolated and dried (as a pure weight range alone e.g. 240 to 280 Kg tells one nothing about the product itself unless one knows how much residual solvent / water is included in the weight found). The yields determined also vary considerably with the Production Campaign Number – the first batch of a campaign usually has a 5 –10% lower yield than the subsequent batches, whilst the last batch of the campaign might have a 5 – 10% higher yield due to the efforts of the production personal to remove as much material as possible from the equipment. Yields in API production are an economic factor and are calculated based on the amount of **pure dry API** obtained from a known quantity of starting material, and is usually express in “Percentage of Theory” (e.g. 86.4 Kg = 84 % , (Expected 78 –85%). For these and other scientific reasons the requirement to give “Yields” – being one of the most valuable pieces of production “know-how” - should be highly restricted.

[REDACTED]: **Replace** the words “Yield ranges (weight and percent) for each manufacturing step”. by the words “**Yield ranges (weights and percent) of the isolated pure drug substance**”.

Lines 475 to 484

COMMENT CTD – Q Section 3.2 S 2.2 does not require ANY of the INFORMATION listed in Lines 479 to 483 and it is difficult to justify many of these requirements for semi-synthetic drugs particularly as some of these requirements are covered by ICH Q 7a as GMP requirements. It is suggested that these requirements, where appropriate are incorporated in the general requirements given under lines 449 to 473 which should read as below, (the **additions being highlighted in bold print**). The non-incorporated lines should be deleted as they are covered by GMP.

[REDACTED]: **Delete** the wording in **Lines 474 to 484** and incorporated the essential issues into lines 449 to 473, as below.

Line 449	(Deleted)
Line 450 and 451	Starting materials or intermediates used in each step, with chemical, biological or when appropriate trade names and quantities required. A range in the quantities may be specified.
Line 451 a	Any pre treatment of the starting material, (e.g. cleaning, grinding)
Line 452 and 453	Solvents, reagents and auxiliary materials used in each step, with chemical, biological or when appropriate trade names and quantities required. A range in the quantities may be specified. Where a manufacturing step involves the use of filtrates (mother liquors) such operations should also be included here.
Line 454 and 455	Type of equipment (e.g. centrifuge)
Line 456 a	Identification of the manufacturing steps including isolation procedures , that are considered critical.
Line 457 and 458	All process controls and their associated numeric ranges, limit, or acceptance criteria. If process controls are carried out on filtrates (mother liquors) these should also be included here.
Line 459	(Deleted)
Line 460 and 461	Identification of intermediates post-synthesis materials and unfinished drug substance that are tested.
Line 462 to 465	(Deleted).
Line 466 and 467	(deleted).
Line 468 to 470	Identification of manufacturing steps that involve fraction collection (e.g. chromatographic purification, the process controls on such operations and the disposal of the unused fractions (e.g. recycling).
Line 471 and 472	Identification of processes that involve combining intermediates or drug substance batches, drug substance and a diluent two or more drug substances)
Line 473	Yield ranges (weights and percent) of the isolated pure drug substance”.

Lines 490 to 491

COMMENT It is a requirement covered by ICH Q 7a GMP Guidance in Chapter 4.4, second paragraph (called § 4.41 in the ICH version of the document) that “dedicated production areas should also be consideredetc. etc **unless validated inactivation and/or cleaning procedures are established**”. The requirement that Bovine-derived materials from BSE countries (which must now include the USA!) are not used or manipulated **in the same facilities** goes well beyond ANY previous GMP requirement for avoidance of cross-contamination including those requirements for avoidance of penicillin contamination (which has a much high chance of causing death from anaphylactic shock than any trace of BSE material). This requirement should be modified, particularly as **it is covered under GMP**.

[REDACTED]: **Replace** the words “in the same facility” with “**in the same equipment unless validated cleaning procedures have been established following applicable GMP**”

Lines 511 and 517

COMMENT ICH Q 7a GMP Guidance specifies no specific clean room classification in the manufacture of non-sterile drug substances. It should be made clear in the wording used in this guidance document.

[REDACTED]: **Add** the words “**for sterile drug substance manufacture**” after “clean room classification at the end of line 511

Line 521

COMMENT Although CTD – Q Section 3.2 S 2.2 uses the words “process controls” these words should be read in conjunction with the previous words “identification of critical steps” as I was informed by a member of the CTD-Q EWG that it was the “**process controls associated with these critical steps**” which is what was meant, i.e. NOT ALL IN-PROCESS CONTROLS. This intention should be reflected in the wording of line 521

[REDACTED]: **Replace** the words “All process controls, critical or otherwise, with the words “**All process controls that are essential during critical process steps**”

Line 522

COMMENT CTD – Q Section 3.2 S 2.2 uses the words “narrative description” to make the difference between the description given in the flow diagram and the description of the process given narratively. The same principle should apply in this document.

[REDACTED]: **Replace** the “the description of the manufacturing process” by “**the narrative description of the manufacturing process**”

Lines 532 to 534

COMMENT The example of “clean room classification” is inappropriate as it **is not a GMP requirement** before the drug substance is rendered sterile or for a non-sterile drug substance (See ICH Q 7a and the comments on Line 511).

[REDACTED]: **Delete** the example given on these three lines.

Line 552

COMMENT Bring the statement found on Lines 581 and 582 (“For most intermediates and drug substances reprocessing need NOT be described in the application”) forward to line 552 to avoid applicants firstly going into details about “reprocessing” only to later find out that this is not required, (which is very sensible).

[REDACTED]: **Add** to Line 552 after “when appropriate”. The following wording: “**For most intermediates and drug substances reprocessing need NOT be described in the application**”

Lines 578 and 579

COMMENT The wording on these two lines is inconsistent with the wording of ICH Q 7a, which term “Reprocessing is introducing an intermediate or API back into the process and repeating other appropriate chemical **STEPS**.(i.e. ICH Q 7a used the plural (STEPS) rather than just the singular (STEP). It was therefore the intention of the ICH Q 7a Expert Working Group to accept multiple chemical steps as “reprocessing” provided that these are “part of the established manufacturing process” This guidance document should follow the same principle.

[REDACTED]: Replace the word “Repetition of multiple reaction steps is considered to be reworking rather than reprocessing” with **“Repetition of multiple chemical steps, provided that these are part of the established manufacturing process is also viewed as reprocessing”**.

Lines 582 to 584

COMMENT The wording “In general the documentation and data to support reprocessing of a production batch should be retained by the manufacturer and be available for review by the FDA on request.” **is a sensible statement** and should eliminate the discussion among less well informed circles that “Data to support reprocessing and recovery must be included in a Type MF” However there needs to be some slight change in wording of this sentence because upto the present the document talks about “manufacturing” and now uses the word “production. The suggested changes are given below.

[REDACTED]: Replace the words “ reprocessing of a production batch” with the words **“reprocessing of an intermediate or drug substance.”**

Lines 587 to 589

COMMENT The example given – reprocessing proteins – is not always the case. In some cases the reprocessing of proteins, e.g. remilling the starting material when it was determined that there was still protein material left in the starting material would not be considered a process with “significant potential for affecting the identity, strength, quality, purity or potency of the drug substance, where as the recrystallisation of certain penicillins or cephalosporins can affect these properties.

[REDACTED]: Replace the words “For example CDER would consider the reprocessing of proteins to be reprocessing operations that should be described in the application” with **“For example CDER would consider the reprocessing of highly unstable drug substances ,such as materials which need to processed at low temperature etc. to minimise degradation, to be reprocessing operations that should be described in the application”**

Lines 591 to 593

COMMENT: The wording “If **frequent** reprocessing is expected the procedure should be included as part of the manufacturing process described in the application” **is highly welcomed** as this is in agreement with the views of the Expert Working Group of ICH Q 7a GMP **Keep this wording**

Lines 602 to 604

COMMENT: The wording “Reworking is subjecting an intermediate or drug substance that does not conform to a standard or specification to one or more manufacturing steps that are different from the manufacturing process described in the application ” is highly welcomed as this is in agreement with the views of the Expert Working Group of ICH Q 7a GMP

Keep this wording

Lines 605 and 607

COMMENT The wording “Repetition of multiple reaction steps is considered to be reworking because the material to be introduced into the process is not similar to the original reactant” is inconsistent with the above wording and the wording of ICH Q 7a which says “Reprocessing is introducing an intermediate or API back into the process and repeating other appropriate chemical STEPS. (i.e. ICH Q 7a used the plural (STEPS) rather than just the singular (STEP). It was therefore the intention of the ICH Q 7a Expert Working Group to accept multiple chemical steps as “reprocessing” provided that these are “part of the established manufacturing process” It was recognised by the ICH Q 7a EWG that the “material to be reintroduced into the process will not be THE SAME (i.e. because possibly a salt of an amine will be reintroduced into the process rather than the amine itself) but will BE SIMILAR (i. i.e. the amine salt rather than the amine). For these reasons the EW G used the words reaction STEPS (rather than reaction CONDITIONS) as these will need to be slightly modified to cope with the slightly different type of intermediate or drug substance being reprocessed

Replace the word “Repetition of multiple reaction steps is considered to be reworking rather than reprocessing” with **“Repetition of multiple chemical steps, provided that these are part of the established manufacturing process is viewed as reprocessing”**.

Lines 607 to 609

COMMENT the lines 607 to 609 will also need to be modified to take account of the proposed changes in lines 605 to 607

Replace the words “Repetition of multiple reaction steps is discouraged because of concerns relating to unexpected impurities and degradants” with **“Repetition of multiple chemical steps, may lead to new impurities or degradants which should be treated following the principles of ICH Q 3 a – Impurities Testing Guidelines**

Lines 622 to 626

COMMENT The wording “The USE of recovered solvents and recycling of filtrates(mother liquors)should be DESCRIBED in S 2.2” can be misinterpreted to mean that the description should include “How solvents are recovered” This is however a “process used to obtain a starting material” and so falls outside the scope of both GMP and an “Application”.

[REDACTED]: Replace the words “The USE of recovered solvents and recycling of filtrates(mother liquors)should be DESCRIBED in S 2.2” with the words “**When recovered solvents are used in certain processing steps or the recycling of filtrates (mother liquors) is carried out this should be indicated at the appropriate steps in the process flow sheet**”

Lines 628 and 629

COMMENT The wording “to improve the quality of the solvent” is not the only reason for using recovered solvents and in many countries solvents have to be recovered for environmental reasons or “mixed” solvents must be separated, e.g. chlorinated from non-chlorinated solvents.

[REDACTED]: Delete the words “to improve the quality of the solvent”

Lines 632 to 636

COMMENT The guidance on solvent recovery operations with the wording “whether any processing is done to improve the quality of the solvent etc is not only ambiguous (because ANY recovery of a solvent will involve some processing) but also contrary to CTD-Q and ICH Q 7a both of which **specifically exclude** the processing of “Starting materials”. It also ignores the fact that the majority of commercially available “virgin” solvents, at least within Europe, are themselves recovered solvents because of the legal requirements to recover materials. Thus even if the drug substance manufacturer himself does not recover the solvents he will generally be using “recovered solvents” which will most likely have come from totally different processes. Thus rather try and regulate the area of starting material supplies, guidance should be given on how to **check** that solvents, whether “virgin” or “recovered” do not increase the levels of impurities in the drug substance above those laid down in the international guidelines such as ICH Q 3 a.

[REDACTED]: Replace the words “The solvent recovery operations need not be described in detail. However information should be provided on whether (1) any processing is done to improve the quality of the recovered solvents with a brief description of the process and (2) the recovered solvent comes only from the manufacture of this drug substance or can come from other sources” with the words “**The solvent recovery operations do need not be described (as this is a GMP issue covered in ICH Q 7a Chapter 14).**”

Lines 639 to 643

COMMENT The guidance on the recycling of filtrates is ambiguous and does not take into account that the number of times material will be recycled will vary with the number of batches manufactured in any campaign, (in 11 month campaigns used in the production of Aspirin with perhaps 2000 batch made in this period the filtrates are recycled 2000 times).

The amount of impurities in a filtrate will of course be considerably higher than even that in the non-filtered material, whereby levels of over 90% impurities in mother liquors are not unusual, however the fact that the mother liquors contain even as little as 5% of the drug substance is often sufficient to make the process economically viable. Whether the level of impurities in a filtrate (mother liquor) is acceptable or **not is not a question of the amount of impurities present** therein but a question of **the level of impurities in the final drug substance**, - that is what the patient takes, not the filtrate.

[REDACTED]: Replace the words “Information should be provided on the maximum number of times material will be recycled and for the process controls on such operations. Data on impurity levels should be provided to justify recycling of filtrates”. with the words **“Process Validation should be used to demonstrate that recycled filtrates do not result in an increase in the level of impurities above those included in the specification or the ICH Q 3 limits. Such data does not need to be submitted but should be available to FDA investigators on request.**

Lines 647 to 653

COMMENT The guidance on the regeneration of materials such as column resins and catalysts, if performed, places at a disadvantage those who carry out such activities themselves against those who have such activities carried out by third parties. (This is almost universally the case on the regeneration of catalysts). Similarly the wording fails to realise that these activities are “treatments of starting materials” and so falls outside the scope of both GMP and an “Application”. The wording should be changed to make it more acceptable for those who do go to the trouble of carrying out such work themselves.

[REDACTED]: Replace the words “The regeneration of materials such as column resins and catalysts should be described in S 2.2 if these operations are performed. The process controls for regeneration should be described in S 2.2 if these operations are performed etc. etc. (up to line 653). with the words **“When the applicant regenerates column materials which are used in critical steps of drug substance manufacture and when the quality of the regenerated materials is also critical for obtaining a drug substance of reproducible quality the methods used to regenerate the materials should be shortly described. If process controls are used to determine if the regenerated material is suitable for further use these should be included in S 2.3.**

Lines 657 to 664

COMMENT The wording of these eight lines is inconsistent with the wording of ICH Q 7a, where the term “Recovery” is used to describe the obtaining of a drug substance from a drug product. In particular the sentence “The recommendations for reworking operations apply irrespective of whether the operation repeats steps that are part of the approved manufacturing process” is absolutely contrary to the ICH Q 7a document.

The Expert Working Group of ICH Q 7a **did not make any difference** “between **REPROCESSING** a drug substance **IMMEDIATELY** after it has been rejected by the Quality Unit (because the level of degradation products was too high) or **REPROCESSING** a drug substance **AFTER SOME MONTHS** (or even years) of storage. Both situations required the intervention of the Quality Unit (because the level of degradation products was too high – irrespective of when). The essential discussion here is **NOT the TIME FACTOR** but the method to be used to obtain a drug substance meeting its specification. If **REPROCESSING** (i.e. using part of the established manufacturing process) **can be used** to obtain a drug substance meeting specification then **this should be encouraged**. Only if reprocessing does NOT result in material meeting the drug substance should one turn to REWORKING. The wording used in this guide should be chosen to ensure that applicant **WHEREVER POSSIBLE uses REPROCESSING** rather than reworking, (because the latter will inevitably introduce impurities which were not in the original material).

[REDACTED]: **Replace** the word “ The recommendations for reworking apply to (1) recovery of drug substance from drug product or drug-product in-process materials or (2) a drug substance after it has been released by the Quality Control Department that undergoes processing to bring the material back into conformance with its specification (e.g. purification to aged material to decrease the level of degradation products to conform with the approved acceptance criteria. The recommendations for reworking operations apply irrespective of whether the operation repeats steps that are part of the approved manufacturing process (See section IV B 3 b)”. with the words **“Wherever possible reprocessing should be used to recover a drug substance from drug product or drug-product in-process materials. Similarly reprocessing should also be used to bring such material back into compliance with its specification, (e.g. purification of aged material to decrease the level of degradation products to comply with the approved acceptance criteria).** **The recommendations for using reprocessing are made to decrease the likelihood of the recovered drug substance will contain new impurities not covered by the original acceptance criteria. (See section IV B 3 b)”**.

Lines 688 and 689

COMMENT: The wording “In general the starting material and the API starting material **should be the same** for a synthetic drug substance **is highly welcomed** as these agrees with the views of the ICH Q 7a GMP Expert Working Group **Keep this wording**”

Lines 694 and 695

COMMENT: The wording: “The recommendations for starting materials provided in this guidance are for application purposes” is clarification but needs to take into account the international agreement of the definition of a API starting material. This is because the CTD-Q Expert Wording Group **assigned to the Expert Working Group of ICH Q7a** at the Tokyo ICH Meeting in August 1998 **the work of defining “What is an APIs starting material”**. Thus the wording: “See ICH Q 7a for recommendations on API starting materials” acknowledges that this is the guideline that should be followed EVEN for APPLICATION PURPOSES.

Keep these two sentences in the guide

Lines 697 and 698

COMMENT: The wording: “Starting materials for a synthetic drug substance are chemical compounds of defined molecular structure that contribute to the structure of the drug substance **is inconsistent with the wording of ICH Q 7a**, where the term concept of a starting material being “A **SIGNIFICANT STRUCTURAL FRAGMENT** of the structure of the API was presented by the EWG of ICH Q 7a at the Tokyo meeting to the Plenary Session of the ICH Committee as being necessary and this was approved. Thus the ICH Q 7a definition of a starting material should be cited here.

[REDACTED]: **Replace** the wording: “Starting materials for a synthetic drug substance are chemical compounds of defined molecular structure that contribute to the structure of the drug substance”. with the words “A **starting material for a drug substance is a material that is incorporated as a significant structural fragment into the structure of the drug substance. Such starting materials are normally of defined chemical properties and structure**”

Line 713

COMMENT: It is **inconsistent** with the wording of Lines 688 and 689 (“In general the starting material and the API starting material should be the same for a synthetic drug substance”) to require “A flow diagram” for starting materials as this falls outside both GMP and the requirement of CTD-Q.

[REDACTED]: **Delete** the words: “A flow diagram”

Line 715

COMMENT: There is a grave risk that the simple wording used in Line 715 (“Justification for the proposed starting material, where appropriate”) may be used to require the Applicant almost to write a PhD thesis on why the particular materials were chosen as starting materials. The Expert Working Group of ICH Q7a spent considerable time on formulating wording in this document which would give very good guidance to manufacturers. Such Drafts were subject to public discussion during the drafting period and the final definition was accepted and signed by the representatives of the three regions. THIS DEFINITION should be taken over here.

[REDACTED]: Replace the words “ Justification for the proposed starting materials, where appropriate with the words: **“A statement that the proposed starting materials are either available commercially or under contract or have been produced in house and have been used successfully to make drug substances of the defined identity, quality and purity.”**”

Line 719

NOTE: **SEPARATE COMMENTS have been submitted by this author on Attachment 1** “Starting Materials for synthetic drug substances” and these comments should be taken into account when revising lines 681 to 719

Line 747

COMMENT: During development the “specification” of a drug substance will change and in order to meet the SUBMITTED Specification of the drug substance changes may have been made in the starting material. These changes are not part of the Application (but would be included in a Development Report).

[REDACTED]: Replace the words: “used to establish the specification for the drug substance” to the words: **“used to establish the specification(s) of the drug substance included in the application.”**

Lines 769 to 777

COMMENT: The title of this section D (Control of Critical Steps and Intermediates”) agrees with the title of the Section 32.S 2.4 in the CTD-Q document. However this CTD-Q document only requires Tests and acceptance criteria for **critical** steps. There is no requirement to include in the Application non-critical test etc. Thus the references to “tests and associated numeric rangesthat are judged to be non-critical” **should be deleted**. It should be pointed out the wording “can be indicated” means that this non-critical tests have to be included, but it is possible to indicate that these are non-critical. This is not the intention of CTD-Q. Thus references to non-critical tests etc should be deleted *in toto* to be in compliance with CTD-Q.

[REDACTED]: Delete completely in Lines 772 to 777 the words: **“Any of these tests and associated numerical ranges, limits, or acceptance criteria for intermediate, post synthesis materials or unfinished drug substance that are judged to be non-critical can be indicated as such. The FDA recommends that non-critical be listed separately from critical tests to distinguish them from the critical tests that constitute the specification for the intermediates, post-synthesis materials or unfinished drug products.”**

Lines 778 to 866

COMMENT: This long section covering over two Quarto pages is obviously drawn up to give guidance to Applicants, However there is always the danger that **the “guidance” can be seen as being a “must requirement”**, particularly as the word “should” is used (see Comments on line 79 and 80). Thus it is suggested that where the “guidance” is not supported by CTD-Q requirements this should be sub-paragraphed to separate it from the main body of the document. Examples are given on the following pages.

Lines 800 to 802

[REDACTED]: (Changes in wording are given in **bold** text).

For example Testing to determine the level of a residual solvent **in** an isolated intermediate may be sufficient to satisfy a test listed in the drug substance specification provided in S 4.1.

If this approach is used however the proposed test should be supported by data that demonstrate that the test results or drug substance performance characteristics do not undergo an adverse change from the in-process stage to the drug substance

Note The data along with the analytical procedure and associated validation **data (unless previously validated e.g. pharmacopeia methods are used)** should be provided in S 2.4. **The validation data if required** should be included in the methods validation package **under R. 3.S)**

Note When the same analytical procedure is used for the in-process test and the drug substance test, the acceptance criteria for the in-process test should be identical to or tighter than the acceptance criteria in the drug substance specification.

Note **If this approach is used** the tests performed in lieu of testing the drug substance should **nevertheless** be included in the drug substance specification (S 4.1) and the results of such tests should be included in the batch analysis report, (e.g. certificate of analysis)

Lines 802 to 837 would be treated similarly to the example given above (e.g. see lines 856 to 864) so that it is clear what is required and what advice is being given in order to expedite the review process

Lines 817 to 819

COMMENT: In spite of the inclusion of the word “usually” the impression is given in this paragraph that if intermediates are tested then these tests should always include tests for assay and impurities. **THIS IS NOT THE CASE:**

It is part of process development to determine which tests **IF ANY** are required to be carried out on isolated intermediates, and the mere fact that it is decided to isolate an intermediate **BUT NOT TEST IT** is one of the pieces of information which should be gathered during process development (it is a recognised scientific principle that an intermediate, when isolated, will be purer than the non-isolated intermediate (– otherwise why isolate it as this reduces the overall yield). However the fact that isolation is required (a critical step?) does not mean that an assay or a determination of impurities is required, it may be sufficient to purely determine the loss on drying in order to calculate the quantity of reagent required in the next step.

[REDACTED]: Replace the words: “A specification for an intermediate should usually include testing for assay and impurities” with the words: “**A specification for an isolated intermediate, if required, might include testing for assay, or residual starting materials or even some other in-process tests e.g. loss on drying. Such testing might be required to confirm that the material is suitable for further processing.**”

Lines 822 and 823

COMMENT: The wording “the intermediate used at the beginning of the semi-synthetic operation” is not in compliance with the ICH Q 7a definition of either an API (drug substance) starting material nor with the ICH Q 7a definition of an intermediate. This wording should be brought into line with ICH wording. In addition information on impurities in such isolated intermediates could very easily lead to a request to “tighten the specification” of these **although the later steps in the process will just do that**, (otherwise the impurities in such intermediates would be detected in the drug substance at a level above that given in the drug substance specification). The whole essence of an application is to prove that when the process is carried out in the manner described **the DRUG SUBSTANCE** to be used in the manufacture of a drug product **has the required safety, quality and efficacy. This will not be the case with the intermediate nor is it necessary.** Thus such information at the beginning of the synthetic operation does not contribute to the overall assessment of the final safety, quality and efficacy of the drug product. It is also not logical to require such information solely when synthetic operations are concerned. Non-synthetic operations will always contain much higher levels of impurities, (ever as high as 99% of impurities!) but this is not asked for.

[REDACTED]: Replace the words: “The FDA recommends that the following information be provided in S 2.4 for the intermediate used at the beginning of the synthetic operations” with the words: “**The FDA recommends that for semi-synthetic drug substances the following information be provided in S 2.4 for all isolated intermediates**”

- **the chemical name, etc., etc.,**
- **the chemical structure of the main constituent**
- **the specification for the isolated intermediate if a specification is essential to ensure the reproducible quality of the drug substance;**
- **tests for impurities if these are to be carried out on the intermediate in lieu of testing the drug substance**

Lines 839 to 850

COMMENT: On line 839 a **totally NEW TERM** – “Postsynthesis Materials” is introduced into this guidance document although there is neither in CTD – Q nor in ICH Q 6 A nor in ICH Q 7a such a term. Bearing in mind the wording of ICH Q 6 a “..... the establishment of a single set of **GLOBAL specifications** for new drug substances and new drug products”, it is less than helpful when one of

the signatories to the ICH agreement introduces terms and requirements which have not been agreed upon by the representatives of the other regions. It is therefore proposed that this section “Postsynthesis Materials” is completely revised to bring it into line with the basic principles of the ICH agreement. A suggestion for such a revision is given below:-

[REDACTED]: Delete in Lines 839 854 and replace with the following text:

“Intermediates”

ICH Q 7a defines an intermediate as a substance that undergoes further molecular change or purification before it becomes an API (drug substance). Thus all materials which appear in the process before the drug substance is obtained in a pure form are also classified as intermediates. Such intermediates can differ from the drug substance in that they may need to be converted to a salt, or they may require further purification before they meet the specification for the drug substance included in the submission. If a specification for an isolated intermediate is proposed this should be included in S 2.4.

The above guidance also is applicable to drug substances derived from biological sources.

Lines 856 to 864

COMMENT: On line 856 a **totally NEW TERM** – “Unfinished drug substance” is introduced into this guidance document although there is neither in CTD – Q nor in ICH Q 6 A nor in ICH Q 7a such a term. Bearing in mind the wording of ICH Q 6 a “..... the establishment of a single set of GLOBAL specifications for new drug substances and new drug products” it makes the understanding of this document, (especially for those who were not fortunate enough to have English as their mother tongue) more difficult. It is therefore proposed that this section “Unfinished drug substances” is revised to bring it into line with the basic principles of the ICH agreement. A suggestion for such a revision is given below:-

[REDACTED]: Delete in Lines 856 to 864 and replace with the following text:

“Drug substances”

Some drug substances may initially be obtained in a quality which does not make them suitable for certain intended uses, e.g. the crystal size may not be suitable for further use and either the drug substance manufacturer or the applicant may mill, (or have the product milled) before it is used in a drug product. Such materials are still classified as “drug substances” because, unlike the above mentioned intermediates, they undergo no further purification before they are further treated.

Note. If a specification for such a drug substance is established and the manufacturer of the drug substance himself carries out (or has carried out under his authority) further treatment e.g. micronising, sieving, blending with an excipient, etc., the specification for both the untreated and the treated material

should be submitted under a material name which is indicative of the status of the material, e.g. “Alphadeltic cryst.” and “Alphadeltic microfine” or “Alphadeltic 150 –340”. If a specification for any untreated material is proposed this should be included in S 2.4 and not S 4.1.

Lines 868 to 877

COMMENT: To those persons who have not deeply studied the CTD-Q requirements it is not immediately apparent that Process Validation data **does NOT need to be submitted** as part of the application except in well defined circumstances, because this comment is lost in the middle of the paragraph. This fact should be made clearer by the introduction of NEW LINES 869 a to 869 d, and deletion of the general comment in Lines 875 to 877.

█: **Insert** Lines 869 a to 869 d as below:

869 a Process validation data for manufacturing processes designed to produce
869 b a non-sterile drug substance do not need to be submitted as part of the
869 c application but must be available before the resulting drug product is
869 d placed on the market (See ICH Q 7a § 12.4, 3rd. Paragraph)¹⁵⁾

Lines 875 to 877

Delete “Submission of other manufacturing process validation information in the application is not necessary for most drug substances¹⁵⁾

Lines 883 to 888

COMMENT: The comment on the submission of validation information for reprocessing and reworking suggests that these two activities are equivalent. This is however rarely the case. The need to carry out process validation when a reworking is involved is higher than when only reprocessing is involved. However as it unlikely that the applicant will have REWORKED a three or more batches of material before the submission this paragraph needs to be reworded to reflect what should be acceptable practice.

█: **Replace** the words “Submission of validation data for reprocessing and reworking operations usually is not warranted etc. etc etc (upto) protein drug substances.” with the words “**Process validation data for reprocessing should only be submitted if such data is required for the original process. Process validation data for reworking, if this has been carried out during development of the drug substance, should be submitted if such reworking itself is included as part of the application, and it has been shown that the reworking procedure has a significant chance of effecting the identity, strength, quality, purity or potency of the drug product, e.g. certain thermolabile drug substances**

Lines 892 to 897

COMMENT: The initial statement “A description of the manufacturing process for the drug substance throughout the various development phases should be provided in S 2.6” gives the impression that the full development history, as would be incorporated into a development report is required.

However this is neither the wording of CTD-Q nor was it the intention of the EWG that such a level of detail should be submitted. This fact should be made clearer by rewording this initial sentence to bring it into line with CTD-Q.

[REDACTED]: Replace the words “A description of the manufacturing process for the drug substance throughout the various development phases should be provided in S 2.6” with the words “**A description and discussion of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing material for non-clinical, clinical, scale-up, pilot and if available production scale batches.**”

Note The prime focus of this **discussion** should be the **effect of** changes in the manufacturing process or manufacturing site **upon the** chemical and physical properties of the drug substance. Manufacturing changes associated with changes in the impurity profile of intermediates **if these were determined should also be described.**

Lines 892 to 897

COMMENT: It must however be recognized that such information on significant changes made to the manufacturing process may no longer be available for “grandfather” drug substances or generic drug substances which are the subject of a new application. Thus a note should be added after lines 904 to make clear that under certain circumstances such information may no longer be available.

[REDACTED]: Insert after line 903 the following note:

Note For old products for which an application for marketing in the US is being made many years after the original market introduction in other countries, it is only necessary to list those significant changes which were carried out **by the applicant** since the original market introduction and which were communicated to the licensing authorities at the time.

Lines 927 to 931

COMMENT: It must however be recognized that such detailed confirmation of the structure of the drug substance is justified for a new chemical entity but not for “grandfather” drug substances or generic drug substances which are the subject of a new application. Thus **either** a note should be added after lines 931 to make clear that under certain circumstances the published identity tests for the drug substance would be adequate, or the requirements of lines 927 to 933 should only apply to new chemical entities.

[REDACTED]: **EITHER insert** in line 927 after drug substance the words
“which are new chemical entities”

OR Insert after line 933 the following note:

Note For old products for which an application for marketing in the US is being made many years after the original market introduction in other countries, it is sufficient to use the pharmacopoeia methods as confirmation of identity.

Lines 981 to 988

COMMENT: The wording of these lines, specifically the wording “that deviate significantly from the conditions used in the manufacturing process etc” are sensible, but should be included as a Note.e.g.

Note Applicants do not need to investigate the occurrence of different forms under conditions that deviate significantly from the conditions..etc etc.

[REDACTED]: **Re-format** lines 981 to 990 to make it clear that this is “advice” and not a “requirement” (Do this by adding the word “Note” and indenting these lines as shown above).

Section S 3 B -Lines 1008 onwards

COMMENT: It should perhaps be pointed out that the wording of these lines is drawn from ICH Q 3A rather than the CTD-Q document. This not immediately apparent. However there are several places in which the requirements of this FDA Guidance document **exceed those which were agreed upon in ICH Q 3 A** etc. an example is that “A discussion should identify organic impurities that were once present in the drug substance but that have been eliminated by process modification” This requirement with no “time limitation” (i.e. used in non-clinical studies) is so broad that it goes well beyond the timeframes included in the “Manufacturing Process Development” (S 2.6). If the impurities have been eliminated in the process development then they should only be of interest for the submission if key toxicology or clinical studies were carried out with batches of product which contained impurities which are no longer present.

[REDACTED]: **Re-word** the introduction to lines 1008 onwards by including the statement UP FRONT that “**Document ICH Q 3 A provides guidance on the content and qualification of impurities in new drug substances including the level below which identification of impurities is not normally considered necessary (< 0.1%).**”

[REDACTED]: lines 1021 and 1022. **Re-word** these lines by replacing the words “Impurities which were once present in the drug substance but that have been eliminated by process modifications” with the words “**Impurities which were present in the batches of drug substance used in key non-clinical or clinical trials but which are now longer above the reporting level**”

Lines 1028 1037 etc.

COMMENT: The term “significant quantities” is used although this wording occurs neither in CTD-Q nor the cited ICH documents on impurities. It has been agreed up within the ICH framework that a “qualification threshold” of (usually) 0.1% should be used. Although there are circumstances under which this may be too high, e.g. highly toxic intermediates etc. nevertheless this number should be used rather than the nebulous term “significant quantities” (which may in fact be well above 0.1% !!)

[REDACTED]: Replace the words “in significant quantities”, whenever they occur with the term “**above the threshold limit**”

Lines 1082 to 1084

COMMENT: Although it is “indicated” that there could be several specifications depending on whether these arise from the drug substance manufacturer, drug product manufacturer and/or applicant etc. etc, it is not clearly indicated that the specification should indicate through the name whether drug substance has been further processed after isolation (See comments on lines 856 to 864). The wording of these lines should be modified to include that comments included under lines 856 to 864.

[REDACTED]: Replace the wording of lines 1082 to 1084 with the wording “**The proposed specification of the drug substance should be submitted under a material name which is indicative of the status of the material, e.g. “Alphadeltic cryst.” and “Alphadeltic microfine” or “Alphadeltic 150 –340”.** There should also be an indication if the drug substance specification is that of the drug substance manufacturer (at time of release), the drug product manufacturer (at time of incorporation into the drug product) or the applicant.

Lines 1110 and 1111

COMMENT: Although the term “sunset provisions” may be understandable by current FDAs, those other people who were not fortunate enough to have US English taught to them at school may have difficulty understanding this term.

[REDACTED]: Replace the wording of lines 1110 and 1111 with the wording “**If it intended that certain tests will be either deleted from the specification(s) or reduced to periodic quality indicator tests (See lines 1135 onwards) this should be indicated in the specification(s). Mention should be made as to when or under what circumstance this could occur.**”

Line 1126

COMMENT: The EWG of ICH q 7a recognized that in the majority of cases a drug substance should not be assigned a “shelf life” but rather a Retest date (See ICH § 11.6). The wording of this Guidance document should be amended to reflect this provision.

[REDACTED]: Replace the wording of line 1126 “Release and shelf-life acceptance criteria when both are used” with the wording “Specification for release and that applicable at the end of the first retest period, if these are different.”

Lines 1135 through to 1188

COMMENT: Although the term “Periodic Quality Indicator Tests” does not occur in any ICH Q document, nevertheless the guidance given here at to what is now being called “skip lot testing” makes it clearer both to the drug substance and the drug product manufacturer that with time certain tests, originally included in the specification may not be useful in “confirming the quality of the drug substance”. Thus rather having to submit a supplementary application to delete certain tests this may be anticipated in the application, and described there. However it could be useful if lines 1145 onwards were classified as “Notes” as they give advice to applicant under what circumstances PQITs may be introduced.

This guidance is very sensible and should be retained, but in a form which makes it clear that this is NOT a requirement.

Line 1205

COMMENT: Welcome is given to the wording an official compendium” as it recognised that other official compendia e.g. Ph. Eur. also have useful test procedures and these also may be drawn up in an application.

Keep this wording

Lines 1219 and 1220

COMMENT: The advice positively commented on in line 1205 is then disregarded in lines 1219 and 1220 where it says “another countries compendia”

[REDACTED]: Delete the wording in lines 1219 and 1220 “another country’s compedium.”

Lines 1229 and 1230

COMMENT: The requirement that analytical validation information should be provided for **all** analytical procedures is contrary to the advice given in other ICH documents, including ICH Q 7a which recognised that analytical validation is not required if “the method employed is included in a relevant pharmacopoeia or other standard references” Analytical validation should only need to be submitted for those methods that have not been given international acceptance by inclusion in standard analytical references ”

[REDACTED]: Add after the wording in line 1230 the words “**unless the method employed is included in a relevant pharmacopoeia or other standard references**”

Lines 1241 and 1242

COMMENT: The requirement that batch analysis report be provided for ALL drug substance batches used for (1) non-clinical studies etc etc is a considerable and unnecessary burden on the researched based pharmaceutical industry particularly is this information is cannot be provided MF holders. Batch analyses should only need to be provided for those batches which are designated as key batches to support the application

[REDACTED]: **Replace** after the wording “all drug substance batches used” with the words “**those batches of drug substance used in key non-clinical, clinical studies and key stability studies**” when this is known by the applicant.

Lines 1244 through to 1284

COMMENT: There is considerable concern that the wording of these 40 lines asks for details which **were not and are not** required by the COMMON technical document. When reviewing the Guidance issued by the European authorities WHICH IS BASED ON THE SAME CTD-Q, it is seen that the level of detail is considerably less than that required in this guidance document. In addition this Guidance may be partially suitable for NEW CHEMICAL ENTITIES but has negligible relevance for MF or ANDA submitters.

We therefore have the situation that an ICH document was drawn up to be used in NEW APPLICATIONS but cannot be applied to existing drug substances – highly penalising the research-based pharmaceutical industry. It should be sufficient to reduce these 40 lines of guidance to JUST 4 by replacing the wording of lines 1246 to 1286 with the wording given below:

[REDACTED]: **Replace** the wording of lines 1246 (starting with) “The batch analysis reports to line 1284 (finishing with) “ ... other tests such as water content” with the text given below:

“The batch analysis reports should give

- **the batch number;**
- **the date of initial release of the batch for its intended use;**
Note: **If the batch was retested because the assigned retest date was past and the batch was still being used in non-clinical or clinical studies the results of the retesting should also be given together with the retest date;**
- **the numerical results obtained at the time when the batch was tested for release;**

Note: **The wording “complies” should only be used when no numerical results were obtained, e.g pharmacopoeia limits test for heavy metals etc.**

Note: Numerical results obtained from tests that are no longer carried out but were carried out at the time of initial release should be included;

- an indication of the principle of the analytical method used, (e.g. UV assay or HPLC against external standard)
- an indication of the use of the batch, e.g. primary stability studies;

Note It can assist the review process if these batch analysis reports are presented in tabulated form rather than including the original certificate of analysis.

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 CTD-Q requires “a justification for the a drug substance specification the ICH Document Q 6a primarily gives guidance on how this justification should be drawn up. The impression is unfortunately given that TOO MANY DETAILS are required. 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