

**Pfizer Comments on:**  
**Draft FDA Guidance "Drug Substance; Chemistry, Manufacturing, and Controls**  
**Information"** 2003D-0571  
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We appreciate the opportunity to comment on the draft guidance. We support the detailed comments provided by PhRMA but would like to offer the following general comments.

**Pfizer Key Comments:**

Pfizer welcomes the FDA initiative to update the 1987 Drug Substance Guidance and we would further welcome an opportunity to meet to discuss our feedback to the draft guidance.

The principles of a *risk-based* approach to drug substance chemistry, manufacture & controls are largely absent from the draft guidance and it is our position that this is inconsistent with current FDA direction. The majority of the general and specific comments below propose risk-based alternates to those in the draft guidance.

CMC requirements for large protein drug substances and small synthetic drug substances differ and a preamble to the guidance should clarify these differences where appropriate.

**Pfizer General Comments**

**1. Inconsistency with ICH guidelines**

Many inconsistencies between the draft guidance content and current ICH guidance were noted. These inconsistencies should be addressed in order to promote alignment with ICH. For impurities, the guidance should reference the appropriate ICH guidance rather than include specific numerical limits. The glossary should be aligned with ICH guidance documents including definitions for qualification, residual solvent, specification, intermediate and retest period.

2003D-0571

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## **2. Registration of process controls, parameters, tests, steps, etc.**

In several instances within the draft guidance, reference is made to the inclusion of 'all/any' process controls, parameters and ranges. It is suggested that "all / any" be changed to "process controls, parameters and ranges that are *critical to quality*".

## **3. Process scale and expected yields**

Under Section IV. Manufacture, there are two references to "yield". Yield, as an indicator of the process performance, should be indicated as a *typical or expected percentage range*, not as a single number.

Under Section IV. Manufacture, the guidance requires a description of the manufacturing steps undertaken *and the scale of production*. We agree that the narrative description should include information about the scale at which the manufacturing process has been operated, but the guidance should indicate that subsequent changes in scale are a GMP issue, covered by validation requirements, and should require not regulatory notification. Note that BACPAC I guidance does not require registration updates for scale changes up to and including the final intermediate

## **4. Starting Materials Selection Criteria**

We recognize that the bullet points described in lines 1730-1733 are important selection principles for starting materials that ensure the quality of drug substance. However, we disagree with the distinction regarding significant and non-significant non-pharmaceutical use. The selection of starting materials should be based on risk-based scientific criteria and all subsequent comments are predicated on this premise.

### **4.1 "Significant non-pharmaceutical use"**

The subdivision of potential starting materials into those that have or don't have a "significant non-pharmaceutical use" should be abandoned. The focus for selecting starting materials should be the capacity of the applicant to determine the suitability of the proposed compounds based upon the applicant's knowledge of the impact of the starting materials quality upon the quality and safety of the drug substance. With the use of this science-based principle, materials that are both commercially available and not commercially available can be considered to be suitable starting materials.

### **4.2 Flow diagrams for Starting Material synthesis**

The requirement that the applicant supply a detailed flow diagram that includes the route of synthesis of the starting materials significantly expands the regulatory commitment beyond the core drug substance synthesis. As long as the applicant has demonstrated that the starting materials (which may be from more than one route of synthesis) meet their specifications and have been qualified to show that there is no impact on drug substance quality, there should be no *requirement* to provide the synthetic scheme for the starting materials. Information, in the form of a flow chart, indicating the starting material synthetic process(es) *may* be useful to evaluate the suitability of its specification and to help clarify the justification of the starting material, but this should not be a requirement.

#### **4.3 "Propinquity"**

As presented in the draft guidance, the starting material selection criterion of propinquity is overly restrictive, and exclusionary of certain commercially available, well characterized materials. It is our position that any processing activity (e.g. crystallization, extraction, salt formation, etc.) that removes impurities, reactants, or post-synthesis materials to the benefit of the quality of the drug substance should be considered a "step" towards meeting the propinquity criterion for a particular drug substance. Further, we believe that there may be circumstances where a drug substance *may* be appropriate to use as a starting material.

#### **4.4 "Isolated and purified"**

It is appropriate to expect that starting materials typically should be isolated but there are circumstances where this may not be possible or desirable. For example, if a starting material is hazardous, it may be preferable to use it *in solution* to avoid solid handling safety issues. The central tenet for a starting material should always be that its quality is adequate and appropriate, and has been justified and qualified for its intended use. The requirement that starting materials must have been subjected to a purification procedure is overly restrictive and potentially exclusionary.

#### **4.5 Starting materials for semi-synthetic drug substances**

The guidance needs to differentiate between semi-synthetic drug substance starting materials and drug substances obtained directly from biological sources, and recognize that starting materials for semi-synthetic drug substances need not be the precursor biological materials. Well-characterized semi-synthetic molecules can be considered as starting materials for drug substances. Information assessing the TSE-risk of a starting material can and should be provided, but the point of TSE-risk should not be a criterion for starting material selection. Consideration should be given to developing a separate guidance on TSE-risk.

#### **4.6 Carryover of impurities**

The position that "a chemical proposed as a starting material should not be the source of significant levels of impurities in the drug substance" contradicts ICH Q3A (Impurities in New Drug Substances) by excluding the accepted practice of qualifying impurities in drug substances. The carryover of the starting material or its impurities into the drug substance is an important point to consider in selecting a starting material, however this should not be an exclusionary criterion. Impurities in the drug substance should be qualified as defined in ICH Q3A (Impurities in New Drug Substances).

#### **4.7 Complexity of structure**

The guidance states that if "advanced" analytical techniques are required to differentiate a proposed starting material from its isomers, analogues, etc., then the material is too structurally complex to be a starting material. Several of the analytical techniques listed as 'advanced' are commonly used and widely available. An applicant should have the option of justifying the use of either a structurally more complex starting material using "advanced" techniques or a larger number of structurally less complex starting materials using traditional characterization techniques. The analytical technology used should be appropriate to the complexity of the starting material.

## 5. Definitions of, and requirements for, Reworking/ Reprocessing/ Recovery operations

We see a discontinuity between the draft guidance and ICH Q7A for the definitions of reprocessing and reworking. The key scientific differentiation between reprocessing or reworking should be the registration holder's knowledge of the process' capacity to remove process impurities and degradation products. If it can be demonstrated that repetition of a part of the registered process can adequately improve the quality of a batch of an intermediate or API, then this should be considered reprocessing. Correspondingly, improving the quality of any batch by a means not described in the registered process is reworking and requires adding the rework procedure to the registration.

## 6. Retesting of Drug Substance lots

Issues regarding drug substance retesting arise from an apparent discrepancy between the guidance definition of Retest Period (lines 2211-2219), which is based on ICH Q1A, and drug substance manufacturers' current drug substance retest practices, which are based on ICH Q7A. We refer the FDA to the Pharmaceutical Technology February 2003 article PhRMA Perspectives on Drug Substance Regulatory Filing Issues: Starting Material, Reprocessing, Retesting, and Critical Controls, which summarizes the differences between these two approaches and provides recommendations for defining Retest Period and which expresses well our position. We agree with the PhRMA position as described in the quote below.

“The preference for retest dating over expiry dating was most recently reflected in *ICH Q7A*. “Expiry and Retest Dating” in Section XI.F (p. 30) states that “an API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.” ICH Q7A defines the terms as follows:

- Expiry date (or expiration date): The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf-life specifications if stored under defined conditions and after which it should not be used.
- Retest date: The date when a material should be reexamined to ensure that it is still suitable for use.

The use of expiration dating is reserved for products that are less stable and a clear indication exists that the material is likely to fall outside of required specifications after a period of time or when there is a specific requirement (e.g. antibiotics).

To address the question of retesting, PhRMA recommends that the revised guideline adopt the following recommendations about the practical interpretation of the term *retest period* for APIs:

- If compliance with the currently filed specification is demonstrated at the end of a retest period, the batch may be used immediately, or a new date for retesting can be established.
- A new date for retesting should be documented internally and based on current retest results, stability data, sound scientific principles, the retest period filed in the NDA/DMF, and cGMP requirements.
- Successive retest periods may not be longer than the previous retest period.

- The retested batch may be used in the manufacture of drug product without further testing until that new retest date, provided that it has been stored under the defined conditions.
- A batch of drug substance may be retested multiple times and assigned successive retest dates if appropriate.
- The filing of a retest period for an API in an NDA or DMF allows for these successive retest dates without specific provision in the application.”

#### **7. Requirements for irrelevant impurity data (e.g., in S.3.2)**

We believe that Section B impurities (lines 1006 – 1074) should be replaced by a reference to Q3A(r)