

Wyeth Pharmaceuticals

Wyeth

July 2, 2004

Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 2003D-0571- Draft "Guidance for Industry: Drug Substance, Chemistry, Manufacturing and Controls Information" (January 2004)

Dear Sir/Madam:

Wyeth is submitting written comments on the draft guidance for industry entitled, "Drug Substance, Chemistry, Manufacturing and Controls Information" (69 FR 929-930; January 7, 2004).

Wyeth is one of the world's largest research-based pharmaceutical and health care companies. It is a leader in the discovery, development, manufacturing, and marketing of prescription drugs and over-the-counter medication, with leading products in women's health care, cardiovascular, central nervous system, anti-inflammatory, infectious disease, hemophilia, and oncology categories, and is also a major manufacturer of preventative vaccines.

In general, Wyeth supports many of the recommendations that are provided on the information that should be included for: (1) Nomenclature, structure, and general drug substance properties, (2) manufacture, (3) characterization, (4) control of drug substance, (5) reference standards or materials, (6) container closure system, and (7) stability, as well as, the structure to facilitate the preparation of applications submitted in CTD format.

However, the more detailed content and scope of this draft guidance results in a divergence of global standards and regulatory requirements for drug substance information, particularly with respect to the level of detail and rigidity concerning starting materials. It is likely that such divergence will result in different requirements and thus greater complexity in global regulatory submission requirements.

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As a result, we believe this draft guidance will decrease flexibility for Industry and/or in Industry's global strategic ability to retain flexibility in sourcing of starting material, API starting material or APIs. As was very successfully accomplished under the auspices of ICH for "Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," there is also a significant opportunity to harmonize Chemistry, Manufacturing and Controls Information for Drug Substance as well.

Additionally, this draft guidance does not incorporate current science based and risk based initiatives ongoing at FDA. These principles should be applied in this guidance, as they would provide sponsors with flexibility without compromising the regulatory information required to support approval of an application.

The PhRMA API Technical Group perspectives on "Drug Substance Regulatory Filing Issues for Starting Materials, Reprocessing, Retesting, and Critical Controls" was outlined in a recent publication (Pharmaceutical Technology, February 2003) and these suggestions should be incorporated into the final guidance. Wyeth fully supports the comments provided by PhRMA in that publication, as well as, the comments provided by PhRMA to the Docket on the draft drug substance guidance.

Wyeth acknowledges the areas of regulatory relief provided by FDA in the guidance related to a) *Periodic Quality Indicator Tests (PQITs)* which can be warranted when a test, performed and reported as part of the batch analysis, has value as an indicator of drug substance quality, b) the *Sunset Test* and the content of a *Sunset Test Protocol* for a test, which provides for the test to be dropped from the specification after an agreed number of production batches have met certain criteria and c) the *Interim Acceptance Criteria* proposed for a specific test because there is some uncertainty whether the same type of results will continue to be observed for subsequent drug substance batches and the contents of a *Proposal for an Interim Acceptance Criteria for a Specific Test*.

Wyeth

We are submitting the enclosed comments in duplicate. Wyeth appreciates the opportunity to comment on the above-mentioned draft guidance for industry.

Sincerely,

A handwritten signature in black ink, appearing to read "Roy J. Baranello, Jr.", followed by the word "for" in a cursive script.

Roy J. Baranello, Jr.
Assistant Vice President
Worldwide Regulatory Affairs

Attachment

Wyeth Pharmaceuticals Comments
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<u>Lines</u>	<u>Comments</u>
688 689	<p>.....In general, the starting material and API starting material should be the same for a synthetic drug substance.....</p> <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • Delete this sentence. By definition the starting material and API starting material are the same for a synthetic drug substance, hence the sentence adds no value. <p>In general, the starting material and API starting material should be the same for a synthetic drug substance.</p>
1037 1038 1039 1040	<p>Attempts should be made to identify all impurities found in significant quantities in the drug substance. The studies to characterize these impurities should be described. FDA regulates a variety of drug substances; no single recommendation applies to all drug substances for the level of an impurity that would warrant identification.</p> <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • Allowances need to be made for fermentation or natural products. Identification of all impurities in such a product is a monumental task.
1683 1684 1685	<p>..... A drug substance that is used to synthesize another drug substance is not an appropriate candidate for designation as a starting material.....</p> <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • Revise the sentence to read: A drug substance that is used to synthesize another drug substance is may not be an appropriate candidate for designation as a starting material. • Add the following sentence: A drug substance may be an appropriate candidate for designation as a starting material providing an appropriate number of synthetic transformations occur. A drug substance should be permissible as a starting material as long as there is an active DMF. This will then meet the requirement of FDA oversight.
1689 1690 1691	<p>The extent of information that should be submitted in the application to justify the proposed starting materials depends on whether or not the chemical has a significant nonpharmaceutical market.....</p> <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • Early on many API starting materials are specific to the API and a significant market may not exist outside of the proposed use in the synthesis of the API.
1696	<ul style="list-style-type: none"> • Starting Materials with a Significant Nonpharmaceutical Market <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • Revise the sentence to read: • Starting Materials with a Significant Nonpharmaceutical Market

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<u>Lines</u>	<u>Comments</u>
1698	<p>A significant nonpharmaceutical market is considered to exist if the quantity of the chemical needed for the production of the drug substance represents only a small fraction of the chemical's total market. This is true whether the chemical is made by the drug substance manufacturer for its own use or is obtained from another firm. If the quality of the chemical made for the nonpharmaceutical market is insufficient to ensure consistent quality of the drug substance and the chemical is further processed to produce material of higher quality, the purification operations should be described as part of the manufacturing process of the drug substance (S.2.2). See section II of this attachment for recommendations on the documentation that should be provided for these starting materials.....</p> <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • Delete this paragraph: A significant nonpharmaceutical market is considered to exist if the quantity of the chemical needed for the production of the drug substance represents only a small fraction of the chemical's total market. This is true whether the chemical is made by the drug substance manufacturer for its own use or is obtained from another firm. If the quality of the chemical made for the nonpharmaceutical market is insufficient to ensure consistent quality of the drug substance and the chemical is further processed to produce material of higher quality, the purification operations should be described as part of the manufacturing process of the drug substance (S.2.2). See section II of this attachment for recommendations on the documentation that should be provided for these starting materials. <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • The sponsor will control/ensure the quality of the starting material by appropriate specifications and proven/defined test methods. It is not necessary to tie the starting material to market usages.
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<u>Lines</u>	<u>Comments</u>
1708	<ul style="list-style-type: none"> Starting Materials without a Significant Nonpharmaceutical Market
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1710	A chemical should not be considered to have a significant nonpharmaceutical market if (1) the
1711	only market for the chemical is to manufacture drug substance;.....
1722	I. SELECTION PRINCIPLES FOR STARTING MATERIALS WITHOUT A
1723	SIGNIFICANT NONPHARMACEUTICAL MARKET
	<u>Wyeth Comments</u>
	<ul style="list-style-type: none"> Revise this section to read: Starting Materials without a Significant Nonpharmaceutical Market
	A chemical should not be considered to have a significant nonpharmaceutical market if (1) the only market for the chemical is to manufacture drug substance;
	I. SELECTION PRINCIPLES FOR STARTING MATERIALS WITHOUT A
	SIGNIFICANT NONPHARMACEUTICAL MARKET
1725	Each proposed starting material without a significant nonpharmaceutical market should be
1726	evaluated with respect to the selection principles described in sections I.A through I.D.....
	<u>Wyeth Comments</u>
	<ul style="list-style-type: none"> Revise this sentence to delete:
	Each proposed starting material without a significant nonpharmaceutical market should be evaluated with respect to the selection principles described in sections I.A through I.D.
1742	A chemical proposed as a starting material should be separated from the final
1743	intermediate by several reaction steps that result in isolated and purified intermediates.
1744	Having several reaction steps and associated purification and isolation steps separating
1745	the starting material and the final intermediate reduces the risk that changes in the
1746	manufacturing steps prior to the starting material would adversely affect the identity,
1747	quality, purity, or potency of the drug substance as these factors relate to the safety and
1748	efficacy of the drug product.....
	<u>Wyeth Comments</u>
	<ul style="list-style-type: none"> Revise this sentence to delete and add:
	A chemical proposed, as a starting material should be separated from the final intermediate by several reaction steps at least one chemical transformation that results in at least one isolated and purified intermediates. Having several reaction steps and associated purification and isolation steps separating the starting material and the final intermediate reduces the risk that changes in the manufacturing steps prior to the starting material would adversely affect the identity, quality, purity, or potency of the drug substance as these factors relate to the safety and efficacy of the drug product.

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<u>Lines</u>	<u>Comments</u>
1753 1754 1755 1756 1757	<p>A reaction followed by multiple purifications should be counted as a single reaction step. The reaction step that produces the final intermediate can be counted as a reaction step for purposes of evaluating propinquity if the final intermediate is isolated and purified. An interconversion of a salt to or from its free acid or base form should not be counted as a reaction step for the purpose of evaluating propinquity.....</p> <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • Further clarification is needed on the isolation and purification of intermediates. Extraction can be purification and should be allowed as a distinct step. Does purification of an intermediate mean that the intermediate has to have an actual, separate purification step?
1770 1771 1772 1773	<p>A chemical proposed as a starting material should be an isolated and purified substance. Identification of an isolated and purified substance as the starting material, as opposed to an in situ and/or crude substance reduces the risk of degradants and/or impurities affecting the identity, quality, purity, or potency of the drug substance.</p> <p><u>Wyeth Comments</u></p> <p>Revise this sentence to add and delete: A chemical proposed as a starting material should be an isolated substance and meet well defined specifications purified substance.</p> <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • Again “ isolated and purified”. The requirement of adequate specifications should be enough.
1777 1778	<p>A chemical proposed as a starting material should not be the source of significant levels of impurities in the drug substance.....</p> <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • Revise this sentence to add and delete: A chemical proposed as a starting material should not be the source of significant levels of impurities in the drug substance provide a drug substance that meets all acceptance criteria covered by toxicity testing and safety studies.
1784 1785 1786	<p>For purposes of selecting proposed starting materials, a significant level is considered to be greater than 0.10 percent in the drug substance (0.20 percent for veterinary drug substances not used in human drug products) of any of the following impurities:</p> <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • The requirement to use the 0.10% level is onerous. Sponsors should be able to demonstrate that their process can tolerate a higher level of impurities. The level allowed should be dictated by appropriate test and evaluation criteria.

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<u>Lines</u>	<u>Comments</u>
1792 1793 1794 1795 1796 1797	Moreover, a proposed starting material should be at or before the point in the manufacturing process where transmissible spongiform encephalopathy (TSE) agents can be introduced into the process. For example, if a chemical is produced using an enzyme that can introduce TSE agents into the process, the proposed starting material should be prior to the enzymatic step regardless of whether the chemical is consistent with all other selection principles.
	<u>Wyeth Comments</u> <ul style="list-style-type: none">• Revise this sentence to add and delete: Moreover, a proposed starting material, which potentially contains should be at or before the point in the manufacturing process where transmissible spongiform encephalopathy (TSE) agents can be introduced into the process. should be identified, and appropriate controls need to be in place to ensure preventio of, or eliminate\ion of TSE in the API. For example, if a chemical is produced using an enzyme that can introduce TSE agents into the process, the proposed starting material should be prior to the enzymatic step regardless of whether the chemical is consistent with all other selection principles.

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<u>Lines</u>	<u>Comments</u>
1807 1808 1809 1810 1811 1812 1813 1814 1815 1816 1817 1818	<p>..... A proposed starting material typically should possess only a limited number of functional groups and structural features that can result in geometric or stereoisomerism for it to be considered readily distinguishable. It is impossible to set meaningful limits on the maximum number of such elements that a starting material can possess to be considered readily distinguishable. However, data demonstrating that instrumental techniques commonly used for identification tests (e.g., ultraviolet-visible spectrophotometry, infrared spectroscopy) are specific can be provided to justify proposed starting materials that the Agency might otherwise consider to be too complex. If advanced techniques suitable for complex structures (¹H-NMR, ¹³C-NMR, 2D NMR, mass spectrometry, elemental analysis, X-ray crystallography, chiral HPLC) are needed to distinguish the proposed starting material from potential isomers and analogs, the chemical is not an appropriate candidate for designation as a starting material.</p> <p>Wyeth Comments</p> <ul style="list-style-type: none"> • Revise this sentence to add and delete: A proposed starting material typically should possess features only a limited that contribute to the molecular structure of the API number of functional groups and structural features that can result in geometric or stereoisomerism for it to be considered readily distinguishable. It is impossible to set meaningful limits on the maximum number of such elements that a starting material can possess to be considered readily distinguishable. However, data demonstrating that instrumental techniques commonly used for identification tests (e.g., ultraviolet-visible spectrophotometry, infrared spectroscopy) are specific can be provided to justify proposed starting materials that the Agency might otherwise consider to be too complex. If Advanced techniques suitable for complex structures (¹H-NMR, ¹³C-NMR, 2D NMR, mass spectrometry, elemental analysis, X-ray crystallography, chiral HPLC) are should be used as needed to distinguish the proposed starting material from potential isomers and analogs, the chemical is not an appropriate candidate for designation as a starting material. <p>Wyeth Comments</p> <ul style="list-style-type: none"> • With today's' instruments, complex molecules should be allowed as starting materials as long as adequate characterization is given.
1827 1828 1829	<p>The chemical name, CAS Registry Number, structure, molecular formula, molecular weight, and relevant physical characteristics (e.g., appearance, physical state, melting or boiling range) should be provided for each proposed starting material.</p> <p>Wyeth Comments</p> <ul style="list-style-type: none"> • There may be times that a designated starting material may not have a CAS number. For reasons of proprietary protection sponsors may not wish to publicly disclose this information. Therefore, this requirement should be deleted.

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<u>Lines</u>	<u>Comments</u>
1833 1834 1835 1836 1837	<p>A flow diagram should be provided showing the complete route of synthesis of the drug substance. Each synthesis branch should begin with chemicals that have a significant nonpharmaceutical market, regardless of whether these chemicals are being proposed as starting materials. The proposed starting materials should be highlighted in the flow diagram.</p> <p>Wyeth Comments</p> <ul style="list-style-type: none"> • Revise this sentence to add and delete: A flow diagram should be provided showing the complete route of synthesis of the drug substance. Each synthesis branch should may begin with chemicals that have a significant nonpharmaceutical market, regardless of whether these chemicals are being proposed as starting materials..... <p>Wyeth Comments</p> <ul style="list-style-type: none"> • Allowance should be made for chemicals outside of the significant non-pharmaceutical market. Provision can be made to show the synthesis in the regulatory filing.
1839 1840 1841	<p>If all of the proposed starting materials have significant nonpharmaceutical markets, this flow diagram should be the same as the flow diagram provided in S.2.2. The flow diagram in S.2.2 can be cross-referenced.</p> <p>Wyeth Comments</p> <ul style="list-style-type: none"> • Revise this sentence to delete: If all of the proposed starting materials have significant nonpharmaceutical markets, this flow diagram should be the same as the flow diagram provided in S.2.2. The flow diagram in S.2.2 can be cross-referenced.
1850 1851	<p>Identification tests for a proposed starting material should be specific. and should be able to discriminate between it and any related compounds that are likely to be present.....</p> <p>Wyeth Comments</p> <ul style="list-style-type: none"> • Revise this sentence to delete the unnecessary text. Identification tests for a proposed starting material should be specific. and should be able to discriminate between it and any related compounds that are likely to be present.
1859 1860 1861 1862 1863	<p>Moreover, FDA recommends that acceptance criteria be established for all organic impurities that occur above 0.10 percent and that a limit of NMT 0.10 percent be established for unspecified organic impurities when there is greater potential for impurities originating from the starting material to carryover to the drug substance (0.20 percent for a veterinary drug substance not used in human drug products).....</p> <p>Wyeth Comments</p> <ul style="list-style-type: none"> • The 0.1% limit on unspecified impurities for a starting material is not practical. Process requirements should be taken into account.

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<u>Lines</u>	<u>Comments</u>
1871 1872 1873 1874 1875 1876 1877 1878 1879 1880 1881	<p style="text-align: center;">1. <i>Starting Materials with a Significant Nonpharmaceutical Market</i></p> <p>When a significant nonpharmaceutical market exists for a proposed starting material, the discussion of the relationship between the proposed starting materials and the selection principles described in section I of this attachment need not be provided. However, an applicant should be prepared to provide documentation demonstrating that a significant nonpharmaceutical market exists for a proposed starting material. Documentation is more likely to be requested for proposed starting materials with complex molecular structures within a few steps of the drug substance and/or where the extent of use in nonpharmaceutical markets is less obvious. When warranted, this documentation should typically consist of the following:</p> <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • Revise this sentence to add and delete: <p style="text-align: center;">1. <i>Starting Materials with a Significant Nonpharmaceutical Market</i></p> <p>When a significant nonpharmaceutical market exists for a proposed starting material, the discussion of the relationship between the proposed starting materials and the selection principles described in section I of this attachment need not be provided. However, an applicant should be prepared to provide documentation demonstrating that a significant nonpharmaceutical market exists for a proposed starting material. A selection criteria for starting materials is where tests and specifications are in place to ensure quality. Documentation is more likely to be requested for proposed starting materials with complex molecular structures within a few steps of the drug substance and/or where the extent of use in nonpharmaceutical markets is less obvious.</p>
1883	<ul style="list-style-type: none"> • A description of the uses other than for drug substance production <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • Revise this sentence to delete: • A description of the uses other than for drug substance production <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> • Suggest deleting because a company will not always be aware of other uses for a chosen starting material. Use of starting material should not be a criterion for selection.

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<u>Lines</u>	<u>Comments</u>
1884 1885	<ul style="list-style-type: none"> Examples of manufacturers who are able to provide quantities suitable for both drug substance production and other markets <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> Revise this sentence to delete: Examples of manufacturers who are able to provide quantities suitable for both drug substance production and other markets <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> This places an unnecessary burden on a company to determine real or potential market uses of starting material. Additionally, allows company to choose manufacturer, or a number of alternate manufacturers.
1886 1887 1888 1889 1890 1891 1892 1893	<ul style="list-style-type: none"> Confirmation that (1) the drug substance manufacturer did not synthesize the chemical, or arrange for another firm to synthesize it, to produce drug substance for clinical trials (phase 1 and phase 2 clinical trials for human drug products); (2) an existing manufacturer of the chemical did not scale up its process to produce sufficient quantities of drug substance for clinical trials (phase 1 and phase 2 clinical trials for human drug products); and (3) the method of manufacture was not provided by the drug substance manufacturer to the other firms that manufacture the chemical (i.e., no technology transfer occurred). <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> Delete this entire bullet point because it is not relevant to the quality of starting material or how it affects the API's quality. Confirmation that (1) the drug substance manufacturer did not synthesize the chemical, or arrange for another firm to synthesize it, to produce drug substance for clinical trials (phase 1 and phase 2 clinical trials for human drug products); (2) an existing manufacturer of the chemical did not scale up its process to produce sufficient quantities of drug substance for clinical trials (phase 1 and phase 2 clinical trials for human drug products); and (3) the method of manufacture was not provided by the drug substance manufacturer to the other firms that manufacture the chemical (i.e., no technology transfer occurred)

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<u>Lines</u>	<u>Comments</u>
1919- 1957	<p>c. Carryover of Impurities</p> <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> In regards to this entire section, c. Carryover of Impurities, identification of all impurities in a fermentation or natural product is a monumental task. Provision should be made for starting materials in this category.
2008 2009 2010	<ul style="list-style-type: none"> Starting materials that are highly purified chemicals obtained from biological sources that had significant nonpharmaceutical markets before they were used in the drug substance synthesis (e.g., Sucrose, tartaric acid). <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> Revise this sentence to delete: Starting materials that are highly purified chemicals obtained from biological sources that had significant nonpharmaceutical markets before they were used in the drug substance synthesis (e.g., Sucrose, tartaric acid).
2016 2017 2018	<p>The recommendations in Attachment 1 apply to starting materials of biological origin that have significant nonpharmaceutical markets and starting materials of synthetic origin for semisynthetic drug substances.</p> <p><u>Wyeth Comments</u></p> <ul style="list-style-type: none"> Revise this sentence to delete: <p>The recommendations in Attachment 1 apply to starting materials of biological origin that have significant nonpharmaceutical markets and starting materials of synthetic origin for semisynthetic drug substances.</p>