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

Subject: Docket No. 2005D-0286
Draft Guidance for Industry on Investigational New Drugs; Approaches to Comply with Current Good Manufacturing Practice During Phase 1.

Dear Sir/Madam:

Amgen is a global biotechnology and pharmaceuticals products company based in Thousand Oaks, CA. We are pleased to provide the attached comments on the *Draft Guidance for Industry on Investigational New Drugs; Approaches to Comply with Current Good Manufacturing Practice During Phase 1.*

If you have any questions regarding our comments, or how we may assist with refinement of this guidance, please contact Barbara Unger at 805-313-1812.

Sincerely,

Barbara W. Unger
Amgen Corporate Quality Compliance

2005D-0286

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Page	Section	Line	Recommendation
	OVERALL		<p>This draft guidance clearly indicates a positive move by FDA and is appreciated by industry. The impact that this guidance makes on the drug development process, however, may not approximate that anticipated by FDA for the following reasons:</p> <ul style="list-style-type: none"> ▪ The EU regulations, and other global regulatory authorities expectations are more stringent than those described in this draft guidance. If a company manufactures phase 1 materials for testing in both US and EU, it is unlikely that an alternative less restrictive quality system will be implemented to support production for US evaluation only. ▪ Further, few, if any pilot plants or contract facilities are restricted to production of Phase 1 material and often the material used to initiate Phase 1 studies is also used in Phase 2 evaluations. Requiring production of additional material under different, as yet undefined, GMP standards (e.g. phase 2) could be an economic burden and increase the cost of drug development. <p>This draft guidance appears to provide value to a subset of manufacturers with perhaps most of the relief going to academic organizations, government laboratories and small virtual companies that do not intend to progress development beyond phase 1. On the positive side, it should increase the number of drugs that are evaluated in Phase 1 studies by these institutions, and thereby increase the number of drugs that pass into later phase development by larger scale pharma organizations. This could have a positive impact on the number of new chemical entities that enter late stage development and are ultimately commercialized. For small, fully integrated to large pharmaceutical companies, these guidelines provide limited relief. To maximize the impact of this effort on a global scale, it might be reasonable to consider this as a topic for future ICH efforts.</p>
	OVERALL		<p>The agency should define what is meant by "Quality Control". Alternatively, we suggest FDA substitute the term "Quality Unit" that more accurately reflects the organization in most companies. Quality Control may be misinterpreted to mean the Laboratory.</p>

Page	Section	Line	Recommendation
2	II Background	68	<p>Currently, footnote 4 on the bottom of page 2 hints to the possibility of additional FDA guidance in the future regarding Phase 2 and 3 CGMP expectations. We suggest that this statement should be moved up into the body of the text (as a supplemental last sentence in line 68) to clearly specify the Agency is planning to issue additional guidance and/or regulations on this topic (which further supports the Agency’s expectations for the application of phase dependent CGMPs).</p> <p>The new sentence could be re-phrased to read: “To reinforce the Agency’s expectations for the incremental application of CGMPs during clinical development, we are planning on developing additional guidance and/or regulations to define the CGMP requirements when producing investigational drugs for phase 2 and phase 3 clinical studies”.</p>
2	II Background	75	<p>The agency should clarify what “certain exploratory products” mean.</p> <p>The sentence could be re-phrased to read: “As the new rule specifies, the particular requirements in Parts 211 (21CFR211) need not be met for most investigational drugs (see Scope section) manufactured for use during Phase 1 clinical evaluation.”</p>
3	II Background	80	<p>“Phase 2 and 3 production will continue to be subject to those portions of 210 and 211 that are applicable” – More clarity is needed on the intention of this sentence. Without additional clarification, it could be interpreted that phase 2 and 3 CGMP expectations are not dramatically different from commercial CGMP expectations (which does not align with the incremental CGMP approach mentioned earlier in this section).</p> <p>The new sentence could be re-phrased to read: “Aligning with the Agency’s incremental CGMP approach, phase 2 and 3 production will continue to be subject to those portions of 210 and 211 that are applicable.”</p>

Page	Section	Line	Recommendation
4	V. Recommendations for Complying with the Statute	158	<p>The Agency should qualify what “most Phase 1 studies” mean by referring to the explanation given in the Scope section of this document.</p> <p>The sentence should be revised to read: “These recommendations are designed to provide approaches to CGMP that appropriately address factors associated with the production of clinical supplies for use in phase 1 clinical studies (see Scope section).”</p>
6	V. Recommendations for Complying with the Statute	205	<p>“A formal evaluation of the production environment to identify potential hazards” is recommended. More clarity is needed on the intention of this recommendation. While most manufacturers perform this evaluation, it is not necessarily recorded in a single written document, particularly at Phase 1. The recommendation appears to increase the regulatory burden by specifically setting this expectation.</p> <p>This bullet point should be revised to read: “The production environment should minimize potential hazards that could impact product quality and safety.”</p>
6	V. Recommendations for Complying with the Statute	212	<p>“Producers should establish production controls based on a risk assessment...” More clarity is needed on the intention of this recommendation. At Phase 1 production, most manufacturing controls address product safety issues because knowledge of the product is limited. Thus, controls necessary to ensure reproducibility and robustness have not yet been identified. Further, this recommendation appears to increase the regulatory burden by setting the expectation that a formal written risk assessment and risk mitigation activities will be documented.</p> <p>This sentence should be revised to read: “Producers should establish production controls for the product and manufacturing process and follow good scientific and quality control principles when implementing specific practices and procedures for CGMP.”</p>

Page	Section	Line	Recommendation
6	V. Recommendations for Complying with the Statute	226	<p>“We recommend that every producer establish a QC plan and document that plan in writing.” We ask that FDA clarify that a specific document entitled “QC plan” is not an expectation. Rather, there are alternatives for meeting this need, such as a Quality Manual, Quality Policy(ies), or SOPs that delineate specific Quality Unit responsibilities.</p> <p>This sentence should be revised to read: “We recommend that every producer identify in writing the responsibilities of the Quality Unit.”</p>
7	V. Recommendations for Complying with the Statute	247- 248	<p>“...it may be justified to have the same individual perform both production and QC functions, including release or rejection of each batch. .” We ask clarification regarding this recommendation. This option appears to be in direct contrast to the fundamental GMP expectations regarding separation of production and quality functions.</p> <p>We recommend that FDA delete this sentence from the guidance because it’s inclusion implies approval of an approach that is clearly in conflict with GMP fundamentals requiring a separate quality function.</p>
7	V. Recommendations for Complying with the Statute	255	<p>We recommend the Agency clarify what criteria might be used to determine “adequate” work areas and equipment.</p> <p>The sentence might be reworded to read: “Any facility, including a laboratory, used for production of investigational new drugs for phase 1 studies should have controls for the work areas and equipment related to the intended use of the product and should minimize the risk for cross contamination.”</p>

Page	Section	Line	Recommendation
7	V. Recommendations for Complying with the Statute	280- 282	<p>“Information to record would include receipt date, quantity of the shipment, supplier’s name, component lot number, investigational product batch number...”</p> <p>The Agency should delete the recommendation that investigational product batch number be included in a component logbook. Generally, raw materials are used as components in manufacture of multiple products, and in most cases it is not known what those products will be at the time components are received. The Agency should indicate the expectation that the manufacturer should be able to trace and identify all raw materials used in manufacture of the product (API, intermediate, drug product), rather than providing a list of information to be recorded.</p>
8	V. Recommendations for Complying with the Statute	305	<p>“A record of laboratory testing and production data that details the components, equipment and procedures used.”</p> <p>This sentence should be revised to read: “A record of production data that details...”. This section addresses production, not laboratory testing. Laboratory testing should be included in section F beginning with line 318.</p>
8	V. Recommendations for Complying with the Statute	316	<p>We would like it emphasized that the Sterile Products guidance applies to drug products only and not APIs unless the API is claimed to be sterile.</p>
8	V. Recommendations for Complying with the Statute	322- 324	<p>“Analytical tests used in production (e.g....) should be scientifically sound (e.g., specific, sensitive, and accurate) and reproducible for the specified purpose. We ask clarification regarding this recommendation. This recommendation appears to imply additional regulatory burden because it implies a level of validation of analytical methods for production of Phase 1 materials.</p> <p>This sentence should be revised to read: Analytical tests used in production (e.g.,...) should be scientifically sound and appropriate for the intended use.</p>

Page	Section	Line	Recommendation
9	V. Recommendations for Complying with the Statute	339- 341	<p>“When feasible, we recommend that the sample consist of twice the quantity necessary to conduct release testing (excluding any testing for pyrogenicity and sterility).” It is not always possible to allocate twice the amount of samples just for retain samples, particularly for products that are highly individualized (e.g. anti-idiotypic antibody to a individual specific B cell idioypic).</p> <p>This sentence should be revised to read: We recommend that the sample consist of a quantity adequate to perform additional testing or investigation if required later.</p>
9	V. Recommendations for Complying with the Statute	374	<p>“All quality control functions.” The word “all” should be eliminated because it is not appropriately descriptive. The Agency should specify which documentation is required. Further, Quality Control may be interpreted to apply only to laboratory activities.</p> <p>This bullet point should be revised to read: Quality unit functions</p>
10	VI. Special Production Situations	389 390	There is no Reference 5 in the reference section.
11	VI. Special Production Situations	449	We recommend that the Agency emphasize the importance of proper storage of retain samples so they may be useful and valid in future investigations and comparison studies, if necessary.

Page	Section	Line	Recommendation
12	VI. Special Production Situations	498-499	<p>“When producing multiple batches of the same investigational product, we recommend that producers periodically conduct and document internal performance reviews.” We ask clarification regarding this recommendation, particularly how it increases the safety of investigational products and assists the Agency in protection of the public health.</p> <p>We recommend that FDA eliminate any recommendation for documented periodic review in this guidance. Current IND regulations (21CFR312.33) require annual reports be made to the Agency, but a periodic quality review is not a statutory requirement until commercial product approval (21CFR211.180(e)). While most commercial manufacturers perform this type of evaluation as part of process development, requiring a separate report for analysis of Phase 1 production increases burden to the industry and does not increase the safety of investigational products.</p>
13	VI. Special Production Situations	516	<p>““(e.g. an air classification of Class 100).”</p> <p>We recommend that this be reworded to read: ...an air classification of Class 100 that is equivalent to ISO 5.</p>