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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-0004**
Draft Guidance for Industry on Nonclinical Safety Evaluation of Drug Combinations

Dear Sir/Madam:

Amgen is a global biotechnology and pharmaceuticals products company based in Thousand Oaks, CA. We are pleased to provide the following comments on the draft guidance, *Nonclinical Safety Evaluation of Drug Combinations*:

General Comment:

Issues of species-specificity and the choice of the appropriate animal species for drug combination toxicology studies may be especially difficult when one of the drugs is a large molecule. This is exemplified by the situation in which the large molecule toxicity profile is limited to nonhuman primates (NHPs), but the small molecule profile is based on rodents and dogs. This situation becomes even more complex if the metabolic profile of the small molecule is best characterized in a species other than NHPs. Since large protein-based molecules often require the use of NHPs to evaluate toxicity, combination with other large molecules or small molecules may present special challenges when considering developmental and reproduction studies when only NHPs can be used. Therefore, we recommend the addition of the following wording to the guidance: **When one or both of the drugs is a protein-based drug, the choice of animal species should be considered on a case-by-case basis, in accordance with the ICH guidance S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.**

Specific Recommendations:

1. The guidance document should provide greater clarity regarding whether the evaluations described are intended to support both clinical development and the marketing application. Lines 19 and 20 state that "This guidance provides recommendations on nonclinical approaches to support clinical study and approval... ." However, the document refers specifically to the studies that may be required to support initiation of clinical studies (eg, Lines 108 through 111 "...direct assessment of the combination by testing in animals may not be needed before the initiation of phase 1 clinical studies"), and each section refers to

the sponsor's "application to develop a combination of two or more drugs." It is unclear whether additional evaluations would be required to support a marketing application (assuming no cause for additional concern arose during the course of clinical development), and we request clarification of the requirements.

2. In Section II.A, the document lists factors to be considered when determining whether further nonclinical studies are required for a combination of 2 or more previously marketed drugs, but does not specifically address potential combinations of large molecules (eg, monoclonal antibodies, cytokines, peptibodies) with other large molecules or small molecules. This issue is particularly pertinent to Items II.A.4 and II.A.5, which address pharmacokinetic and toxicologic interactions. When comparing the profile of 2 large molecules or of a small and a large molecule, minimal overlapping pharmacokinetics, metabolism, or toxicity might be expected. For example, the pharmacokinetic profile of a protein-based drug (mAb) does not involve most metabolic pathways associated with small molecules. Furthermore, if a protein-based drug shows primarily exaggerated pharmacology as its principal adverse effect, and that observation does not overlap with another specific protein's nonclinical profile, then additional nonclinical studies may reveal little additive or synergistic toxicity. Therefore, we suggest the addition of the following sentence to Section II.B after Lines 108 to 111: **When the combination drug includes a protein-based drug, pharmacokinetic and metabolic interactions are unlikely, and therefore testing of the combination may not be necessary. The need for testing of the combination will depend on the product, clinical indication, and intended patient population, as described in the ICH guidance *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.** We suggest that similar wording be added to Sections III and IV, for combinations of a previously marketed drug with an NME and combinations of 2 NMEs, respectively.
3. Lines 128 to 135 discuss the conditions under which combination studies might be conducted in a single species and when the use of 2 species might be required. When one of the drugs is a large molecule that is active only in NHPs, the use of a second species may not be appropriate. Therefore we recommend the addition of the following sentence to Line 135: **In any case, studies with large-molecule drugs should not be conducted in species in which the molecule is not active.**
4. Lines 197 and 254: We recommend that reference to ICH guidance *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* be added to the discussion of general toxicity studies for combinations of drugs when one or both is a new molecular entity.

If you have any questions regarding our comments, or how we may assist with further development of this guidance, please contact Jenny Peters at 805-447-8840.

Sincerely,



Jenny Peters
Amgen Regulatory Affairs