RXi Pharmaceuticals
Next Generation in RNAi

June 9, 2008

Nicolas Rossignol
European Commission, DG Enterprise & Industry, Unit F2 'Pharmaceuticals'
B-1049 Brussels - Belgium 45 Avenue d'Auderghem

Dear Dr. Rossignol;

I am Vice President of Pharmaceutical Development at RXi Pharmaceuticals. We are a small (<25 person) discovery stage biopharmaceutical company in the U.S. pursuing the development of therapeutics based on RNA interference (RNAi) for the treatment of human disease.

I am writing to express concern that RNA-based therapeutics may be considered as gene therapy under the definition proposed in section 2.2.1 of the document entitled "IMPLEMENTATION OF THE 'ADVANCED THERAPIES' REGULATION". While I recognize and support the effort to improve regulation of advanced medicinal products, I am very worried that **including *synthetic* RNA compounds in this broad definition of gene therapy will put unnecessary regulatory restrictions on several very promising classes of therapeutics**, including RNA interference, aptamers and immunomodulatory compounds. Given that **RNA-based compounds do not integrate into the genome and are not in themselves oncogenic**, regulatory requirements applicable to true gene therapy therapeutic candidates do not directly apply and would impose significant regulatory hurdles that are not scientifically founded and which not would ultimately provide any significant safety benefit to the patient.

While the primary concern is of course safety, the effects of imposing regulations that are not scientifically or clinically supported are long reaching. If RNA-based compounds fall under the classification of gene therapy and its associated regulatory requirements (among these evaluation of oncogenic potential, biodistribution studies to gonads, reproductive and developmental toxicity studies and studies to evaluate integration), research and clinical support for RNA-based therapeutics may diminish, time to the clinic would extend and fewer beneficial RNA-based therapies may ultimately advance to the clinic, especially in Europe. This potential 'cost' is very high in terms of future patient care.

There is precedent for synthetic oligonucleotides to be regarded as Chemical Entities, and two have been approved. **RNA-based compounds, including those transcribed in vitro or chemically synthesized, do not replicate and have no**

60 Prescott Street Worcester, MA 01605 T 508-767-3861 F 508-767-3862 W www.rxipharma.com

risk of integration into the genome. As such it is logical to exclude RNA-based compounds from the general definition of gene therapy and to continue to evaluate them based on strategies currently in place and as outlined in chapter 4.1 of the "Guideline On Strategies To Identify And Mitigate Risks For First-In Human Clinical Trials With Investigational Medicinal Products" (EMEA / CHMP / SWP / 28367 / 07). Gene transfer approaches using a variety of vectors do clearly fall under the definition of gene therapy of the proposed regulation and so the regulatory requirements for these classic gene therapy approaches apply (outlined in chapters 2.4.2 and 2.5.2 of the regulation).

As a part of the ever growing community of scientists interested in the research and development of RNA-based therapeutics, **I respectfully ask that the European Commission reconsider the definition of "gene therapy" included in the proposed regulation. Based in part on the arguments presented above, it is reasonable to exclude RNA-based compounds and limit the definition to nucleic acids based medicinal products that are able to integrate into the human genome.**

Sincerely,

Pamela A. Pavco, Ph.D.

VP Pharmaceutical Development
RXi Pharmaceuticals
60 Prescott Street
Worcester MA 01605 USA