LEE T. GRADY, PH.D.

THOMAS P. LAYLOFF, PH.D.
Supply Chain Management System
1616 Fort Myer Drive, 12th Floor
Arlington, VA 22209

Dear Dr. Layloff: January 26, 2010

With regard to the issue stated by you relevant to a filing, this letter advises that I was Director of the USP Division of Standards Development and USP Vice President and Director of Standards Development from January 1980 until January 2000. As you recalled, I frequently made mention of one or more of the following facts at the podium in various regional, national and international meetings. Although I drafted the content all of these *Prefaces* the drafts were reviewed by many specialists in public standards. The Pharmacopeias then were published and distributed internationally.

Let me state with the greatest possible force that never over a 20-year period has anyone submitted a challenge to any of these statements or submitted data contrary to their meaning. That means in writing, by formal visitation to USP Headquarters, or by informal comment in the hallways at meetings. My time ended at USP in 2000, although I continued as an expert for five years which included frequent contact with the scientific staff at headquarters. Again, no report of any such challenge was forthcoming. Lack of challenge was exhibited by the Food and Drug Administration, brand name and generic companies. It is well known that all of these factors reviewed compendial text in great detail. These are to be taken as settled matters from the point of view of the science and technology of dissolution and bioequivalence.

USP XXI, 1985, *Preface, lvi*: "Concern continued in this revision period for the bioavailability, or physiological availability of formulated articles. Of equal significance was the recognition of the strength of dissolution testing as a tool for quality control. Thus, equivalence and dissolution behavior was sought in light of both bioavailability and quality control considerations.

Experience has demonstrated that where a medically significant difference in bioavailability has been found among supposedly identical articles, a dissolution test has been efficacious in discriminating among these articles. Because the USP sets forth attributes of an acceptable article such a discriminating test is satisfactory because the dissolution standard can exclude definitively any unacceptable article. Therefore, no compendial requirements for animal or human tests (*In vivo,* **USP 23**) of bioavailability are necessary. The practical problem has been the obverse, that is, dissolution tests are so discriminating of formulation factors that may only sometimes affect bioavailability, that is, it is not uncommon for a clinically acceptable article to perform poorly in a typical dissolution test. …

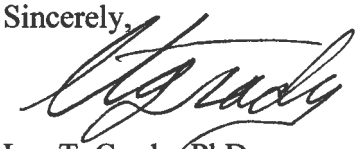
1205 CAROL RAYE STREET
MCLEAN, VA 22101-2620
LTGRADY@VERIZON.NET
(703) 356-7830

There is no known medically significant bioinequivalence problem with articles where 75% is dissolved in water at 37° in 45 minutes with the use of either official apparatus at the usual speed. A majority of monographs have that as a requirement."

USP XXII, 1990, *Preface, xliii,* added text to the last paragraph: "Medically significant cases of bioinequivalence rests mainly on just four causal factors: particle size of an active ingredient; magnesium stearate in access as a lubricant-glidant; coatings, especially shellac; and inadequate disintegrant. Every one of these factors is reactive to dissolution testing. (There is no known medically—etc.) The assistance of acid sometimes is justified. (A majority of monographs have such requirements.)"

USP 23, 1995, *lvi* (and ***USP 24,*** 2000) added: "… where 75% of an article is dissolved in water or acid at 37° in 45 minutes in the official basket or paddle apparatus operated at the usual speed, that is, USP First Case. (A majority of monographs have such requirements.) USP First Case performance is recognized as a reliable formulation objective in the United States and bears attention worldwide for product development where in vivo bioavailability testing is not readily available."

Sincerely,



Lee T. Grady, PhD
Vice President and Director Emeritus
United States Pharmacopeia

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