Paper No._____

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIODELIVERY SCIENCES INTERNATIONAL, INC.
Petitioner

v.

RB PHARMACEUTICALS LIMITED
Patent Owner

US Patent No. 8,475,832
Issue Date: July 2, 2013

Title: SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

Inter Partes Review No. Unassigned

DECLARATION BY PHILIP T. LAVIN, PH.D.
UNDER 37 CFR § 1.132

I, Philip T. Lavin, do hereby make the following declaration:

1. I have over 35 years of experience in the field of biostatistics as a Brown University, Harvard School of Public Health, and Harvard Medical School faculty member, a Principal Investigator, an FDA Advisory panel member, and an expert consultant to the pharmaceutical, biotechnology, and medical device industries leading to the approval of over 40 products to date. I currently am the founding member and senior executive of a Boston-based biostatistics consulting practice and a research foundation.

2. I have participated in the design, analysis, presentation and publication of clinical studies since 1974 after receiving my PhD in Applied Mathematics from Brown University. I have authored or co-authored over 150 peer-reviewed publications and have been internationally recognized for my contributions to developing biomarkers (CA-125 and PSA), assessing prognostic factors for oncology studies**,** treating cardioplegia**,** designing more efficient Phase II cancer studies by measuring tumor response, and optimizing liver and kidney transplants. I have been the senior biostatistician for 36 PMA/HDE approvals. In addition, I have served on multiple FDA Advisory panels since 1983 and have served as the Principal Investigator for Data

Coordinating Centers for multiple government-sponsored clinical studies. My *curriculum vitae* is attached.

3. By experience developing and analyzing diagnostic tests and biomarkers for over 30 years, I am knowledgeable in the interpretation of coefficient of variation (CV).

4. By experience developing and analyzing products for testing bioequivalence for over 25 years, I am knowledgeable in the interpretation of the 80-125% bioequivalence range.

5. I have been asked to review US Patent No. 8,475,832 issued July 2, 2013, and consider the Examples. I have relied solely upon the July 2, 2013 patent in reaching my conclusions.

6. Bioequivalence Ranges: Table 2 presents maximum concentration (C_{max}) and area under the curve (AUC) data for two Suboxone® tablet doses (2 mg/0.5 mg and 16 mg/4 mg of buprenorphine/naloxone, respectively). Table 3 presents the acceptable 80%-125% bioequivalence ranges for the same two Suboxone® tablet doses. Tables 2 and 3 both show that C_{max} and AUC are dose dependent for buprenorphine and naloxone in that the higher dose C_{max} and AUC values for each were 5-6 times higher than the lower dose values. Contrary to the dose-specific data in Table 3, the supporting text following

Table 3 states that the drug-specific bioequivalence lower bound is 80% of the lower bound for the lower dose (2 mg/0.5 mg) and the upper bound is 125% of the upper bound for the higher dose (16 mg/2 mg). The broader drug-specific bioequivalence ranges are inconsistent with the traditional bioequivalence, which is dose-specific because, as true for the Suboxone® tablets, the C_{max} and AUC of each drug are highly dose dependent. The consequence of the broader drug-specific ranges is to overstate Suboxone® tablet bioequivalence by including ranges that encompass dosages that have C_{max} and/or AUC values well outside the dose-specific 80-125% bioequivalence ranges.

7. Examples 6, 7, and 8 Suboxone® Sublingual Data Re-use: Examples 6, 7, and 8 each use the identical data (T_{max}, C_{max}, AUC_{last}, AUC_{inf}, and $T_{1/2}$) for Suboxone® Sublingual (*i.e.*, Suboxone® tablets) in the related tables. Table 6 of Example 6, Table 8 of Example 7, and Table 10 of Example 8 each use the same buprenorphine data for Suboxone® tablets. Similarly, Table 7 of Example 6, Table 9 of Example 7, and Table 11 of Example 8 each use the same naloxone data for Suboxone® tablets. But it is statistically impossible for new experiments to have been conducted and yield identical results for Suboxone® tablets three times in three different comparisons. Contrary to the

related description, the buprenorphine and naloxone absorption of all three Test Formulations could have been determined in a single in vivo study and the three Examples retrospectively constructed. The statistical impossibility of obtaining identical Suboxone® tablet data undermines the credibility of the comparisons to establish bioequivalence since the Test Formulation data were collected under different experiments according to the explanation in the Examples. This casts doubt on any bioequivalence conclusion based on the data.

8. Examples 6-8 Coefficient of Variation Magnitudes: Data Tables 6-11 each contain the CVs for a drug and respective endpoints. It is noted that the Suboxone® tablet buprenorphine CVs range from 24.77% to 46.60% in Tables 6, 8, and 10, and the Suboxone® tablet naloxone CVs range from 25.32% to 41.33% in Tables 7, 9, and 11. These CVs are large; typical CVs are in the 10% range. Thus the stated outcomes are unusually variable, which calls into question the confidence in the comparisons with the Test Formulations given the large variation in the endpoints for the control Suboxone® tablets. This further undermines any bioequivalence conclusion based on the data.

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