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Pharmacokinetic Parameters of a Novel Sildenafil Oral Liquid Suspension Administered to Healthy Adult Men Under Fasted Conditions

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Abstract: ***Sildenafil citrate is a phosphodiesterase type 5 inhibitor that has been proven safe and effective as an oral therapeutic agent for the treatment of erectile dysfunction. A novel liquid formulation of sildenafil citrate (ASP-001) has been developed as an alternative to currently marketed products. Fifty-six healthy male volunteers were randomized in a prospective, open-label, single center, two-way crossover comparative bioavailability study. Under fasting conditions, each participant received a single 100 mg oral dose of the Test (ASP-001) and Reference (Viagra film-coated tablets) formulations in a randomized sequence with a washout interval of at least 6 days between treatment periods. Blood samples were collected at baseline and up to 24 hours post-dose to assess the pharmacokinetic profile and relative bioavailability of sildenafil and piperazine N-desmethyl-sildenafil. Plasma samples were assayed by a validated LC-MS/MS bioanalytical method specific for sildenafil and piperazine N-desmethyl sildenafil. After single-dose administration, the test formulation ASP-001 was bioequivalent to the tablet form regarding the extent of systemic exposure, but not to the rate of sildenafil absorption. A faster rate of absorption within the first 5 to 20 minutes post-dose was observed with ASP-001, and C_{max} modestly exceeded bioequivalence criteria compared with reference tablets. Bioequivalence was established for the active metabolite piperazine N-desmethyl-sildenafil for both rate and extent of absorption. No oral irritation was reported. Adverse events occurred at similar rates in both treatment periods and treatment groups across test and reference products. The results suggest that the ASP-001 formulation may be a safe and effective alternative to currently marketed products for the treatment of erectile dysfunction.***

Keywords: erectile dysfunction, comparative bioavailability, pharmacokinetics

1. Introduction

Erectile dysfunction (ED) is defined as the consistent or recurrent inability to achieve or maintain penile erection that is sufficient for sexual satisfaction [1]. The prevalence of ED increases with age and is estimated at 5% for men aged 20-39 years and at 70% for men 70 years or older [2, 3]. This medical condition is associated with depression and anxiety and has a substantial negative impact on quality of life for both patients and their partners [4].

The physiological mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation, which then activates the enzyme guanylate cyclase, resulting in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing for increased blood flow [5, 6]. Sildenafil enhances the effect of nitric oxide by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum [7]. This provides for extended time for cGMP to degrade in the penile smooth muscle and allows for erection for a longer period of time.

Sildenafil citrate was the first oral therapeutic agent for the treatment of ED and has been marketed in the United States as Viagra by Pfizer, Inc. since 1998. The film-coated oral tablets are available in doses of 25, 50, and 100 mg. Viagra has been evaluated in 21 randomized, double-blind, placebo-controlled trials in more than 3,000 patients with ED of various etiologies (organic, psychogenic, mixed) consistently demonstrating a statistically significant improvement compared to placebo [8-10]. The most commonly reported side effects with Viagra tablets include headache, flushing, dyspepsia, abnormal vision, nasal congestion, back pain, myalgia, nausea, dizziness, and rash [9].

Sildenafil is rapidly absorbed after oral administration with a mean bioavailability of 41% (range 25% to 63%) [9]. Maximum concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing under fasting conditions. Pharmacokinetic parameters are dose-proportional over the recommended dosage range of 25 to 100 mg. The mean steady state sildenafil volume of distribution is 105 L which is suggestive of distribution into tissues. It is eliminated primarily by hepatic metabolism (CYP3A4 major route and CYP2C9 minor route) and is converted to an active metabolite (piperazine N-desmethyl-sildenafil). with properties similar to the parent sildenafil. Plasma concentrations for the metabolite are about 40% of those observed for sildenafil; the metabolite accounts for about 20% of the pharmacologic effects. Sildenafil and its active metabolite are both highly bound to plasma proteins (96%) and each has a terminal half-life of about 4 hours. Sildenafil is excreted as metabolites predominantly in feces (~80% of orally administered dose) and to a lesser extent in the urine (~13% of administered dose).

Aspargo Laboratories, Inc. (Englewood Cliff, NJ, USA) has developed an oral liquid suspension of sildenafil (ASP-001)

that is delivered as an oral liquid and has the advantages of ease of storage, portability, and overall convenience as compared to the tablet dosage form. A study was conducted to determine the pharmacokinetics of sildenafil citrate and its active metabolite, piperazine N-desmethyl sildenafil, in plasma of fasted healthy male volunteers after a single oral dose of 100 mg of ASP-001 and 100 mg of Viagra tablets.

2. Materials and Methods

2.1 Study Design

An open-label, single center, two-way crossover study to evaluate the pharmacokinetics, safety, and tolerability of 100 mg of ASP-001 (Test product) and 100 mg Viagra film-coated tablets (Reference product) administered orally to fasted healthy male volunteers was conducted to compare the rate and extent of absorption of the liquid and tablet dosage forms of sildenafil. A single dose of the oral liquid suspension consisted of 8 actuations of the bottle pump for a total delivered dose of 100 mg sildenafil. The Test and Reference products were orally administered in two sequential treatment periods separated by a wash-out interval of at least 6 days. The dosing sequence order was determined based on a computer-generated randomization schedule. Once qualified for the study, participants were randomized and checked in for confinement at a Phase 1 clinical trial unit (CTU) the evening before dosing (at least 14 hours prior to dosing).

Following at least a 10-hour fasting period, the first treatment was administered with baseline and subsequent pharmacokinetic sampling. Water was restricted from at least 1 hour prior to dosing until at least 1-hour post-dose in each period. No fluids were allowed except for water given with dosing of reference Viagra tablets. Water was not provided with the Test product ASP-001. Participants were discharged from the CTU following the collection of the final sample at 24 hours post-dose and determination of adverse events. After the 6-day washout, participants returned to the CTU, were rescreened, admitted for confinement, and crossed over to the alternative treatment. Study procedures were repeated in the second treatment period.

A total of 24 blood samples were collected during each treatment period at pre-dose baseline (0hr), every 5 minutes through 80 minutes post-dose, 90 minutes, and at 2-, 4-, 8-, 12-, 16-, and 24-hours post-dose. Samples were collected sequentially via direct venipuncture or catheter. After refrigerated centrifugation, plasma was separated and transferred to pre-chilled and labeled polypropylene tubes. Samples were stored frozen (-20°C) within 120 minutes of sample collection and remained frozen until the time of analysis. Plasma samples were assayed utilizing a fully validated LC-MS/MS method by Cliantha Research (Toronto, ON, Canada).

Safety assessments included vital signs, physical examinations, oral irritation, dizziness and headache evaluations, ability to swallow, post-dose coughing, and electrocardiogram (ECG). Mouth and throat anatomical sites were evaluated for irritation/inflammation on a scale from 0 (none/normal) to 3 (severe). Dizziness and headache were evaluated on a scale from 0 (no headache/dizziness) to 5 (intolerable and unable to verbally communicate because of headache).

The protocol was reviewed and approved by the local ethics committee and all participants provided written informed consent prior to any study procedure.

2.2 Patient Population

Healthy male volunteers aged 18 to 55 years with body mass index (BMI) between 18.0 and 29.9 kg/m^2 and body weight 50 to 100 kg were recruited for participation in the study. All volunteers were in good physical health as documented by medical history, physical examination, vital sign assessments, 12-lead ECG, clinical laboratory assessments, and general observations. Men with significant disease, hepatic impairment, known hypersensitivity to sildenafil, history of clinically significant allergies, history of drug abuse in the last year, blood donation within the last 3 months, or hormone replacement therapy within the last 6 months were excluded.

Men had to agree to either abstain from sexual intercourse or use an acceptable method of birth control from the time of screening to 4 weeks after the last study procedure. They were restricted from consuming caffeine/xanthine-containing products, beverages containing more than 5% fruit juice, foods containing poppy seeds, and alcohol or alcohol-containing products for 48 hours prior to each dosing and throughout their stay at the CTU.

2.3 Outcome Measures

Primary outcome measures were the pharmacokinetic parameters of sildenafil including

- the maximum measured plasma drug concentration (C_{max});
- the area under the plasma concentration versus time curve calculated using the linear trapezoidal rule from the zero time point to the last quantifiable concentration (AUC_{last});
- the area under the plasma concentration versus time curve from zero to infinity calculated by adding C_{last}/λ_z to AUC_{last} where C_{last} is the last quantifiable concentration and λ_z is the elimination rate constant (AUC_∞);
- the rate of absorption (C_{max}/t_{max});
- the time to C_{max} (t_{max});
- the terminal elimination rate constant (λ_z); and
- the half-life calculated as 0.693/ λ_z ($t_{1/2}$).

Secondary outcome measures included an assessment of oral irritation, dizziness, and headache, as well as the type and frequency of adverse events.

2.4 Statistical Considerations

Pharmacokinetic parameters of sildenafil and its metabolite in plasma were calculated using a non-compartmental analysis of Phoenix® WinNonlin® professional software (Pharsight Corporation, Mountain View, CA, USA) or SAS® statistical software (SAS Institute Inc, Cary, NC, USA). The rate and extent of absorption were compared using analysis of variance for a crossover design on log-transformed data. The statistical analysis considered sources of variation including

sequence, subject within sequence, period, and treatment. Descriptive statistics were used to summarize the data.

A sample size of 56 was required to evaluate bioequivalence assuming a true ratio of 100%, 90% power, and intrasubject variability of 25%. To establish bioequivalence, the 90% confidence interval of geometric means of the Test to Reference ratio for sildenafil pharmacokinetic parameters C_{max}, AUC_{last} and AUC_{∞} should be within 80.00% to 125.00%. A total of 41 participants was required to establish superiority for absorption rate of ASP-001 over Viagra tablets with 90.52% power based on a 1-sided ratio of means test for a 2x2 crossover design for continuous response data with significance level 0.025. A post hoc analysis using the TTest procedure, which is used to test for the equality of means for a two-sample (independent group) t-test, was performed evaluating the mean sildenafil concentration at each time point of sample collection.

3. Results

The study recruited healthy adult men between November and December 2023 from a single center in Canada (Cliantha Research, Mississauga, Canada). Fifty-six men were randomized and 52 completed the study having received a total sildenafil dose of 200 mg over both Test and Reference periods (100 mg ASP-001 and 100 mg Reference). Of the 4 participants who did not complete the study, 2 discontinued due to a non-treatment related adverse event (1 in the Test period and 1 in the Reference period both due to an upper respiratory viral infection) and 2 were withdrawn per investigator decision. All 56 participants were included in the safety analyses and the 52 subjects who completed the study were included in the pharmacokinetic analysis. The average age of the randomized cohort was 40.2 years (±9.96), average weight was 78.4 kg (±10.16), and average body mass index was 25.8 kg/m^2 (±2.46). Plasma pharmacokinetic parameters for sildenafil and its metabolite are summarized in Table 1 and Table 3, respectively. The study was conducted only after independent ethics committee approval and in accordance with the ICH Guideline on Good Clinical Practice and Declaration of Helsinki.

3.1 Bioequivalence Assessment

Pharmacokinetic results demonstrate similar overall oral bioavailability and exposure to sildenafil from ASP-001 and tablet dosage forms based on AUC (Table 1). The 90% confidence interval of the Test to Reference ratio for AUC_{last} and AUC_{∞} were within the pre-specified acceptance criteria for bioequivalence between 80.00% and 125.00%. The mean (geometric) peak concentration for ASP-001 was 16% higher than for film-coated tablets (508.80 ng/mL vs 440.09 ng/mL). Plasma concentrations for both dosage forms declined rapidly after reaching C_{max} (Figure 1). With respect to C_{max}, ASP-001 and film-coated tablets were not bioequivalent (Table 1); the Test to Reference ratio for C_{max} was outside of the 90% confidence interval acceptance range, with an upper confidence bound of 131.47%.

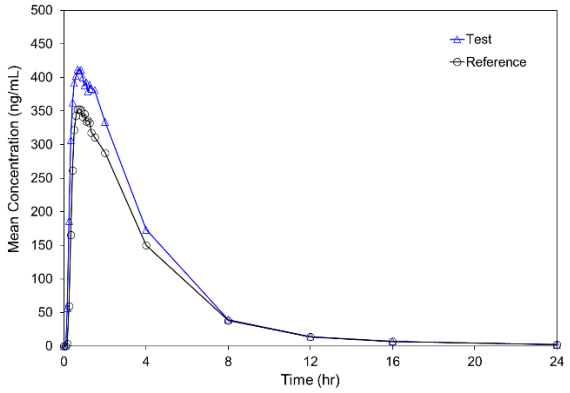

Figure 1: Linear mean sildenafil concentration vs time for ASP-001 (Test) and Viagra tablets (Reference)

Piperazine N-desmethyl sildenafil, an active metabolite of sildenafil, AUC values were similar following administration of each treatment (Table 3; Figure 2). The 90% confidence interval for C_{max}, AUC_{last}, and AUC_{∞} all fell within the acceptance limits demonstrating bioequivalence across dosage forms for the metabolite.

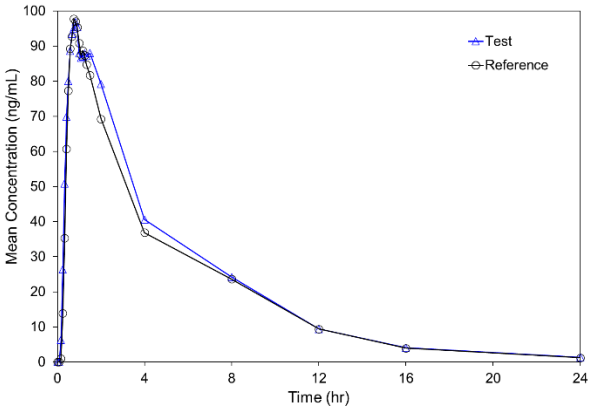

Figure 2: Linear mean piperazine N-desmethyl-sildenafil concentration vs time for ASP-001 (Test) and Viagra tablets (Reference)

3.2 Absorption Rate Assessment

An exploratory analysis showed a faster rate of absorption for the initial post-dose period (5-20 minutes) when evaluating each sample collection time point for ASP-001 as compared to the tablet dosage form ($p<0.05$; Table 2). While sildenafil mean C_{max} and C_{max}/T_{max} were numerically higher for ASP-001 than the film-coated tablets, the rate of absorption was not statistically significantly faster when evaluated over all time periods ($p=0.1486$).

Table 2: Mean Plasma Concentration for ASP-001 and Viagra Tablets at Each Time Point (ng/mL)

Time Point	*ASP-001 (Test)*	*Viagra Tablet (Reference)*	*P-Value*
5 min	0.615	0.000	0.0122*
10 min	56.668	3.161	0.0080*
15 min	186.500	59.227	0.0024*
20 min	306.900	165.500	0.0151*
25 min	362.900	261.600	0.0885
30 min	391.800	322.000	0.2446
35 min	402.000	343.000	0.3150
40 min	412.300	352.100	0.3063

Time Point	*ASP-001 (Test)*	*Viagra Tablet (Reference)*	*P-Value*
45 min	410.000	353.000	0.3302
50 min	411.400	351.800	0.3173
55 min	399.900	341.300	0.3090
60 min	388.200	345.400	0.4579
*p<0.05			

3.3 Safety Results

Sildenafil administered as an oral liquid suspension as a single dose was well tolerated. There were no deaths or serious adverse events reported in the study. Overall, 23 (41.1%) of participants experienced an adverse event, including 15 participants in the Test period and 13 in the Reference period. Adverse events reported by more than one participant in the Test period were headache (16.4%), blood pressure decrease (5.5%), dizziness (5.5%), and visual impairment (3.6%). In the Reference period, common adverse events included dizziness (7.4%), headache (7.4%), somnolence (7.4%), and visual impairment (3.7%). One severe event of syncope deemed unrelated to the treatment was reported by a participant in the Reference period. Post-dose cough or inability to swallow were not reported by any study participant. The majority (92%, 23/25) of adverse events occurring in the Test period were mild in severity and all resolved without clinical sequalae within the study period. None of the participants discontinued the study due to a treatment-related adverse event. There were no clinically significant abnormalities on ECG or laboratory values.

All scores for oral irritation at all locations tested were 0 (normal) both before and after treatment for all subjects in all treatment periods. Four participants reported dizziness (score>0) in the Test period compared to five participants in the Reference period. Corresponding numbers for participants reporting headache (score >0) were eight and five, respectively. All dizziness scores were 1 or 2 (tolerable) except for one participant in the Reference period who had a rating of 5 (intolerable) at one timepoint. All headache scores in both treatment periods were 1 or 2 (tolerable). All episodes of dizziness or headache resolved within the 24-hour post-dose period.

4. Discussion

This comparative bioavailability study assessed pharmacokinetic parameters C_{max} and AUC, rate of absorption, and adverse events following single-dose administration of ASP-001 and reference film-coated sildenafil tablets in healthy male volunteers. The Test product ASP-001 was found to be bioequivalent to the reference Viagra tablet with respect to sildenafil systemic exposure, as reflected in the 90% confidence intervals for AUC_{last} and AUC_{∞}. ASP-001 and the reference tablet were not bioequivalent with respect to C_{max}, with a modestly higher maximum sildenafil concentration for ASP-001. The mean sildenafil concentration in plasma for ASP-001 was statistically significantly higher than reference Viagra tablets at time points 5 to 20 minutes post-dose indicating a faster rate of absorption, which could represent a clinically meaningful difference to ED patients and their partners. This data pattern is not considered to be unexpected based on the liquid oral dosage form and potential for more rapid absorption. Given the broad therapeutic index of sildenafil at labeled dosages for the treatment of ED, the higher C_{max} observed is not believed to be clinically significant. Safety ratios compare the highest exposure levels of sildenafil that did not cause toxicity in animals to the maximum therapeutic exposure in humans; for peak plasma concentration these safety ratios were 19:1 in rats and 8:1 in dogs, highlighting the low risk for toxicity in humans [11]. Further, the clinical safety profile for ASP-001 showed that adverse events were consistent with those presented in reference Viagra labeling.

Sildenafil is rapidly absorbed and cleared from the body. This study supports the known pharmacokinetics of sildenafil with maximum plasma concentrations achieved within 1 hour of dosing under fasting conditions and a terminal half-life of 3-5 hours [12]. The N-desmethyl-sildenafil metabolite had similar characteristics to the parent drug and was found to be bioequivalent relative to reference Viagra.

Adverse events in the study were transient and mild or moderate in severity. Events associated with ASP-001 treatment were related to known effects of sildenafil including vasodilatory and visual effects [13]. Sildenafil has modest peripheral vasodilator properties given its role in the NO/cGMP pathway which may explain the headache and dizziness in some participants. While sildenafil can cause small decreases in blood pressure, clinically significant hypotension is rare. Visual side effects observed in this study may be related to the ability of sildenafil to inhibit PDE6 which is found in human retinas, although it is 8-17 times more selective for PDE5 in the corpus cavernosum [7]. The inactive peppermint oil present in the ASP-001 formulation may cause oral mucosal irritation; however, all oral irritation evaluations post-dose were considered normal. Data from this study supports the favorable safety profile of the Test product after a single oral dose of 100 mg liquid sildenafil.

An ideal oral treatment for ED would be easily and discreetly administered, have good tolerability with lack of central nervous system effects, have reliable efficacy, and have a prompt onset of clinical effect for an appropriate duration after administration of a single dose [12]. Different dosage forms relative to the originally marketed Viagra tablet have been evaluated to further address these needs. In the present study, sildenafil delivered via an oral liquid formulation exhibited rapid oral absorption based on the plasma concentration profile, particularly in the first 5-20 minutes, compared to Viagra tablets. The availability of alternative dosage forms over conventional tablet formulations provides expanded options to meet individual needs of patients and their partners. The ASP-001 liquid dosage form administered under fasted conditions delivered the intended total dose, as it met bioequivalence criteria for AUC compared to Viagra tablets. ASP-001 provides an alternative that is effective and safe while being more convenient and discreet than an oral tablet, as the intended sildenafil dose can be accurately delivered in a range of settings, without water, directly from a bottle-pump presentation.

5. Conclusion

The administration of sildenafil 100 mg as an oral liquid formulation (ASP-001) in healthy men was bioequivalent in terms of extent of absorption compared to reference 100 mg Viagra tablets. Faster absorption rates were observed from 5 to 20 minutes post-dose with ASP-001. The safety profile showed that the treatment was well tolerated and adverse events were consistent with known effects of the drug. Study pharmacokinetic data confirm the similarity between the two dosage forms, suggesting that the ASP-001 formulation may be a safe and effective alternative to currently marketed products for the treatment of ED.

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Table 1: Sildenafil Pharmacokinetic Parameters and Determination of Bioequivalence

Parameter	*ASP-001 (Test)[a]*	*Viagra Tablet (Reference)[a]*	*Test to Reference Ratio (%)[b]*	*90% Confidence Interval (%)*
C_{max} (ng/mL)	606.84 ± 399.15	533.72 ± 319.02	115.61	(101.67, 131.47)
AUC_{last} (ng/mL * h)	1781.96 ± 1131.69	1530.38 ± 717.17	113.50	(104.45, 123.32)
AUC_{∞} (ng/mL * h)	1797.97 ± 1138.96	1549.56 ± 727.86	113.12	(104.13, 122.88)
C_{max}/t_{max} (ng/mL/h)	1051.75 ± 1070.92	755.62 ± 647.48		
t_{max} (h)	0.71 (0.25-4.08)	0.81 (0.33-4.05)		
λ_z (1/h)	0.20 ± 0.07	0.21 ± 0.08		
$t_{1/2}$ (h)	3.77 ± 1.18	3.88 ± 1.48		

[a]Arithmetic mean ± standard deviation shown for all except t_{max} which is shown as median (range).
[b]Ratio of geometric means.

Table 3: Piperazine N-desmethyl-sildenafil Pharmacokinetic Parameters

Parameter	*ASP-001 (Test)[a]*	*Viagra Tablet (Reference)[a]*	*Test to Reference Ratio (%)[b]*	*90% Confidence Interval (%)*
C_{max} (ng/mL)	134.19 ± 86.40	134.50 ± 100.52	108.98	(97.70, 121.57)
AUC_{last} (ng/mL * h)	509.76 ± 315.47	476.21 ± 318.99	110.59	(103.85, 117.76)
AUC_{∞} (ng/mL * h)	521.43 ± 321.59	492.35 ± 326.37	110.45	(103.70, 117.63)
C_{max}/t_{max} (ng/mL/h)	175.40 ± 162.34	182.80 ± 202.34		
t_{max} (h)	0.96 (0.33-4.08)	0.88 (0.42-8.05)		
λ_z (1/h)	0.19 ± 0.05	0.20 ± 0.05		
$t_{1/2}$ (h)	3.81 ± 0.90	3.69 ± 1.01		

[a]Arithmetic mean ± standard deviation shown for all except t_{max} which is shown as median (range).
[b]Ratio of geometric means.

Author Profile

Steven A. Kaplan, MD, FACS is Professor of Urology at the Icahn School of Medicine at Mount Sinai, Director of The Men's Health Program of the Mount Sinai Health System, and Chair of Research of the American Urological Association. He is a diplomat of the American Board of Urology and a Fellow of the American College of Surgeons. He is a recognized authority on the study of benign diseases of the prostate, the association of metabolic factors and voiding dysfunction and a though leader on digital Men's Health.

Jason Moore received B.A. and M.S. degrees from Texas A&M University and an M.B.A from University of Houston. He is a drug-development consultant in the biopharma industry, with a focus on

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Robert Niecestro, PhD is currently Head of Regulatory Affairs for Aspargo Labs. Robert was a co-founder and served as the Vice President of Clinical and Regulatory Affairs for Axsome Therapeutics from 2012 until September 2018. Robert was responsible for the in-licensing of IV tramadol into Fortress Biotech and was also one of the co-founders of Avenue Therapeutics. Robert was a co-founder of Cyprium Therapeutics and assisted in the in-licensing and CRADA with the NIH for Copper Hisitidinate for Menkes Disease. Robert was a co-founder and served as the Executive Vice President of Clinical and Regulatory Affairs for TG Therapeutics from 2012 to February 2018 and is currently consulting with TG Therapeutics on their anti-CD20 monoclonal antibody for the treatment of multiple sclerosis and neuromyelitis optica. Robert served as the Vice President of Regulatory Affairs for Keryx Biopharmaceuticals from 2004 to 2012. Prior to 2004, Robert held numerous senior management positions in the pharmaceutical industry including at Andrx Laboratories, Eisai, Inc., and Organon, Inc. Robert has been involved in the filing of over 60 INDs; approval of 14 New Drug Applications or Biologic Licensing Agreements with the FDA; has over 75 peer-reviewed scientific presentations, abstracts and/or publications, and holds 4 patents. Robert completed his graduate and post-graduate work at the University of Illinois at Chicago.