UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

—

APOTEX INC.,
Petitioner

v.

CELGENE CORPORATION,
Patent Owner

—

Case IPR2023-00512
U.S. Patent No. 8,846,628
Issued: September 30, 2014

Title:
ORAL FORMULATIONS OF CYTIDINE ANALOGS AND METHODS OF USE THEREOF

DECLARATION OF HANNAH K. BATCHELOR, Ph.D.

By: _____

February 10, 2023

TABLE OF CONTENTS

I, Hannah K. Batchelor, Ph.D., of Glasgow, UK, declare as follows:

I. INTRODUCTION

1. I have been asked by counsel for Apotex Inc. ("Petitioner") to investigate and provide opinions relating to the *in silico* modeling of pharmacokinetic ("PK") properties following the oral administration of non-enteric formulations of 5-azacytidine for the above-captioned *inter partes* review ("IPR").

2. I understand that Petitioner petitions for IPR of certain claims of U.S. Patent No. 8,846,628 ("'628 patent") and request that the United States Patent and Trademark Office ("USPTO") cancel the challenged claims. I further understand that Celgene Corporation ("Patent Owner") purports to own the '628 patent.

3. In preparing this Declaration, I have reviewed and considered the documents identified in Section IV in light of the general knowledge in the relevant art. In forming my opinions, I relied upon my education, knowledge, and experience, including in the fields of biopharmaceutics and pharmaceutical science, and considered the level of ordinary skill in the art as discussed below.

4. I expect to be called to provide expert testimony, if necessary, regarding the opinions and issues considered in this Declaration. This Declaration identifies my opinions to date. I reserve the right to amend or supplement this Declaration, if allowed under the relevant rules, to address any issues raised by Patent Owner's expert(s) or resulting from further discovery relating to any of the

opinions stated herein. I may also testify as to the matters set forth in any additional reports, declarations, witness statements, and/or testimony submitted by Patent Owner.

II. QUALIFICATIONS

5. I am a Professor in Pharmaceutics at the University of Strathclyde in the Strathclyde Institute of Pharmacy and Biomedical Science in Glasgow, UK. From August 2015 to July 2020 I served as a Senior Lecturer in Pharmaceutics, Formulation and Drug Delivery at the University of Birmingham in the School of Pharmacy in Birmingham, UK. From 2015 to 2018 I served as a Director of Research, and from April 2012 to August 2015, I served as a Pediatric Formulations Research Fellow, also at the University of Birmingham.

6. Prior to my time at the University of Birmingham, I was a Research Portfolio Manager at the Heart of England NHS Foundation Trust (HEFT) between 2011 and 2012; a Senior Scientist in Biopharmaceutics at AstraZeneca between 2008 and 2011; a Lecturer in Pharmaceutics at Aston University in Birmingham, UK between 2000 and 2007; and a Formulation Scientist at Reckitt and Colman (now ReckittBenckister) between 1996 and 1997.

7. I earned a Ph.D. in Drug Delivery from the University of London, School of Pharmacy in London, UK. My Ph.D. research was investigating bioadhesive potential of alginate as a means of enhancing therapy for gastric reflux

by forming a coat on the esophagus. It was funded by Reckitt Benckiser and the EPSRC and resulted in four publications and influenced the advertising campaign for Gaviscon® showing the product coating the esophagus. I earned my Bachelors of Science in Pharmacology and Chemistry from the University of Sheffield in Sheffield, UK. I also have a Graduate Certificate in Statistics with Medical Applications from the University of Sheffield, and a Postgraduate Certificate in Learning and Teaching (SEDA accreditation as a Teacher in Higher Education) from the University of Aston.

8. My research focuses on pediatric biopharmaceutics and development of age-appropriate medicines for children. Specifically, I develop testing strategies to predict *in vivo* performance; undertake pediatric *in silico* modeling to optimize pharmacokinetic study design and work to understand the impact of drug-food interactions within pediatric populations. I am actively involved in involvement of children and young people in research, particularly clinical research that impacts upon the treatment of this population.

9. To date, I have received in excess of £2.5m in research funding and have supervised more than 15 PhD students to completion. My current live funding (>£600k) supports 6 PhD students and a research technician. I have been invited to present my research at several relevant international conferences including: European Paediatric Formulation Initiative (EuPFI); American

Association of Pharmaceutical Scientists (AAPS); Controlled Release Society and the Royal College of Paediatrics and Child Health annual meeting.

10. I have authored or co-authored chapters of several books in my field. I am a member of the Editorial Board for two journals in my field, *Biopharmaceutics and Drug Disposition* and *Nature Scientific Reports*, and am an editor of two books, including *Biopharmaceutics: From Fundamentals to Industrial Practice*, John Wiley & Sons Ltd. I also peer review for the following publications: *AAPS PharmSciTech*; *Acta Biomaterialia*; *Acta Paediatrica*; *Advanced Drug Delivery Reviews*; *Archives of Disease in Childhood*; *BMJ Paediatrics Open*; *British Journal of Clinical Pharmacology*; *European Journal of Hospital Pharmacy*; *European Journal of Pharmaceutical and Biopharmaceutics*; *European Journal of Pharmaceutical Science*; *Expert Opinion on Drug Delivery*; *International Journal of Pharmaceutics*; *Journal of Asthma*; *Journal of Controlled Release*; *Journal of Drug Targeting*; *Journal of Pharmacy and Pharmacology*; *Molecular Pharmaceutics*; *Nanomedicine*; *Pharmaceutica Analytica Acta*; *Pharmaceutical Research*; *Pharmaceutical Sciences*; *PLOSOne*; *and The Journal of Pediatrics*.

11. I am listed as an inventor on at least one patent or patent application.

12. I am the current Chair of the Academy of Pharmaceutical Scientists (APS), and have served as a committee member and Chair on the

Biopharmaceutics focus group within APS and as a committee member of the New Scientists Focus Group within APS. I am a Workstream Leader of the biopharmaceutics theme within the European Paediatric Formulation Initiative (EuPFI). I am also a member of UNGAP (The European Network on Understanding Gastrointestinal Absorption-related Processes), Expert Advisory Group on Medicinal Chemistry to the British Pharmacopoeia, Standards Committee for IPEC (International Pharmaceutical Excipients Committee), Drug Delivery Research Network (DDRN) (founding member), and Young Academic Network for Chemical Engineers (YANCE). I also serve as a formulations expert within the Connect 4 Children Collaborative Network for European Clinical Trials for Children (c4c).

13. A summary of my education, experience, publications, awards and honors, patents, publications, and presentations is provided in my CV, a copy of which is attached as Exhibit A to this Declaration.

14. I am being compensated for my time in connection with this IPR at my standard consulting rate, which is £250.00 per hour. My compensation is not dependent in any way upon the outcome of this matter.

III. PERSON OF ORDINARY SKILL IN THE ART

15. I have been asked to investigate and provide opinions from the perspective of a person of ordinary skill in the art ("person of ordinary skill" or

"POSA") at the time of the priority date of the challenged claims of the '628 patent, which I understand is December 5, 2008.

16. I understand that a POSA relating to the subject matter of the '628 patent would have had (1) a Pharm.D., or a Ph.D. in pharmaceutical sciences, chemical engineering, chemistry, or related discipline; and (2) at least two to four years of experience with pharmaceutical design, formulation, development, and/or manufacturing of oral dosage forms. A POSA may also work as part of a multidisciplinary team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others in the team to solve a given problem. To the extent necessary, this person would have worked in collaboration with others with the requisite education and experience in candidate drug selection, clinical use, clinical testing, design, formulation, development, and/or manufacturing of pharmaceutical oral dosage forms.

17. I have applied this definition of a POSA herein.

IV. DOCUMENTS

18. In preparing this Declaration, I reviewed and considered the documents identified in the below table:

Exhibit No.	Description
1014	Chan et al., "5-Azacytidine Hydrolysis Kinetics Measured by High-Pressure Liquid Chromatography and 13C-NMR Spectroscopy,"68 (7) J Pharma. Scis. 807 (1979) ("Chan")

Exhibit No.	Description
1017	Marcucci, G., et al., "Bioavailability of Azacitidine Subcutaneous Versus Intravenous in Patients With the Myelodysplastic Syndromes," 45 J. Clin. Pharmacology 597 (2005) ("Marcucci")
1018	Thomson, A., "Back to basics: pharmacokinetics," 272 Pharma. J 769 (2004) ("Thomson")
1027	GastroPlus version 5.2 Manual ("GP5.2 manual")
1039	Buck et al., *Prediction of Human Pharmacokinetics Using Physiologically Based Modeling: A Retrospective Analysis of 26 Clinically Tested Drugs*, Drug Metabolism & Disposition, 35(10):1766–1780 (2007) ("Buck")
1040	Dannenfelser et al., *Development of Clinical Dosage Forms for a Poorly Water Soluble Drug I: Application of Polyethylene Glycol–Polysorbate 80 Solid Dispersion Carrier System*, J Pharma. Sci., 93(5):1165–1175 (2004) ("Dannenfelser")
1041	Press Release, Simulations Plus, Inc., "Simulations Plus Releases GastroPlus(™) 5.2" (Nov. 30, 2006) ("GP5.2 PR")
1042	IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Pharmaceutical Drugs, Vol. 50, 1990 ("IARC")
1043	Israili et al., *The Disposition and Pharmacokinetics in Humans of 5-Azacytidine Administered Intravenously as a Bolus or by Continuous Infusion*, Cancer Res. 36:1453–1461 (1976) ("Israili")
1044	Kuentz et al., *A strategy for preclinical formulation development using GastroPlus™ as pharmacokinetic simulation tool and a statistical screening design applied to a dog study*, Euro. J. Pharma. Sci., 27:91–99 (2006) ("Kuentz")
1045	Li et al., IV-IVC Considerations in the Development of Immediate-Release Oral Dosage Form, J Pharma. Sci. 94(7):1396–1417 (2005) ("Li")
1046	Obach et al., *The Prediction of Human Pharmacokinetic Parameters from Preclinical and In Vitro Metabolism Data*, J. Pharma. & Exp. Thera., 283(1):46–58 (1997) ("Obach")
1047	Parrott & Lavé, Prediction of intestinal absorption: comparative assessment of gastroplus™ and idea™, Euro. J. Pharma. Sci., 17:51–61 (2002) ("Parrott")

Exhibit No.	Description
1048	Simulations Plus, Inc., Form 10-QSB (January 16, 2007) ("SLP 10-QSB")
1052	The SDF file for the PubChem compound entry for Azacitidine (PubChem CID 9444) (September 16, 2004) ("Conformer3D_CID_9444 (1).sdf"), printed to PDF
1053	ADMET Predictor Output file ("Azacitidine ADMET.txt"), printed to PDF
1054	CDD file for 200 mg dose ("Azacitidine 200 mg.cdd"), printed to PDF
1055	IV plasma concentration-time data file for 200 mg dose ("Azacitidine 200 mg.ipd"), printed to PDF
1056	Result data file for 200 mg dose ("Azacitidine 200 mg All Data.txt"), printed to PDF
1057	CDD file for 400 mg dose ("Azacitidine 400 mg.cdd"), printed to PDF
1058	IV plasma concentration-time data file for 400 mg dose ("Azacitidine 400 mg.ipd"), printed to PDF
1059	Result data file for 400 mg dose ("Azacitidine 400 mg All Data.txt"), printed to PDF

V. SUMMARY OF OPINIONS

19. *In silico* modeling of PK properties (AUC, C_{max}, and T_{max}) following the oral administration of 200 mg and 400 mg non-enteric coated ("non-EC") tablets of 5-azacytidine to a human test subject results in the following PK properties:

PK Property	Simulation Result
AUC (area under the curve)	264.72 ng*h/mL (200 mg dose) 529.46 ng*h/mL (400 mg dose)
C_{max} (maximum plasma concentration achieved during a period of time)	105.3 ng/mL (200 mg dose)

	210.6 ng/mL (400 mg dose)
T_{max} (time necessary to reach C_{max})	67.2 min (200 and 400 mg dose)

(Appx II.D, Appx II.E, Appx III.D, Appx III.E; EX-1056; EX-1059.)

VI. BACKGROUND AND STATE OF THE ART

A. Pharmacokinetics

20. Pharmacokinetics ("PK") is the study of the relationship between drug administration and the resulting levels of that drug in the body. (EX-1018, Thomson at 769 (summarizing principles of pharmacokinetics and important parameters).) One important aspect of PK is drug concentration in plasma, or "plasma concentration." A profile that reports plasma concentration of a drug over time (i.e., a plasma concentration-time profile) can be used to calculate PK properties such as: (1) Area Under Curve ("AUC") (total amount of drug present in the plasma over a period of time, measured by the area under the curve of the plasma concentration-time profile); (2) C_{max} (maximum plasma concentration achieved during a period of time); and (3) T_{max} (time necessary to reach C_{max}). (EX-1017, Marcucci at 599-600 (reporting pharmacokinetic properties of 5-azacytidine following subcutaneous or intravenous administration); EX-1027, GP5.2 manual at 39 (user manual for GastroPlus software version 5.2).)

21. The PK of a drug may inform how to optimize its dose, dosing schedule, or even dosage form. In particular, this information may be used to

maintain the drug's plasma concentration within its therapeutic window for a desired period of time, which may inform drug product design or how it is administered to make it more effective, safe, and/or convenient. (EX-1018, Thomson at 769.)

B. *In Silico* Modeling of PK Properties of Oral 5-Azacytidine

22. Drug development, particularly clinical testing of drug product candidates, is expensive and time consuming. (EX-1046, Obach at 46 (study validating human PK prediction methods); EX-1047, Parrott at 51-52 (evaluation of *in silico* prediction software, GastroPlus, as a tool for drug discovery and development); EX-1045, Li at 1413 (predictive tools are important to minimize costly animal and human experiments during drug development).) One method of mitigating the time and expense associated with clinical testing was to utilize *in silico* methods. *In silico* physiologically-based pharmacokinetic methods were developed for modeling PK of oral dosage forms, enabling scientists to more readily identify the best candidates for drug product development. (EX-1047, Parrott at 51-52; EX-1045, Li at 1413; EX-1039, Buck at 1766 (confirming successful human PK predictions by GastroPlus for 26 clinically tested drugs); EX-1044, Kuentz at 99 (GastroPlus successfully modeled drug absorption based on preformulation data).) These models were routinely used during early drug discovery, preclinical development, and clinical trials. (EX-1039, Buck at 1766;

EX-1044, Kuentz at 92-93; EX-1045, Li at 1409-1410; EX-1047, Parrott at Abstract; EX-1048, SLP 10-QSB at 21 ("GastroPlus is the 'gold standard' in the industry for its class of simulation software" and used by "virtually every major pharmaceutical company").)

23. Physiologically-based *in silico* models have been routinely and widely used since the early 2000s to determine the expected PK of orally administered pharmaceutical compositions. (EX-1039, Buck at 1766; EX-1044, Kuentz at 93; EX-1045, Li at 1409-1410; EX-1047, Parrott at 52; EX-1041, GP5.2 PR ("This latest release of GastroPlus adds several important improvements … new features [of version 5.2] provide greater accuracy for certain types of simulations . . . we're now getting reports from the field that GastroPlus simulation results are becoming required in many of their internal project reports"); EX-1027, GP5.2 manual.) *In silico* modeling had been recognized as being able to accurately predict *in vivo* PK for orally administered drugs. (EX-1047, Parrott at 51; EX-1039, Buck at 1766.)

24. The clinical bioavailability and *in vivo* PK for 5-azacytidine dosage forms were well known for SC and IV administration. (EX-1017, Marcucci.) Based on the foregoing and known physical and chemical properties of 5-azacytidine, *in silico* models of the oral dosage forms of 5-azacytidine could have readily been constructed.

25. One example of a routinely-used and widely-known PK modeling software is GastroPlus (version 5.2) ("GP5.2").[1] (EX-1041, GP5.2 PR; EX-1027, GP5.2 manual at 4-9.) GP5.2 and its earlier versions were available before 2007, before the priority date of the challenged claims of the '628 patent, which I understand is December 5, 2008. (EX-1027, GP5.2 manual (dated November 2006).)

26. Major pharmaceutical companies such as Roche, Johnson & Johnson, and Novartis employed GastroPlus (EX-1044, Kuentz at 91 (reporting use of GastroPlus at Roche in clinical formulation development); EX-1039, Buck at 1766 (reporting validation of GastroPlus predictions by Johnson & Johnson Pharmaceutical Research and Development); EX-1040, Dannenfelser at 1165 (Novartis using GastroPlus to predict the oral bioavailability of a compound)), demonstrating that this software was "the tool of choice" for modeling PK when integrating *in vitro* and *in vivo* data with *in silico* prediction. (EX-1047, Parrott at 60; EX-1044, Kuentz at 93; EX-1045, Li at 1409-1410). GP5.2 and its earlier versions were capable of generating *in silico* models for oral dosage forms based on *in vivo* intravenous PK results. (EX-1041, GP5.2 PR; EX-1027, GP5.2 manual;

[1] GP5.2 was commercially available from Simulations Plus (https://www.simulations-plus.com/).

EX-1018, Thomson at 769-70; EX-1039, Buck at 1766; EX-1044, Kuentz at 93; EX-1045, Li at 1409-1410; EX-1047, Parrott at 52.)

27. Another useful feature of GP5.2 is its ability to model the *in vivo* rate of chemical degradation based on *in vitro* degradation data. (EX-1027, GP5.2 manual.) Such degradation data for 5-azacytidine was well known and reported in the literature. (EX-1014, Chan.) Thus, GP5.2 accounts for any degradation in the gastrointestinal tract when determining the PK of an oral dosage form of 5-azacytidine.

28. Prior to testing known compositions such as 5-azacytidine in humans, a POSA would have been motivated to obtain data on *in silico* modeling, for example, from others of skill in the art that a POSA may have collaborated with, using GP5.2 based on at least reduced time and cost considerations.

VII. *IN SILICO* MODELING OF PK PROPERTIES FOLLOWING THE ORAL ADMINISTRATION OF 200 MG AND 400 MG NON-ENTERIC COATED TABLETS OF 5-AZACYTIDINE

29. I have been asked to investigate and provide opinions relating to the *in silico* modeling of PK properties following the oral administration of a 200 mg non-EC tablet of 5-azacytidine and a 400 mg non-EC tablet of 5-azacytidine.

30. *In silico* modeling of PK properties following the administration of a **200 mg** non-EC formulation of 5-azacytidine to a human test subject resulted in an AUC of 267.72 ng*h/mL, a C_{max} of 105.3 ng/mL, and a T_{max} of 67.2 minutes. *In*

silico modeling of PK properties following the administration of a **400 mg** non-EC formulation of 5-azacytidine to a human test subject resulted in an AUC of 529.46 ng*h/mL, a C_{max} of 210.6 ng/mL, and a T_{max} of 67.2 minutes.

31. GP5.2 inputs and results are discussed below for the simulation that I conducted.

A. GastroPlus Inputs

32. GastroPlus simulation (i.e.*, in silico* modeling) involves input of compound, physiology, PK, and simulation parameters. All parameters for the simulation were known and available to a POSA including structural information, degradation characteristics, and known PK of other dosage forms. Such parameters were inputted, and the simulation was run, in line with how a POSA would have used the GastroPlus software.[2] (*See, e.g.*, EX-1041, GP5.2 PR; EX-1027, GP5.2 manual; EX-1045, Li at 1409-1410; EX-1047, Parrott at 52.)

[2] Certain relevant inputs were analyzed in the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) or PKPlus modules to generate certain parameters used by GP5.2. The output from the ADMET analysis is provided herewith. (EX-1053, Azacitidine ADMET.TXT.) This is consistent with how a POSA would have used the GastroPlus software.

1. Generation of Support Files

33. GastroPlus utilizes well-known information, including structural information to generate values for physiochemical properties of a drug, for use in pharmacokinetic simulation. (EX-1041, GP5.2 PR; EX-1027, GP5.2 manual; EX-1045, Li at 1409-1410; EX-1047, Parrott at 52; *see also* Appx I.A.) These physiochemical properties include molecular weight, logP, solubility, diffusion coefficient, estimated effective permeability, plasma protein binding, and volume of distribution. (Appx I.A.2.) The 3D structure of 5-azacytidine was obtained from PubChem as an SDF file.[3]

34. To the extent a compound degrades following oral administration, chemical stability data can be used to model the amount of the compound that remains available for absorption. The degradation rate constants for 5-azacytidine hydrolysis in aqueous buffer solutions at 37 °C were reported for various pH values between 4.5 and 8.0. (EX-1014, Chan at 810, Table II, 811, Fig. 8.) The percent degradation per hour can be calculated using the following equation:[4]

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[3] The PubChem compound entry for Azacitidine (PubChem CID 9444) was created on September 16, 2004. The SDF file was obtained from https://pubchem.ncbi.nlm.nih.gov/compound/Azacitidine#section=3D-Conformer and is provided herewith. (EX-1052.)

[4] Adapted from equation 3 of Chan. (EX-1014, Chan at 809.)

$$\% \text{ degradation/hr} = 100 - (100\ e^{(-k * 60)}),$$

where k is the degradation rate constant

35. Based on the reported degradation rate constants reported in Chan, the percent degradation per hour were calculated for each of the pH values as shown in the table below.

pH	***Degradation rate constant***	***% degradation/hr***
4.5	15.6×10^{-3} M, $min^{-1} = 0.0156\ min^{-1}$	60.78
5.6	11.2×10^{-3} M, $min^{-1} = 0.0112\ min^{-1}$	48.93
7.0	7.33×10^{-3} M, $min^{-1} = 0.00733\ min^{-1}$	35.58
7.4	12.8×10^{-3} M, $min^{-1} = 0.0128\ min^{-1}$	53.61
8.0	35×10^{-3} M, $min^{-1} = 0.035\ min^{-1}$	87.75

36. The above data was entered into GastroPlus to generate a chemical degradation data file (CDD file). (Appx I.B; EX-1054, Azacitidine 200mg.cdd; EX-1057, Azacitidine 400mg.cdd.)

37. Predictions of distribution and clearance can also be generated based on *in vivo* human preclinical intravenous pharmacokinetic data or *in vitro* data. (EX-1046, Obach at 46-47.) *In vivo* human preclinical intravenous pharmacokinetic data for 5-azacytidine was reported. (EX-1017, Marcucci at 600, Table 1, Fig. 1.) The data reported in Figure 1 of Marcucci was extracted using image-to-data software to ensure its accuracy. Figure 1 of Marcucci and the data extracted therefrom are reproduced below:

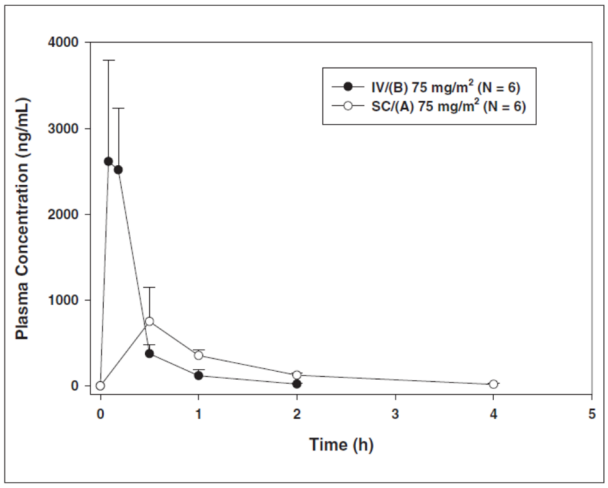


Figure 1. Mean azacitidine concentration-time profile for subcutaneous (SC) and intravenous (IV) treatments.

Time (h)	Plasma Concentration (ng/mL)
0.0	0
0.08	2620
0.17	2514
0.5	377
1.0	119
2.0	27

38. The intravenous plasma concentration-time data from Marcucci was entered into the PKPlus module in GastroPlus to generate an intravenous plasma data file (IPD file). (Appx I.C; EX-1055, Azaciditine 200mg.ipd; EX-1058, Azaciditine 400mg.ipd.) PKPlus generated compartmental models and a non-compartmental model for calculating PK parameters from the plasma concentration-time profile. (Appx I.D.) The two-compartment model was selected based on the teachings in Israili that the analysis of *in vivo* data "fits a 2-compartment model ($r > 0.95$)." (EX-1043, Israili at 1455, 1457; Appx I.D.4.)

The R^2 value of 0.9995 reported by PKPlus confirmed that the Marcucci data fit the two-compartment model. (Appx I.D.4.)

2. Compound Parameters

39. The parameters related to properties of the drug compound, 5-azacytidine, were entered in the "Compound" tab.

40. First, inputs relating to the dosage form and initial dose were selected to reflect the non-EC tablets containing either 200 mg or 400 mg of 5-azacytidine. (Appx II.A; Appx III.A.) Specifically, an immediate release (IR) tablet was selected as an input for the dosage form to reflect the non-EC tablets containing either 200 mg or 400 mg of 5-azacytidine. Values for subsequent doses were not changed and kept at 0 mg as the model was for a single dose response.

41. Next, well-known information related to the chemical properties of 5-azacytidine were available to a POSA, including from the International Agency for Research on Cancer (IARC). (EX-1042, IARC at 47-63.) Such information for 5-azacytidine included the molecular formula ($C_8H_{12}N_4O_5$), molecular weight (244 g/mol), and solubility in various solvents at different pH values. (EX-1042, IARC at 47-48; EX-1043, Israili at 1458.) The pH for the reference solubility was set at pH 1.1 to reflect the pH of stomach acid and the solubility at that pH 1.1 was utilized. (EX-1042, IARC at 48 (28 mg/mL in 0.1 N hydrochloric acid).) The diffusion coefficient was calculated by GastroPlus based on molecular weight. In

addition, the octanol-water partition coefficient of the neutral drug molecule is disclosed as being <0.005. (EX-1043, Israili at 1458.) The logP of 5-azacytidine can be calculated from the partition coefficient using the equation below:

$$\log_{10} (\text{Partition Coefficient}) = \text{LogP}$$

$$\log_{10} (0.005) = - 2.3$$

42. The parameters based on the known physical and chemical properties of 5-azacytidine were generated by the ADMET module and thereafter utilized. (Appx II.A.; Appx II.A.1; Appx III.A.; Appx III.A.1; EX-1053.) Additionally, previously generated chemical degradation data was utilized, as I described above in Section VII.A.1.

43. Finally, the remaining inputs included dosage volume (250 mL), particle size (25 μm), mean precipitation time (900 seconds), and drug particle density (1.2 g/mL). (Appx II.A; Appx III.A.) Default values for these parameters were prepopulated and were left unchanged, which is consistent with how a POSA would have used the GastroPlus software.

3. Physiology Parameters

44. The parameters that define the type of clinical trial to be simulated and the model used for the simulation were entered in the "Physiology" tab. The prepopulated default values of "Human – Physiological – Fasted" and "Opt logD Model" for the ASF Model were unchanged. (Appx II.B; Appx III.B.)

4. PK Parameters

45. The PK related parameters such as the subject's body weight, blood/plasma concentration ratio, unbound percent in plasma, and distribution and clearance related values can be entered in the "Pharmacokinetics" tab. (Appx II.C; Appx III.C.) The blood/plasma concentration ratio (~0.8) and unbound percent in plasma (>99%) for 5-azacytidine was known. (EX-1043, Israili at 1453, 1458.) The distribution and clearance related values generated by PKPlus (EX-1055; EX-1058) from the PK data in Marcucci (EX-1017) were loaded and the body weight was entered based on the average body weight (76.8 kg) reported in Marcucci. (EX-1017, Marcucci at 599.) All other parameters were unchanged from their default values.

5. Simulation Parameters

46. All remaining simulation parameters are specified in the "Simulation" tab. The previously generated chemical degradation data was loaded. The default option of "Built-in pKa-based Solubility Model" and default simulation length or 24 hours was used. (Appx II.D; Appx III.D.)

B. Simulation Results

47. The results of the simulation for the oral administration of 200 mg and 400 mg non-EC tablets of 5-azacytidine to a human test subject are summarized in the table below.

PK Property	Simulation Result
AUC (area under the curve)	264.72 ng*h/mL (200 mg dose) 529.46 ng*h/mL (400 mg dose)
C_{max} (maximum plasma concentration achieved during a period of time)	105.3 ng/mL (200 mg dose) 210.6 ng/mL (400 mg dose)
T_{max} (time necessary to reach C_{max})	67.2 min (200 and 400 mg dose)

(Appx II.D, Appx II.E, Appx III.D, Appx III.E, EX-1056; EX-1059.)

VIII. CONCLUSION

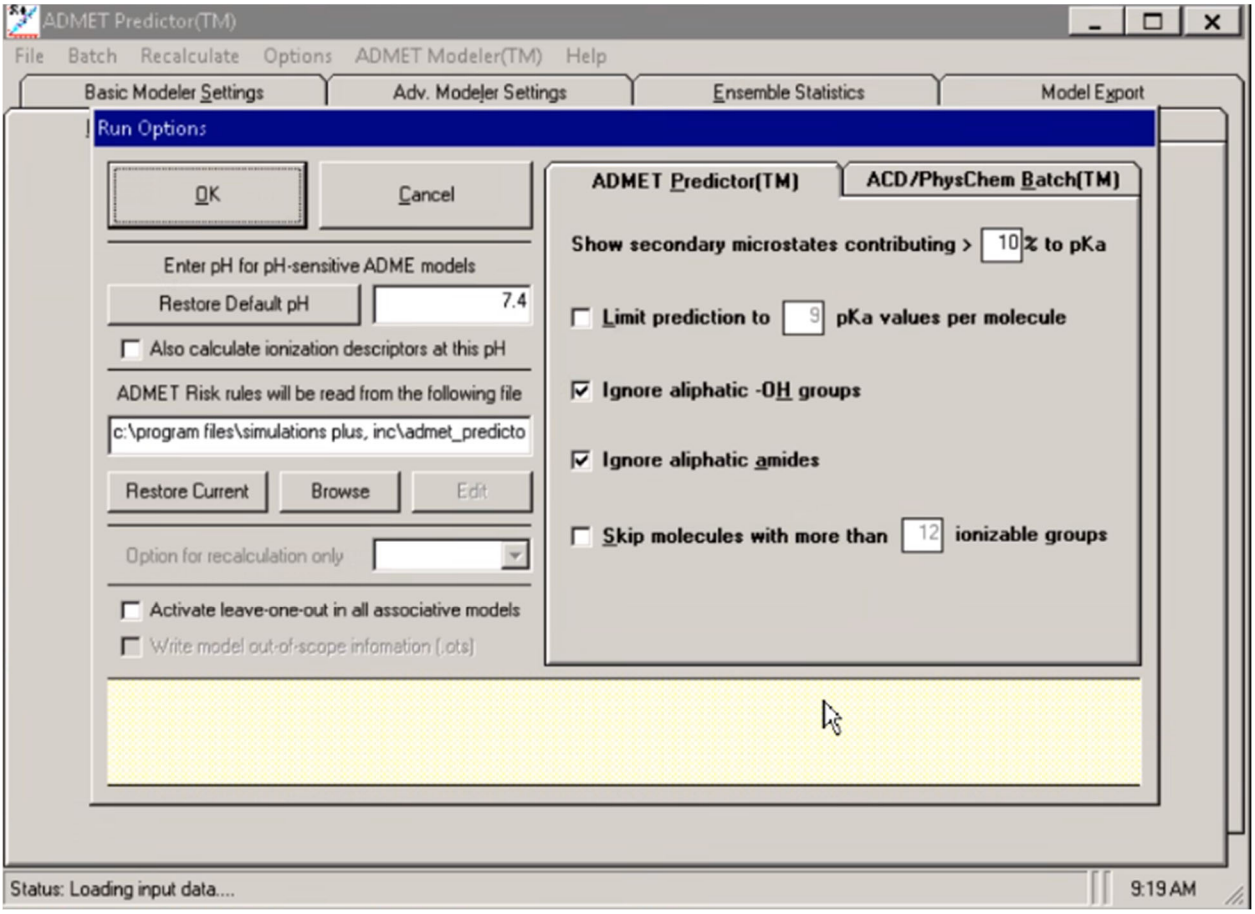
48. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

APPENDIX

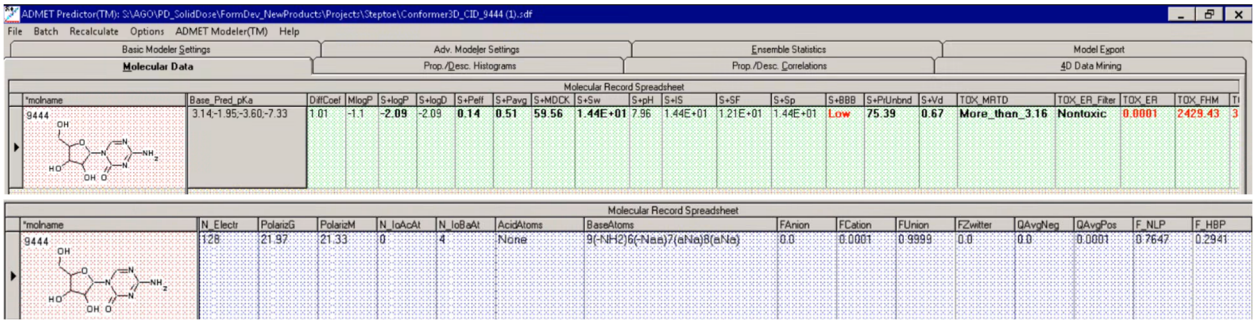
Appx I. Generation of Support Files

Appx I.A. ADMET

Appx I.A.1 ADMET Predictor Input

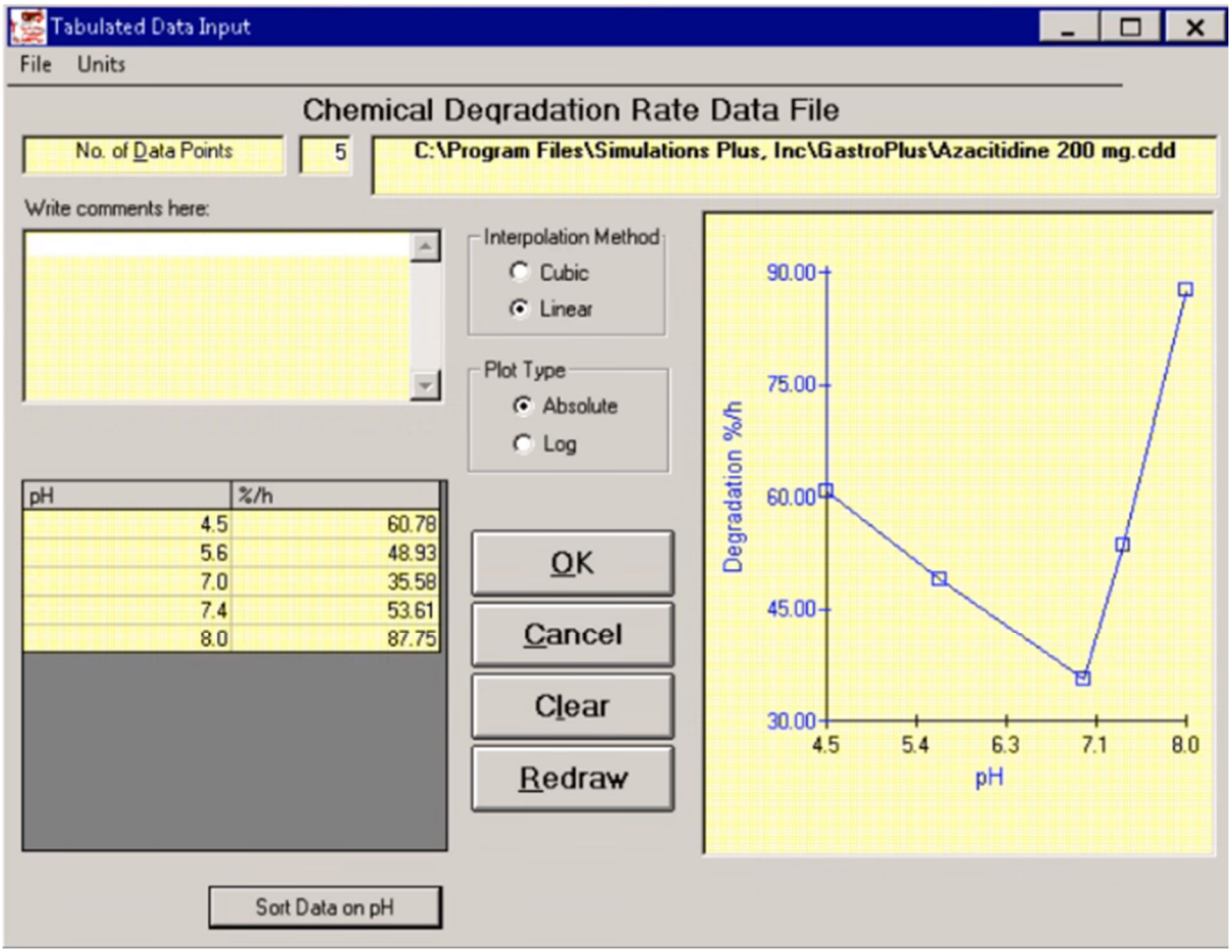


Appx I.A.2. ADMET Predictor Output[5]



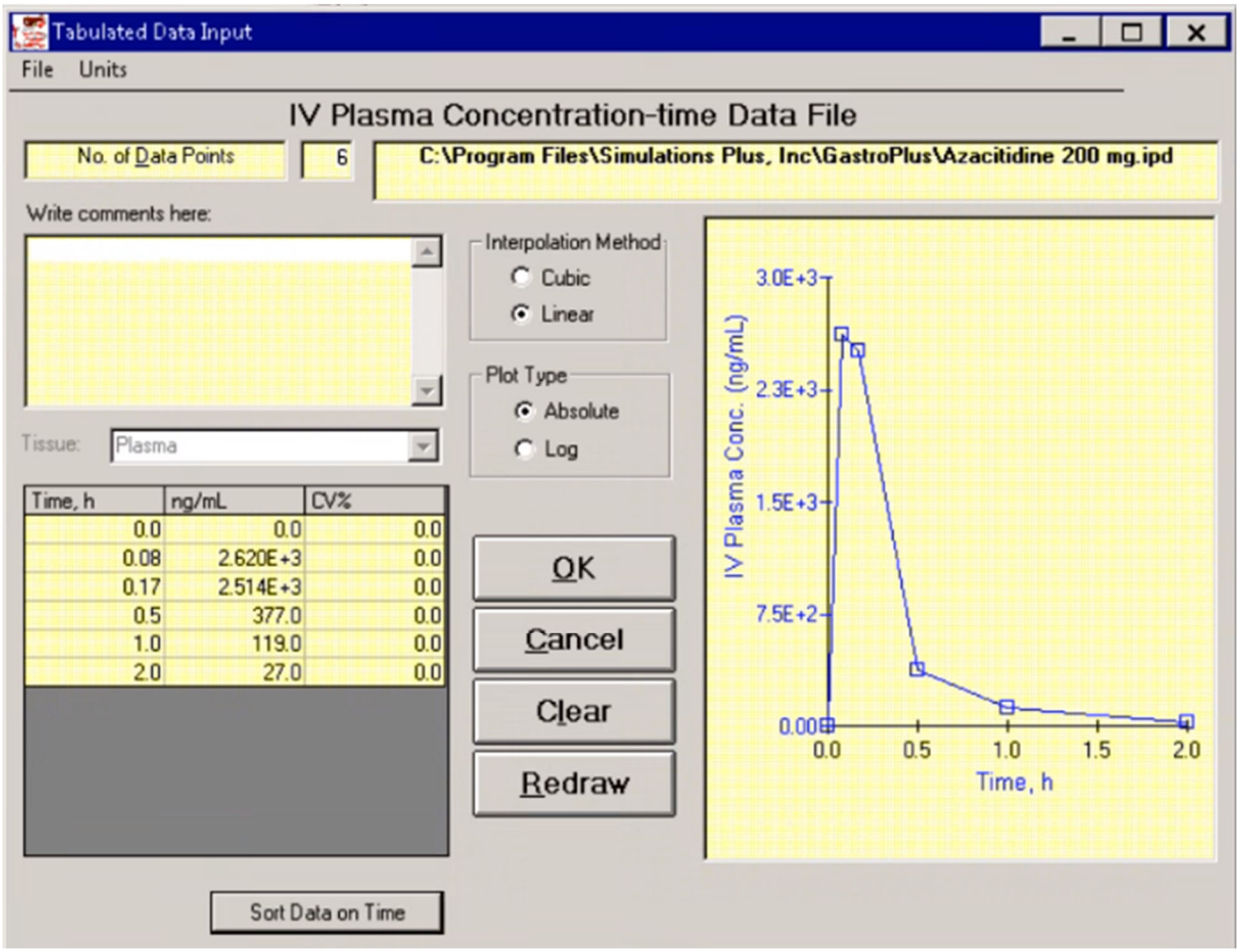
[5] The ADMET predictor output file is provided herewith. (EX-1053, Azacitidine ADMET.txt.)

Appx I.B. Chemical Degradation Rate Data[6]



[6] Chemical degradation rate data file is provided herewith. (EX-1054, Azacitidine 200mg.cdd.)

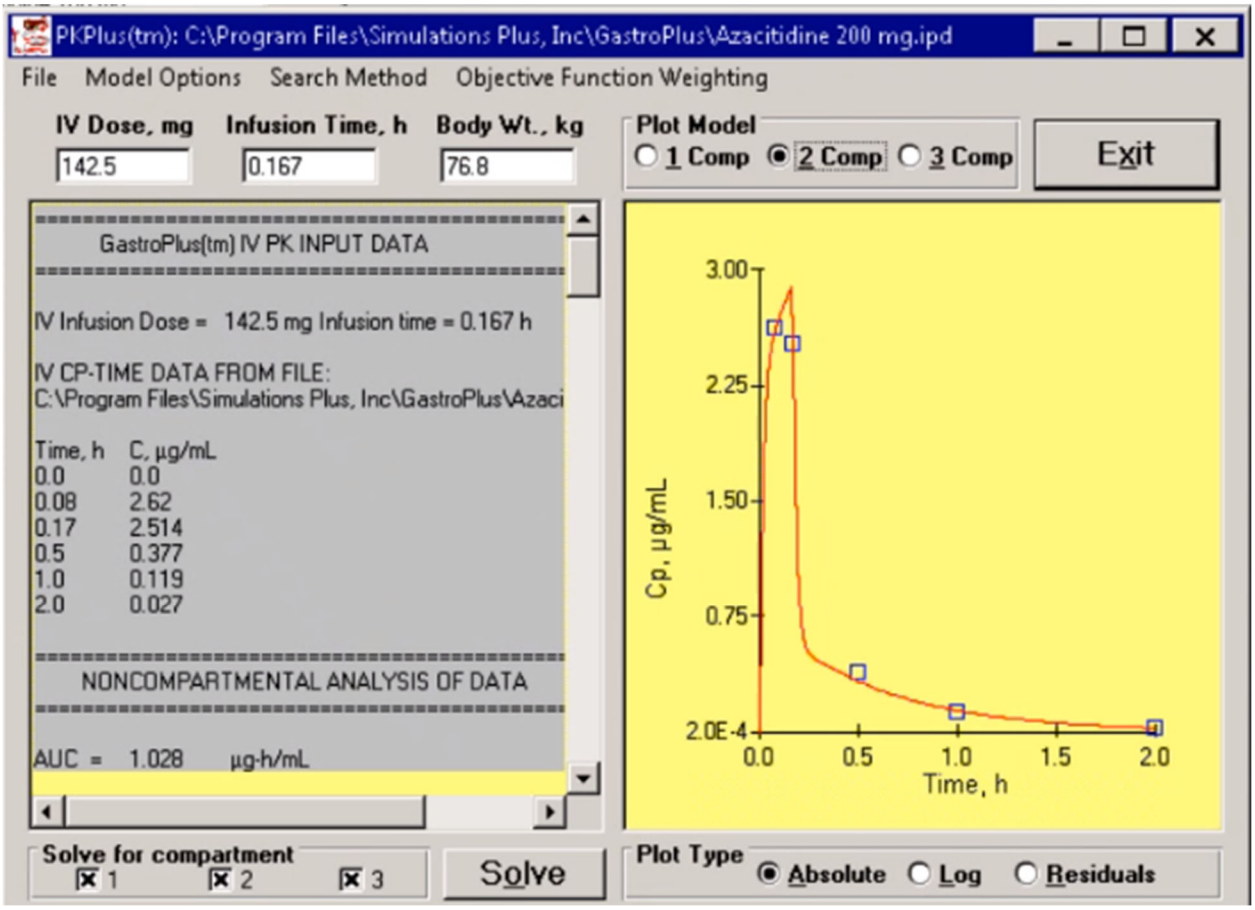
Appx I.C. IV Plasma Concentration-Time Data[7]



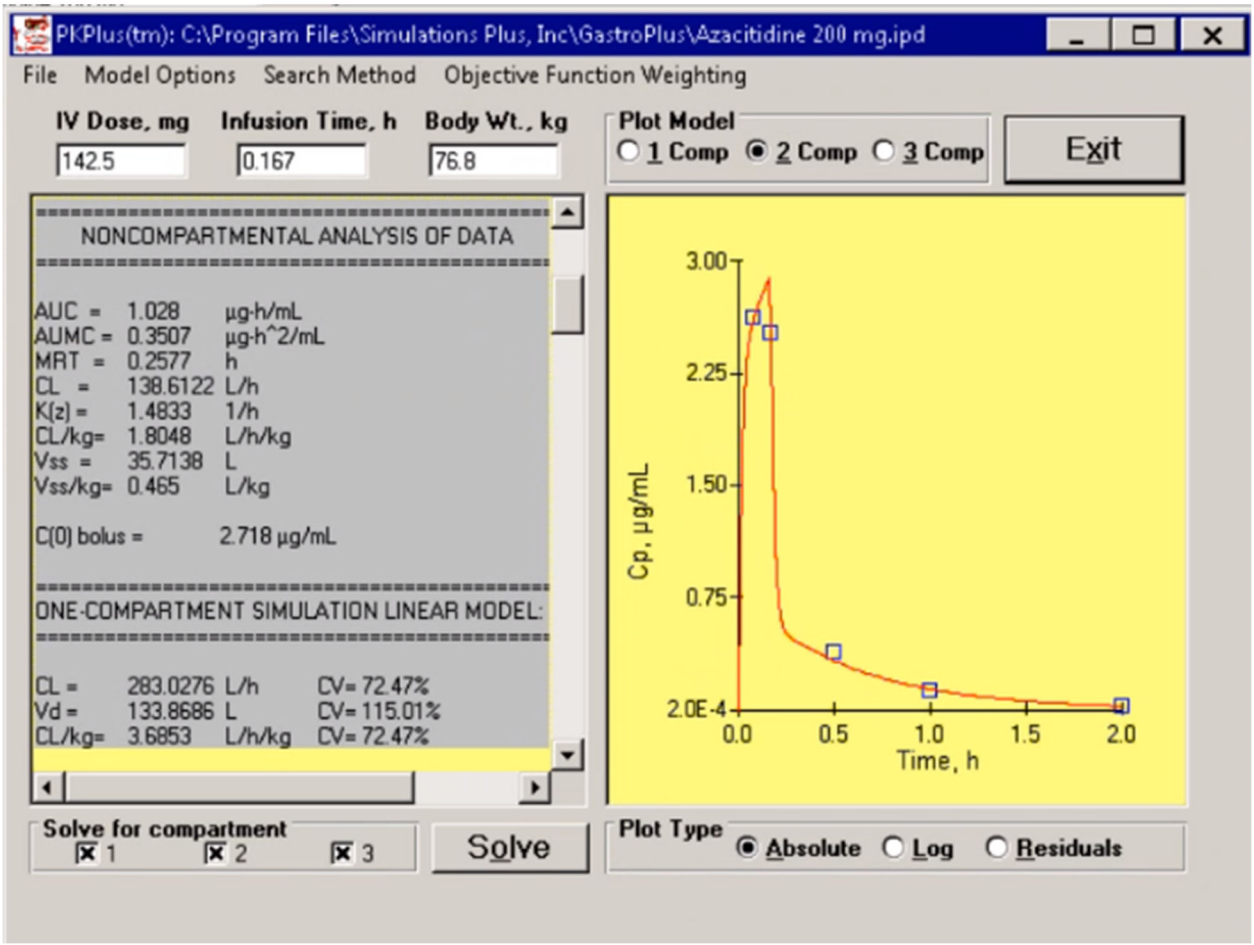
[7] The IV plasma concentration-time data file is provided herewith. (EX-1055, Azacitidine 200mg.ipd.)

Appx I.D. PKPlus Models from IV PK Data

Appx I.D.1. Input Data

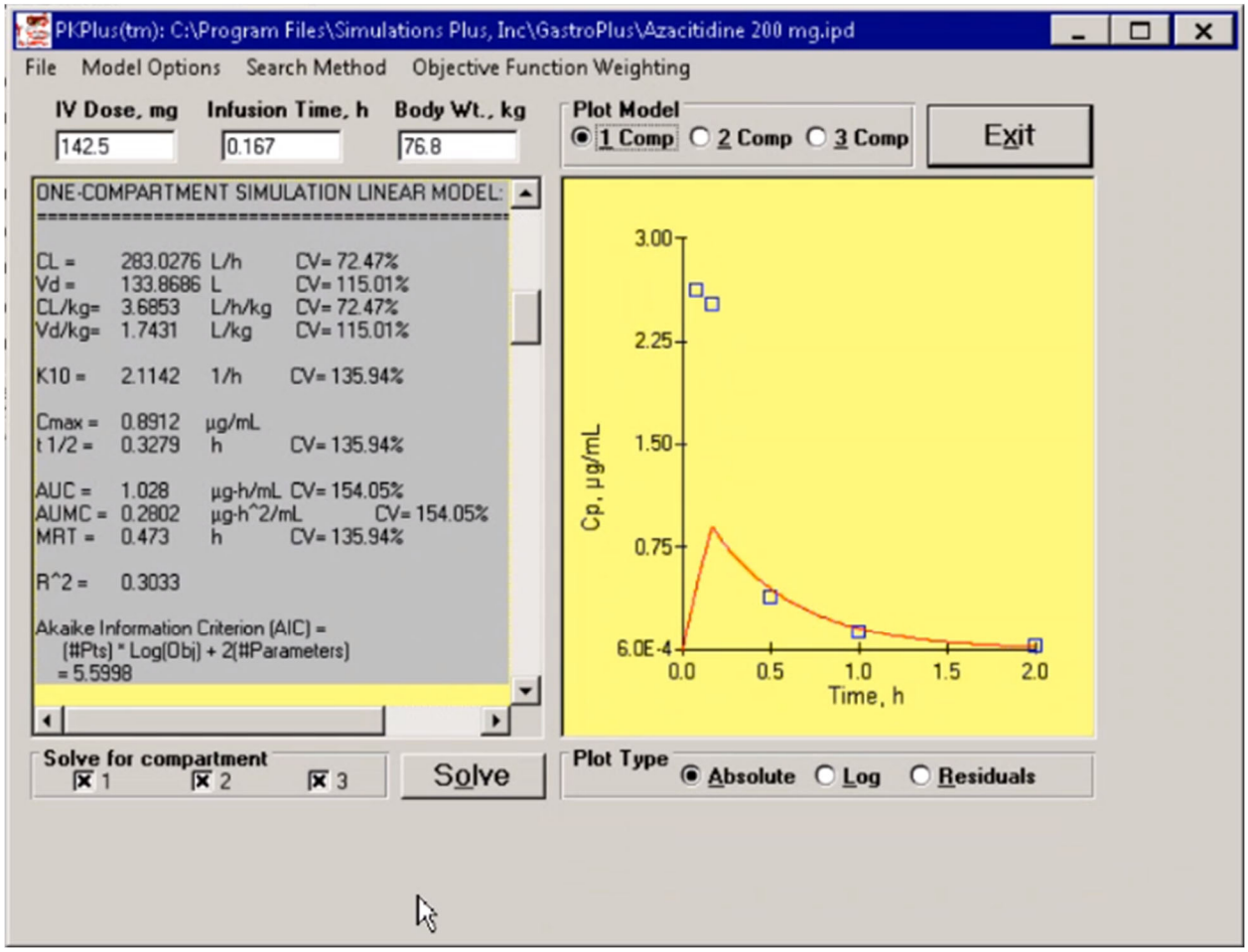


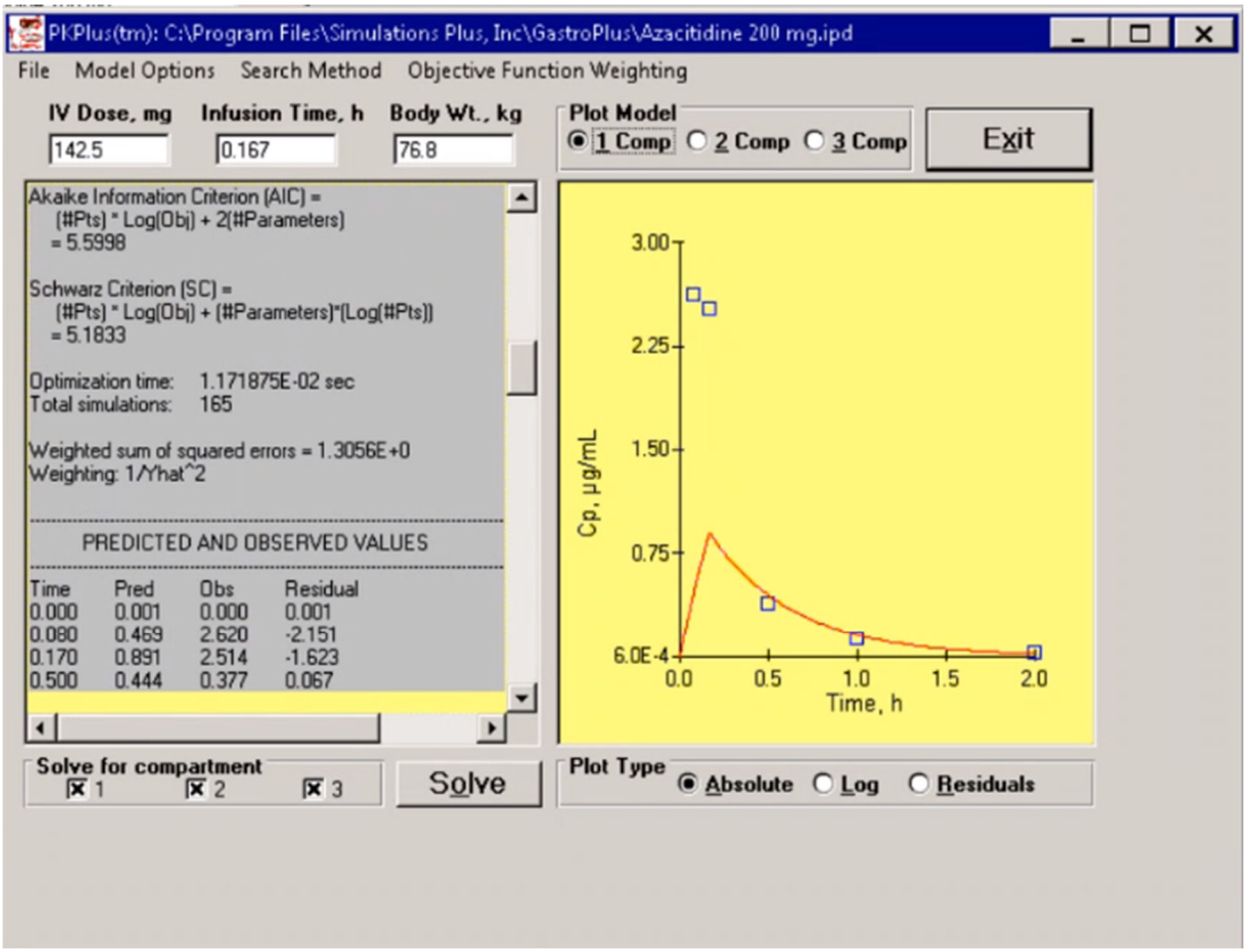
Appx I.D.2. Noncompartmental Analysis of Data[8]

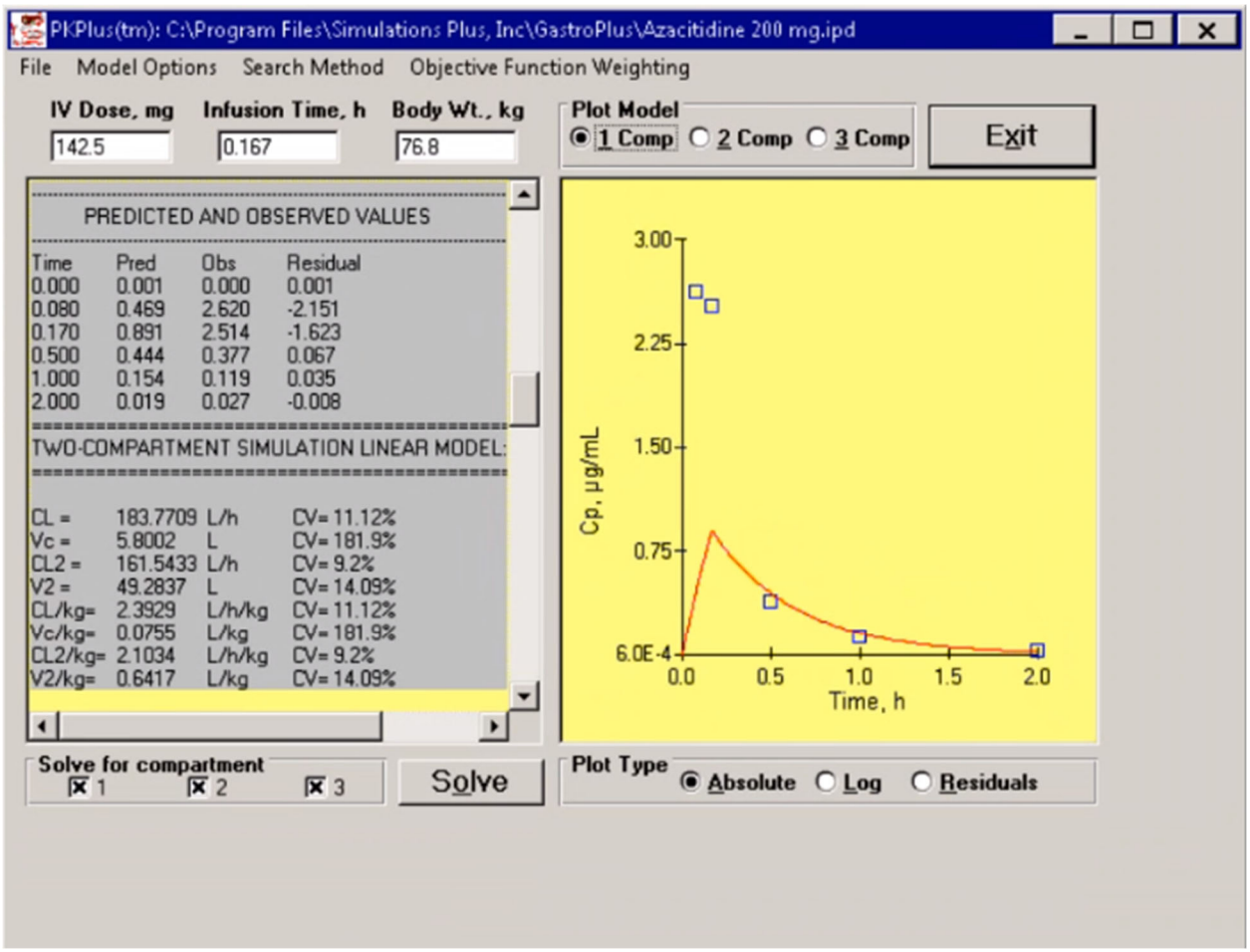


[8] This figure reflects the results of noncompartmental analysis of data in the left hand window. For the sake of clarity, the plot model graph on the right hand side shows the plot for a 2 compartmental model.

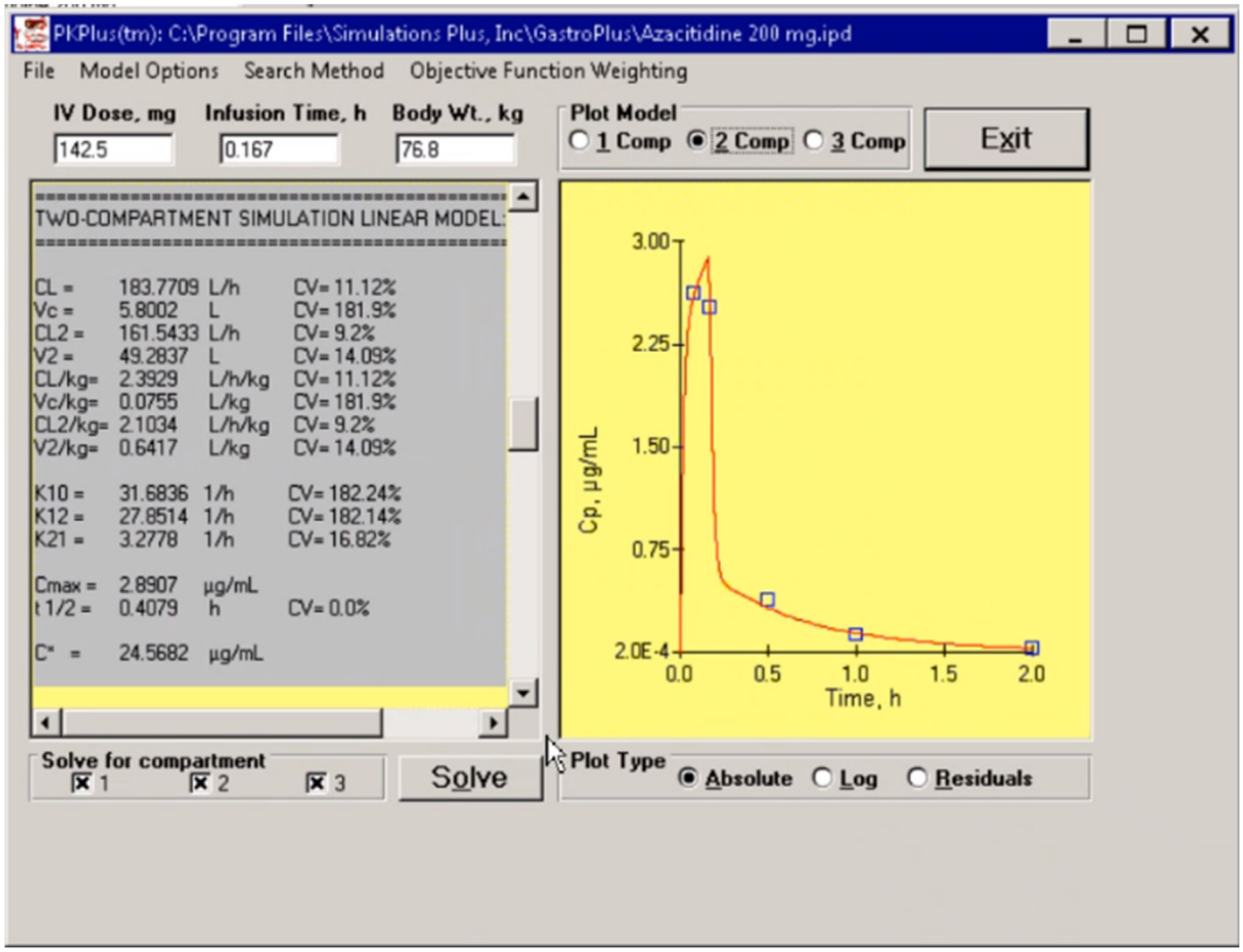
Appx I.D.3. One-Compartment Simulation Linear Model

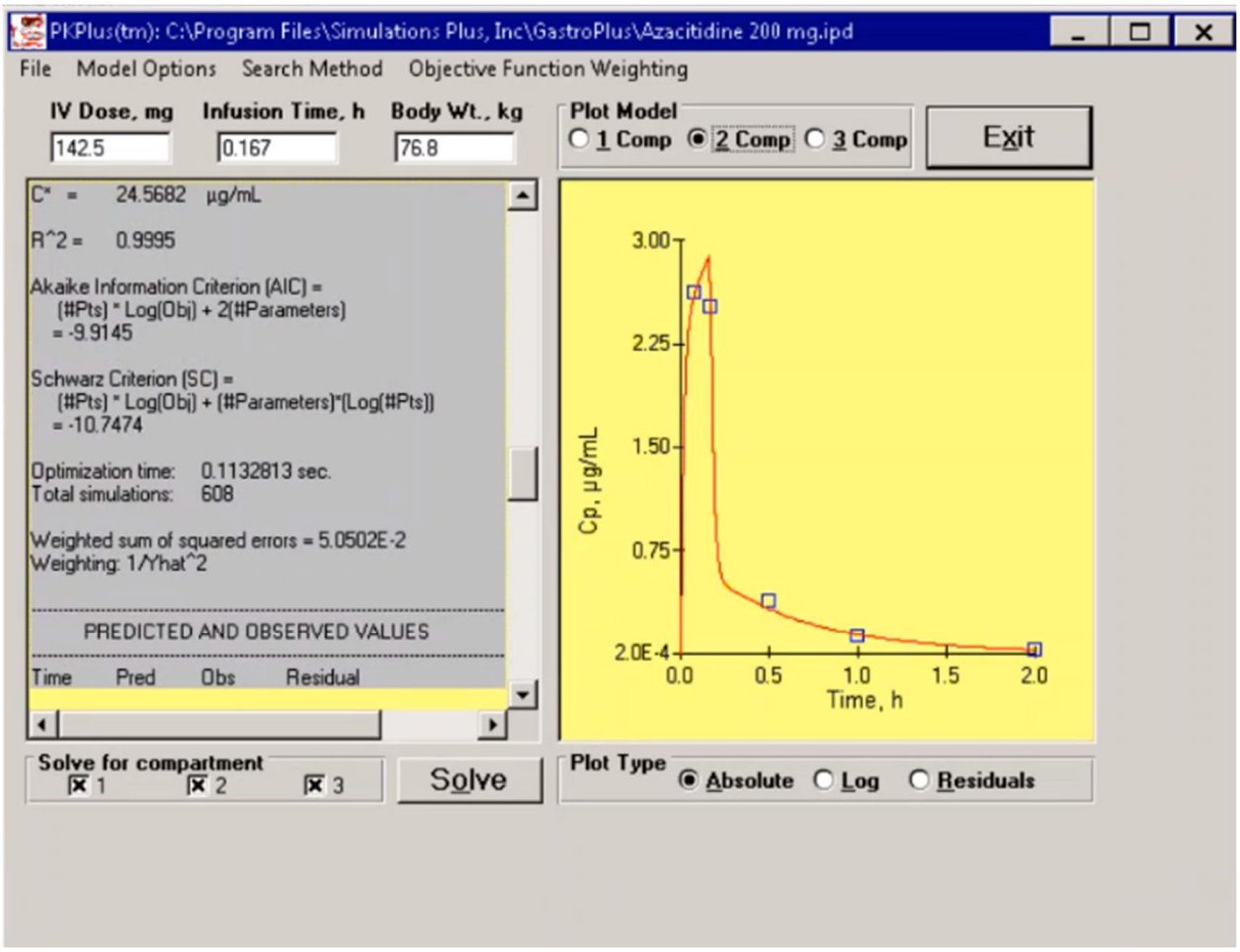


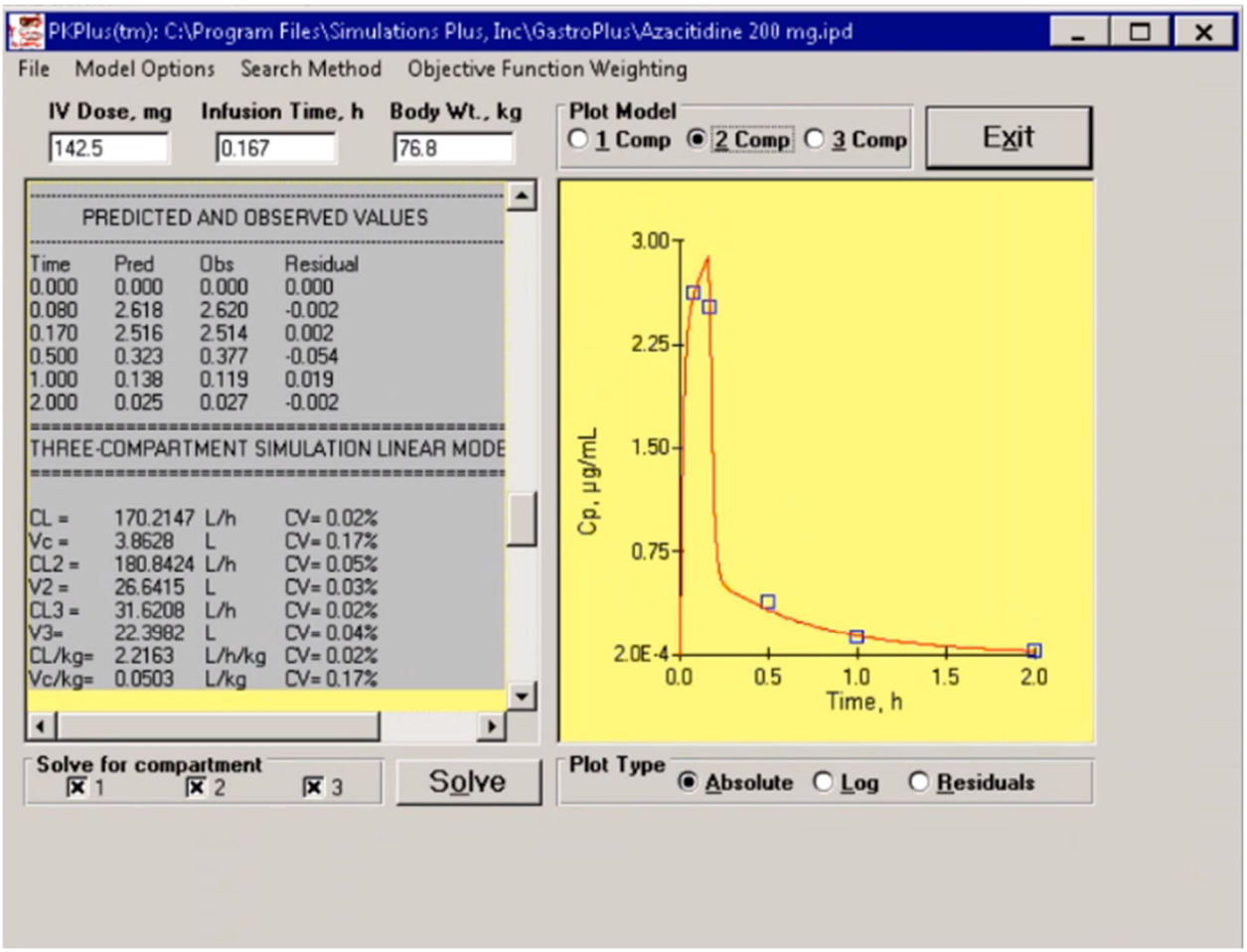




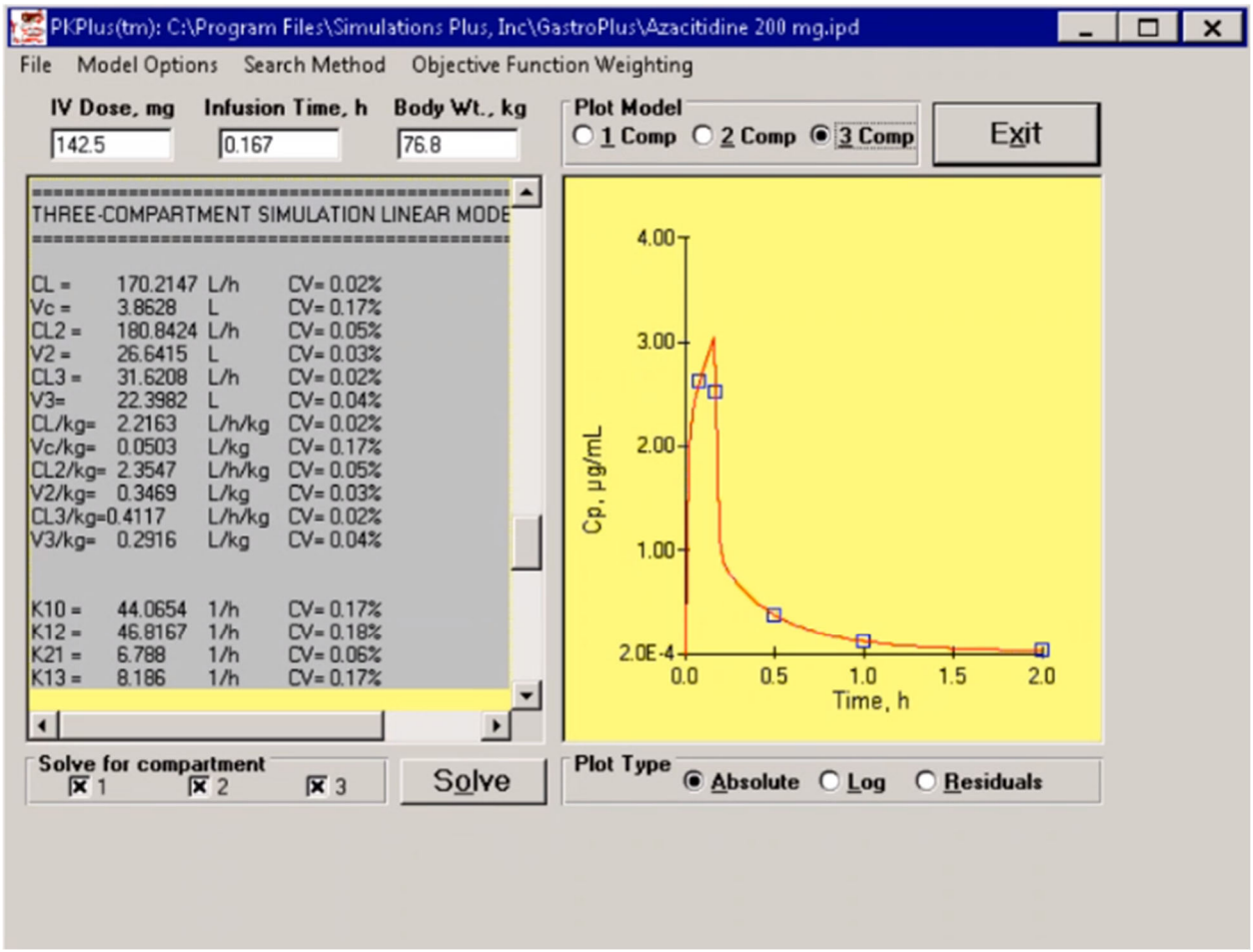
Appx I.D.4. Two-Compartment Simulation Linear Model

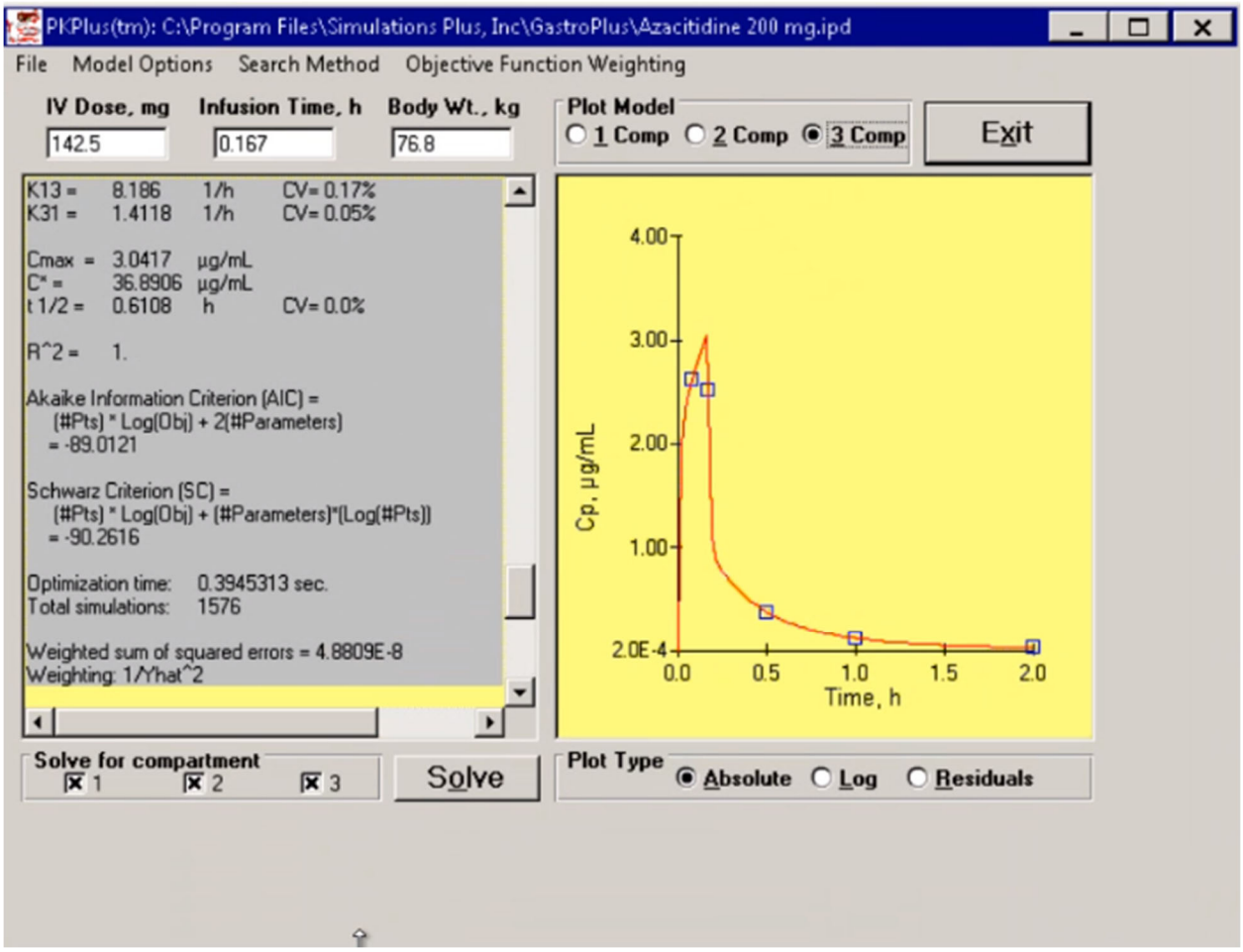


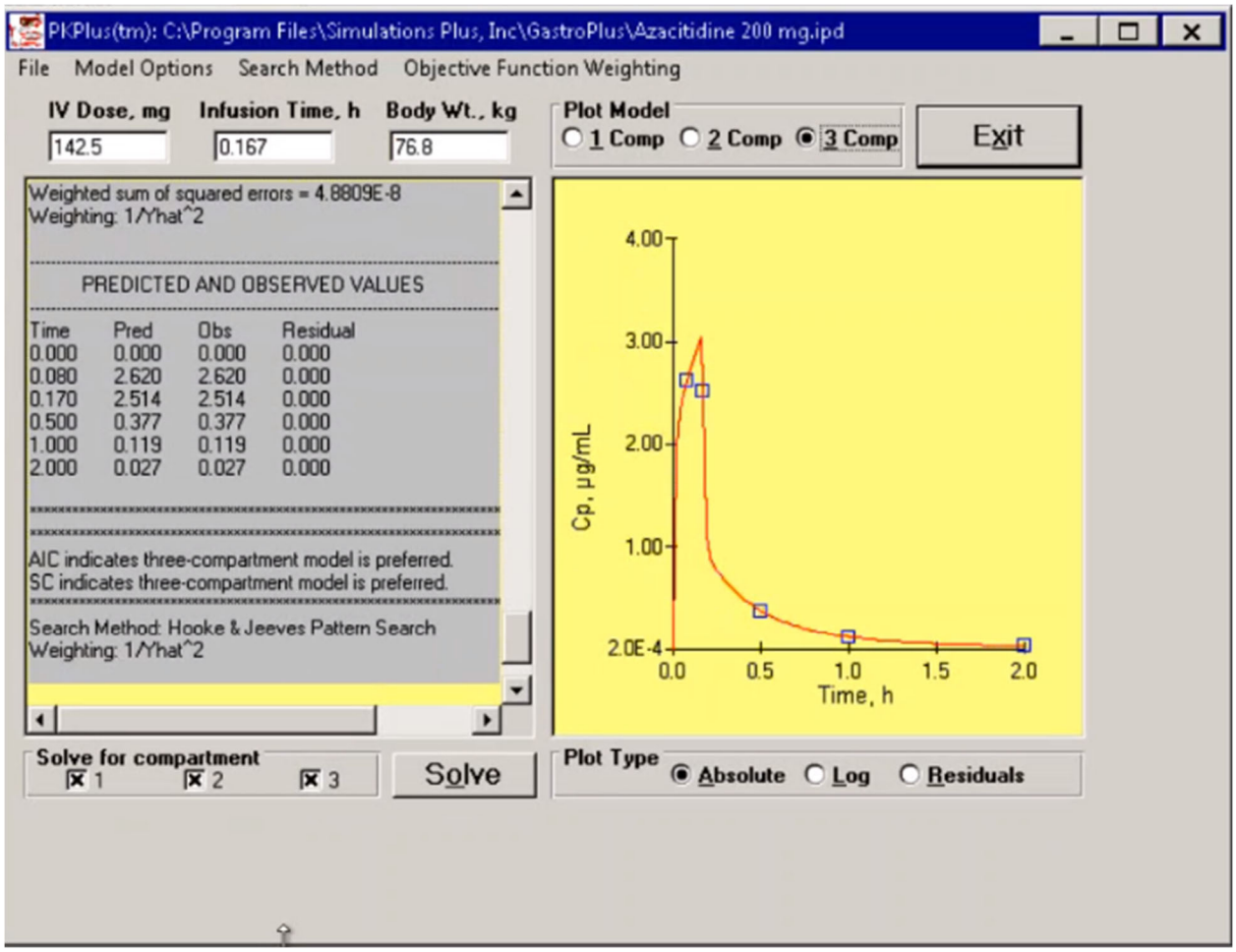




Appx I.D.5. Three-Compartment Simulation Linear Model

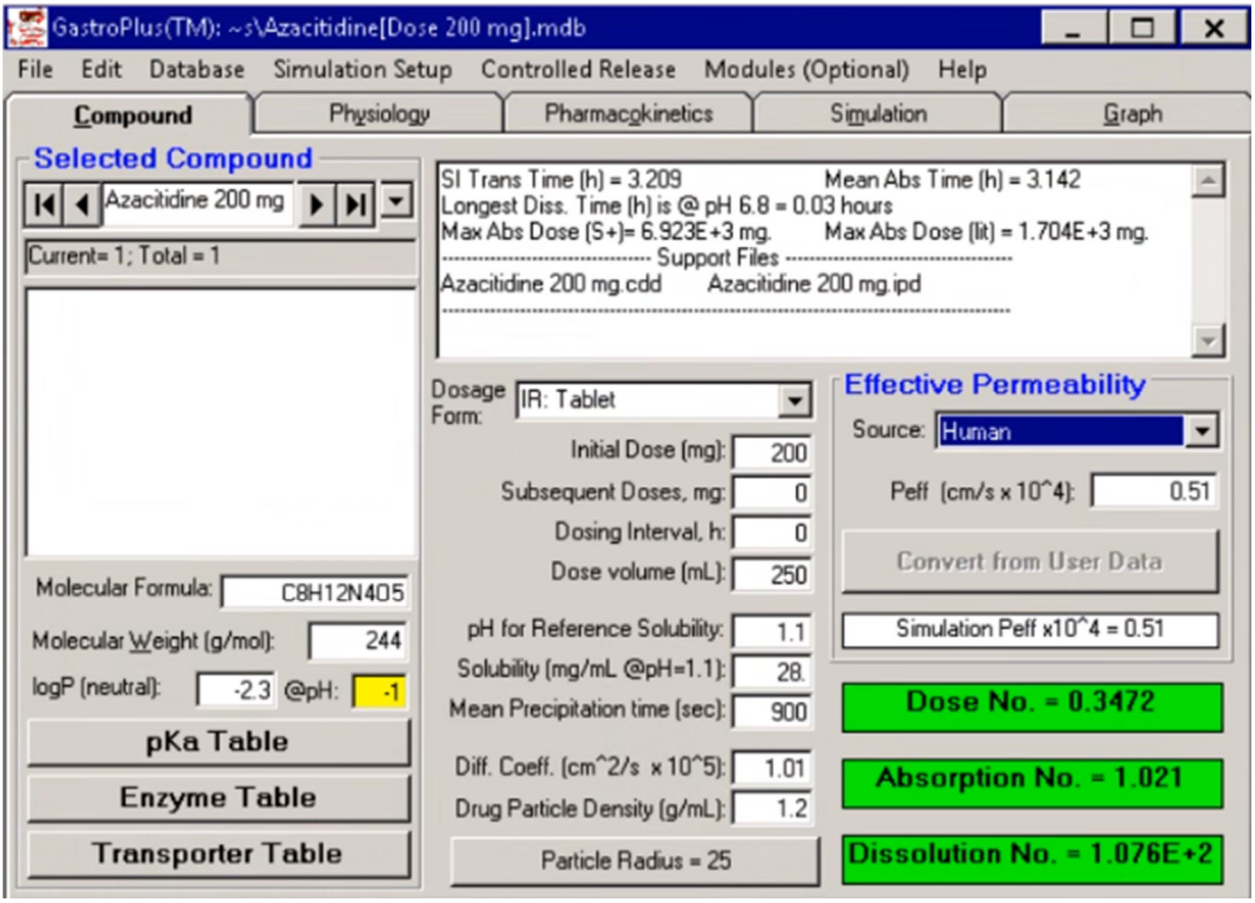




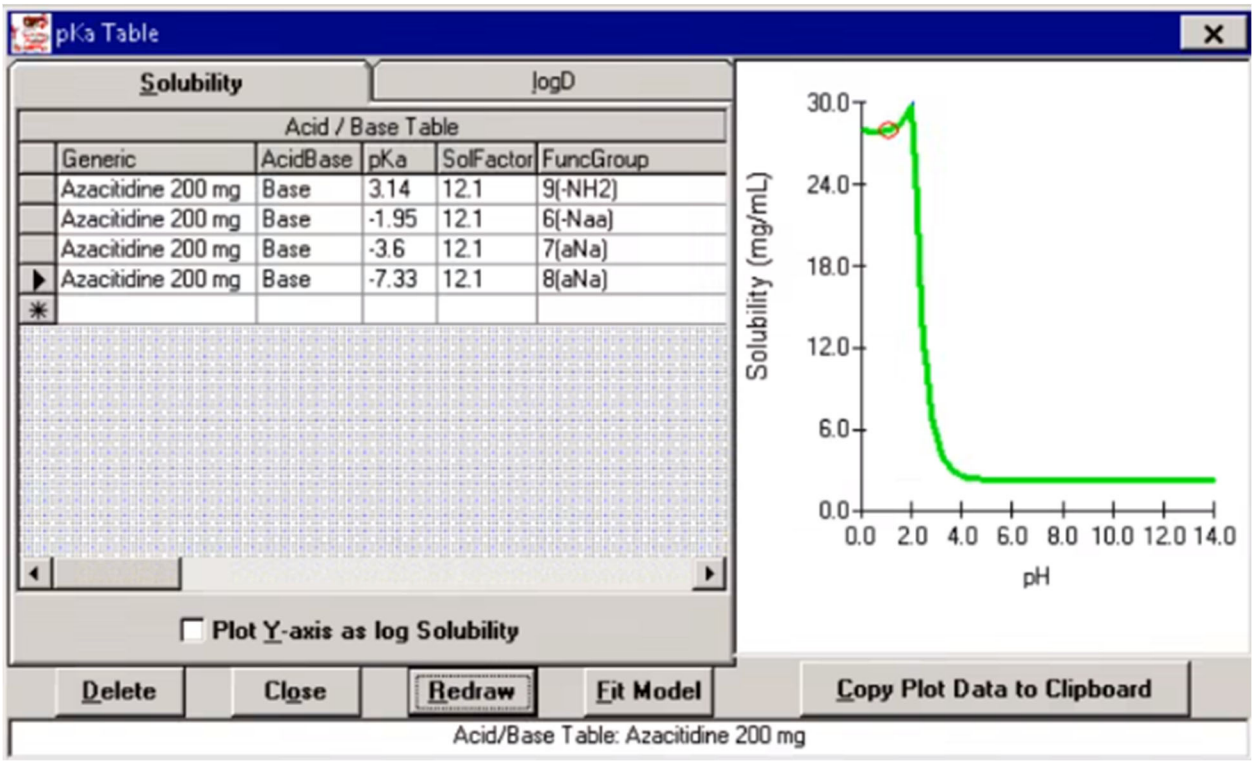


Appx II. Model Results for 200 mg Dose

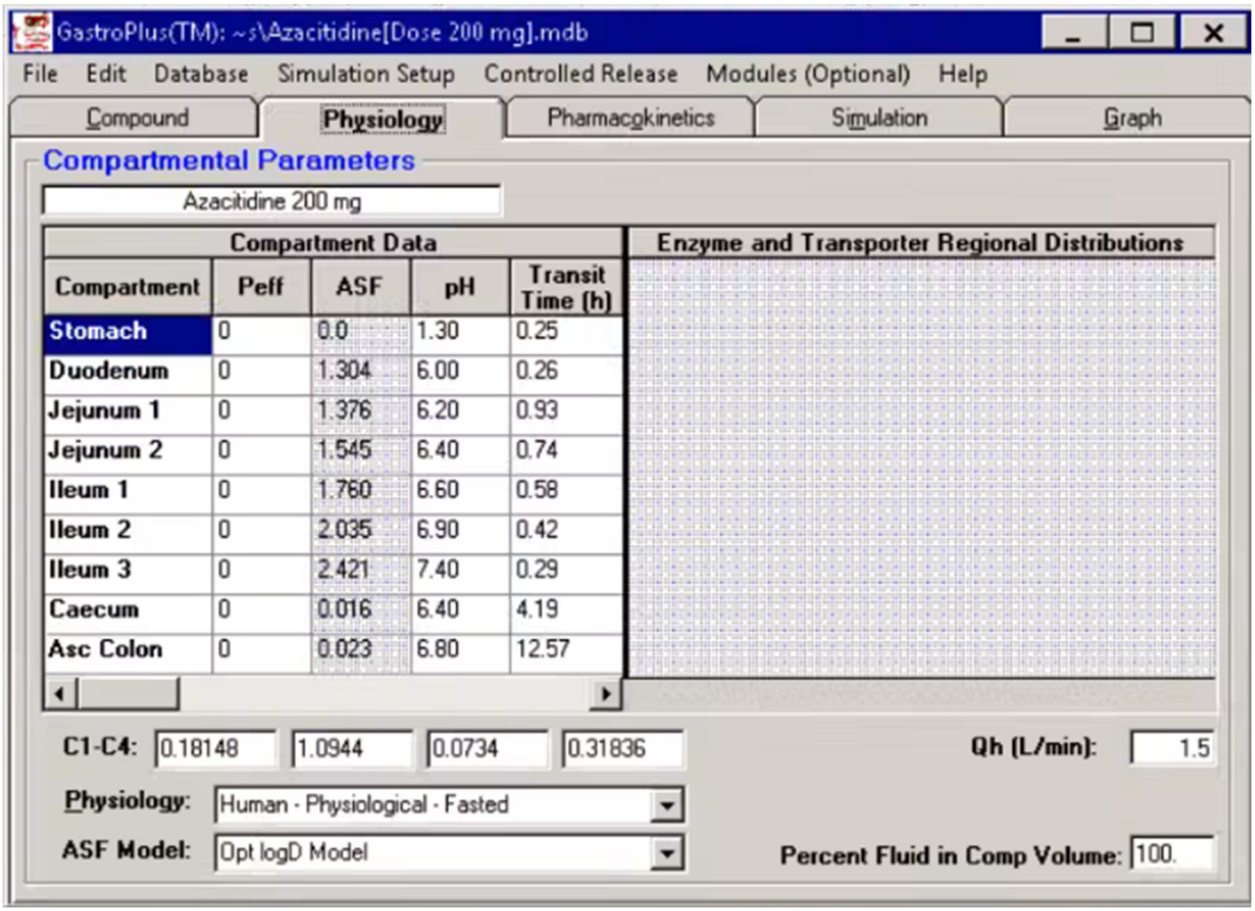
Appx II.A. Compound Tab



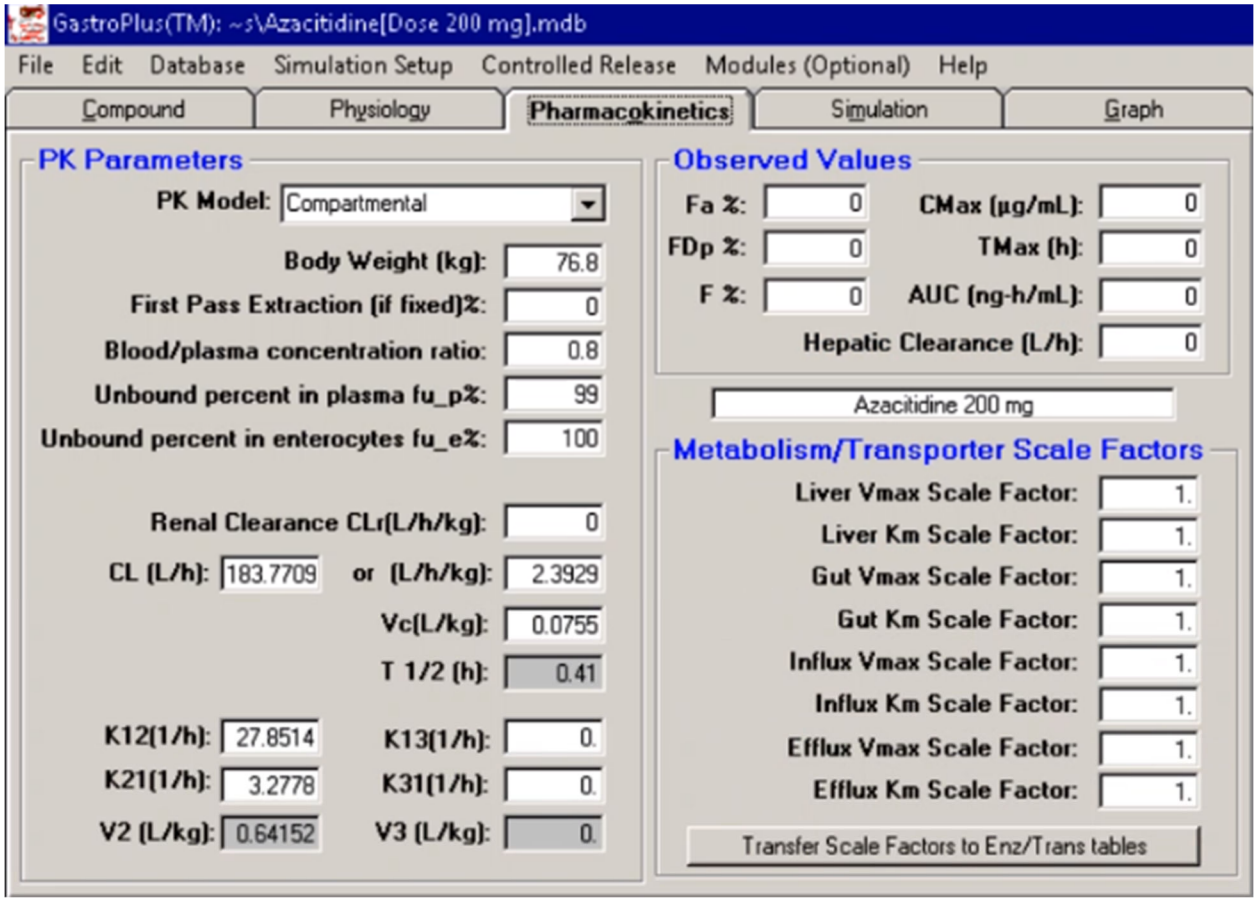
Appx II.A.1. pKa Table



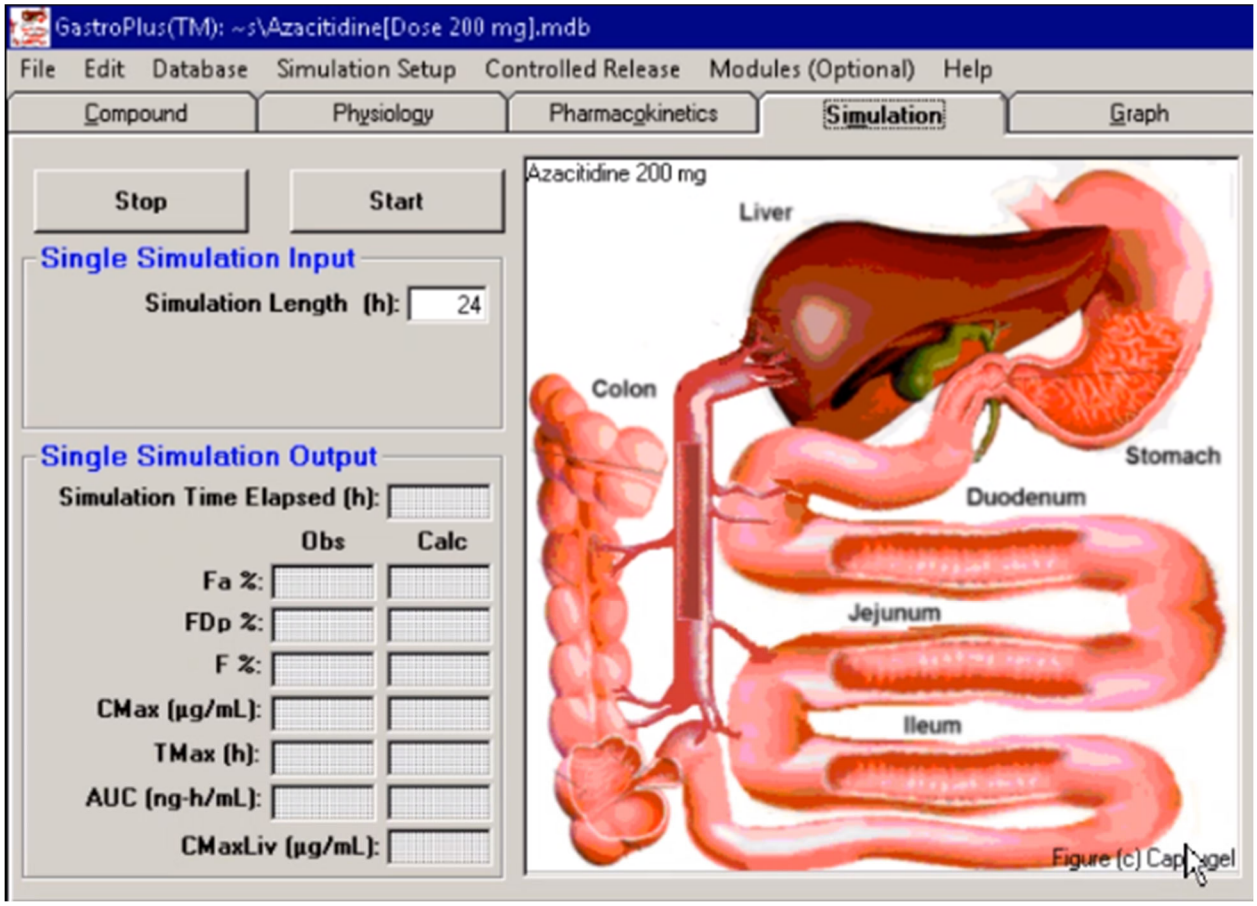
Appx II.B. Physiology Tab

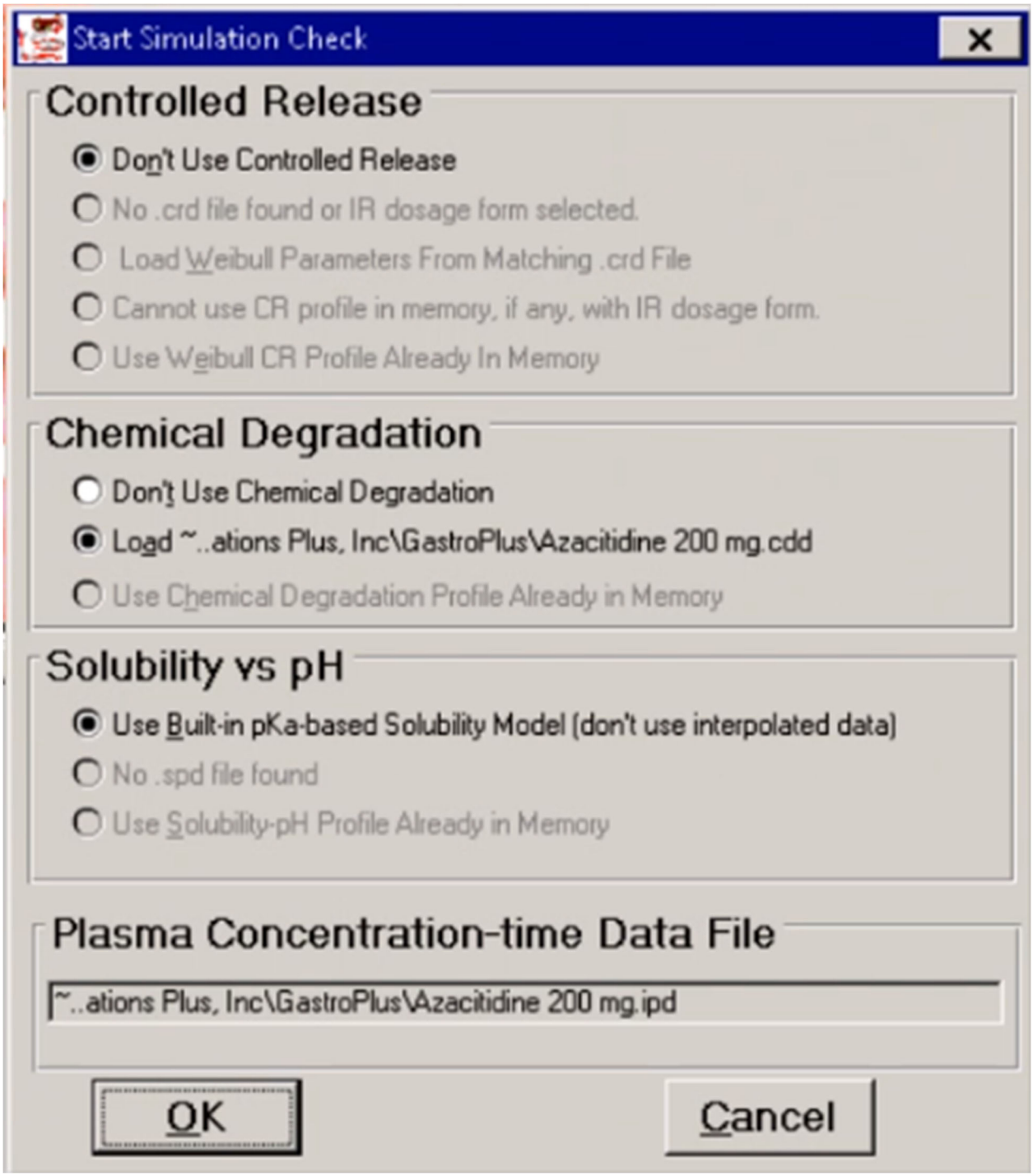


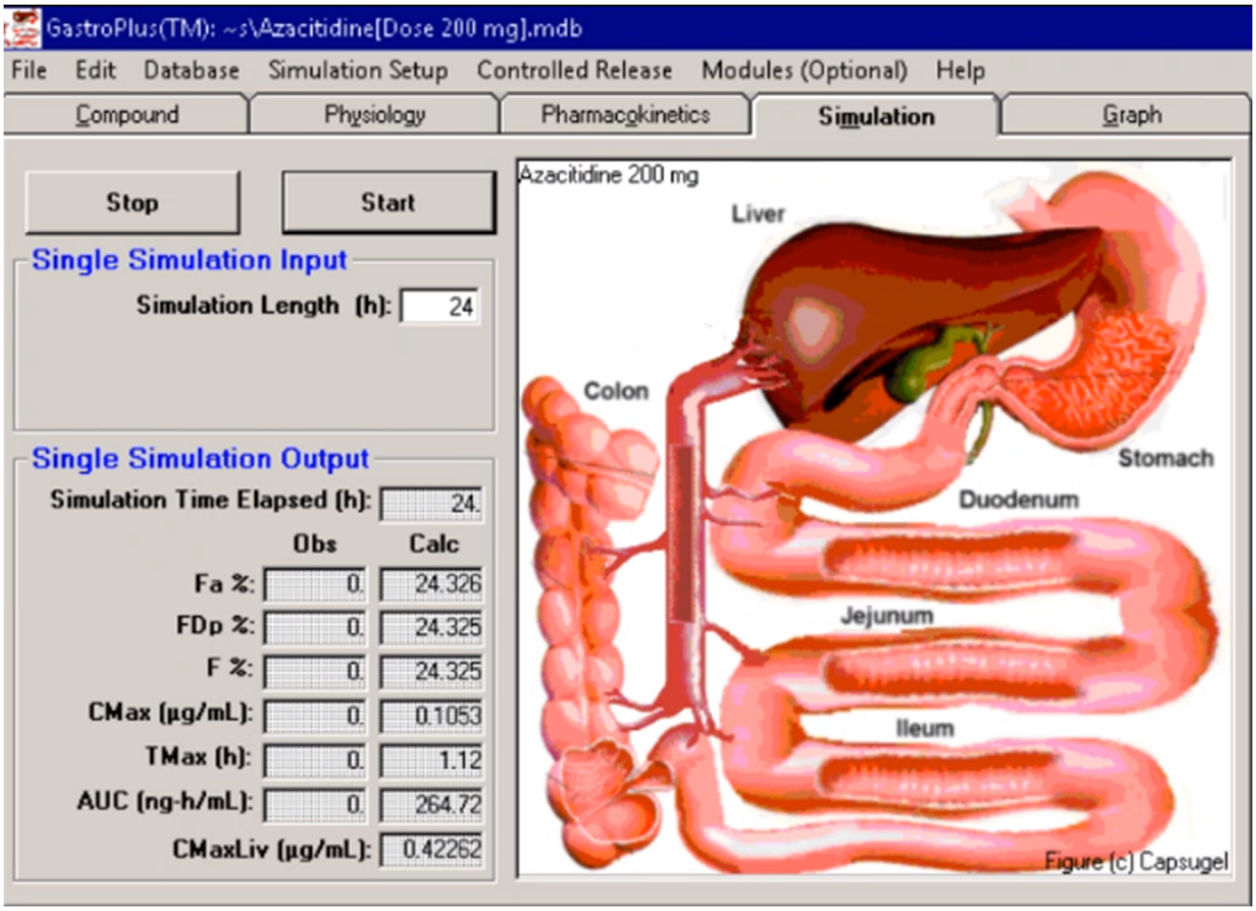
Appx II.C. Pharmacokinetics Tab



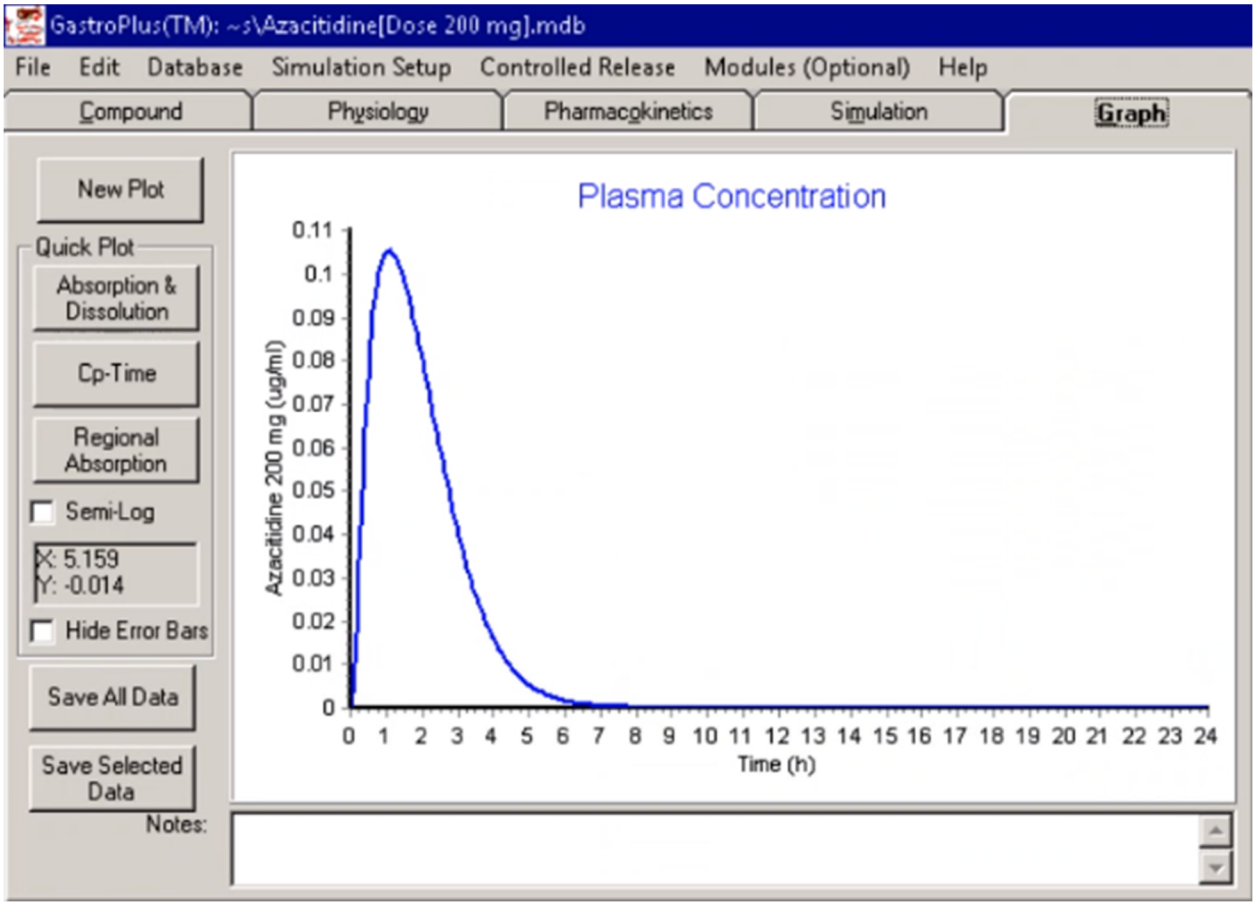
Appx II.D. Simulation Tab



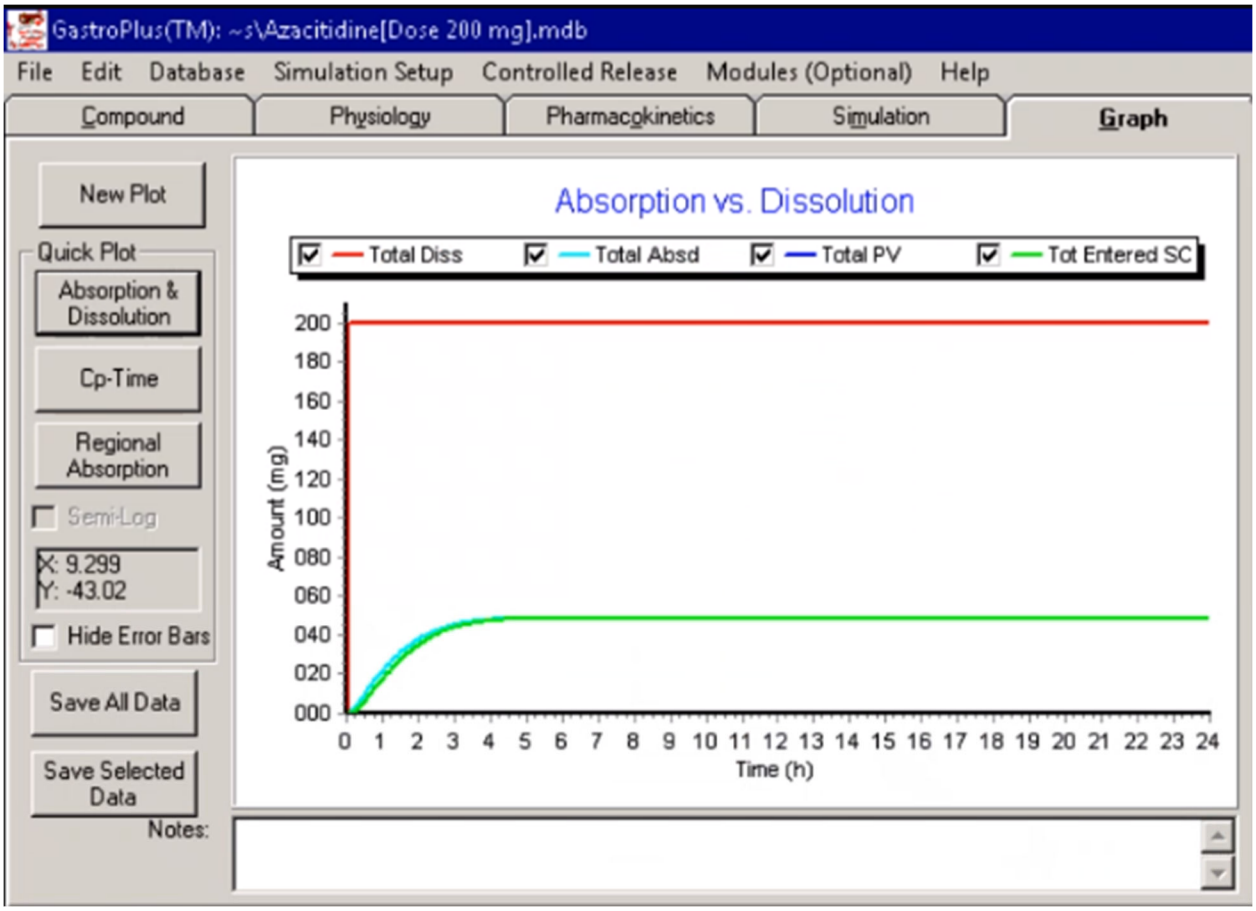




Appx II.E. Graph Results Tab[9]

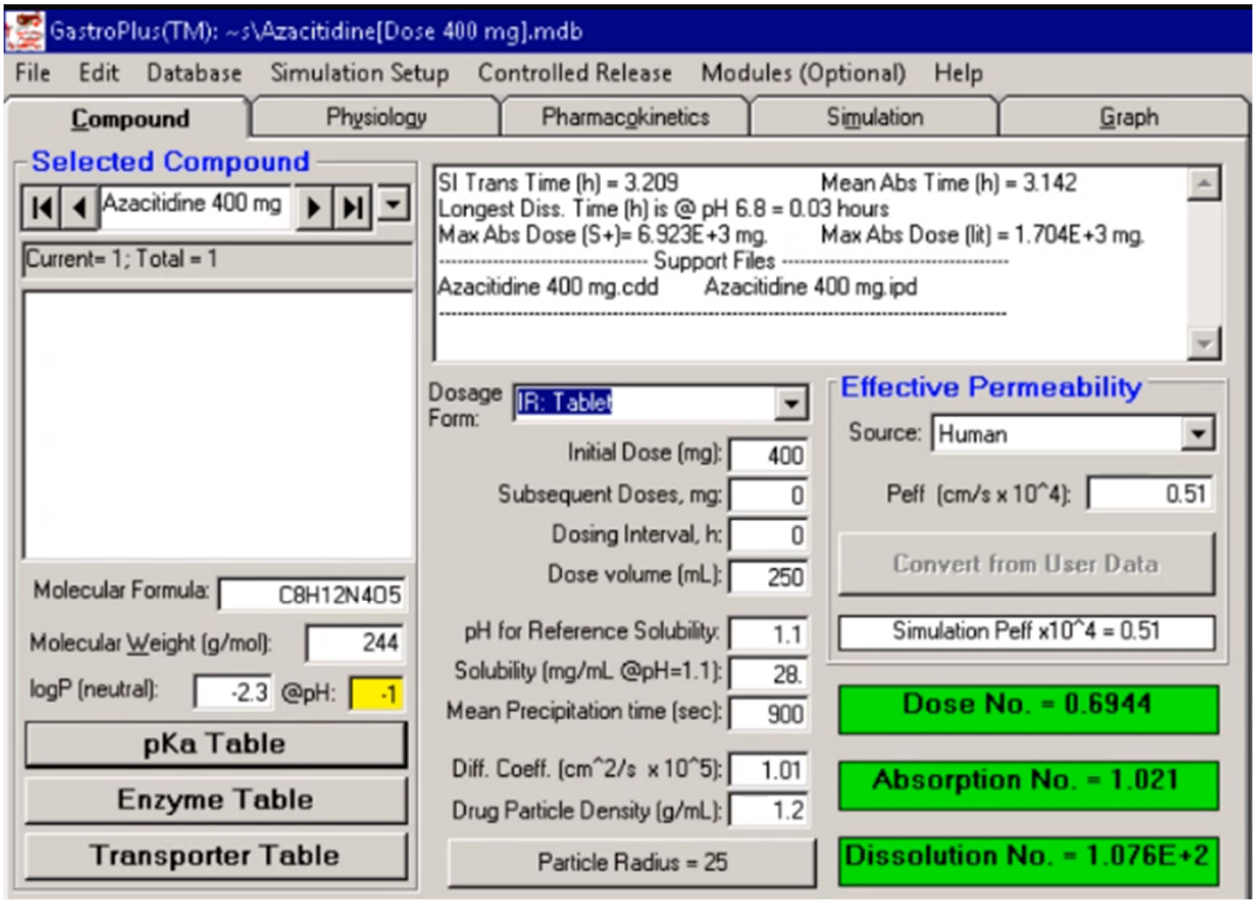


[9] The "Azacitidine 200 mg All Data.txt" file (EX-1056) was obtained by clicking the "Save All Data" button. The GastroPlus database file for this model was also saved.



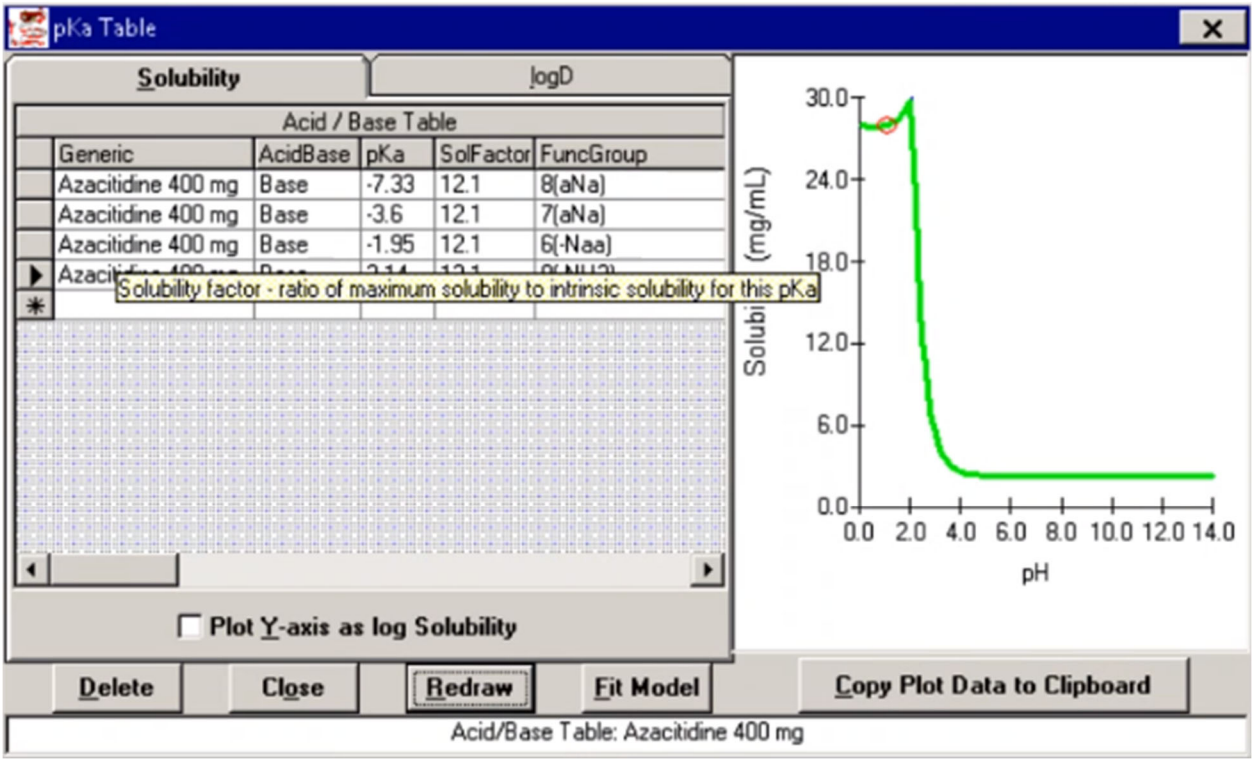
Appx III. Model Results for 400 mg Dose

Appx III.A. Compound Tab[10]

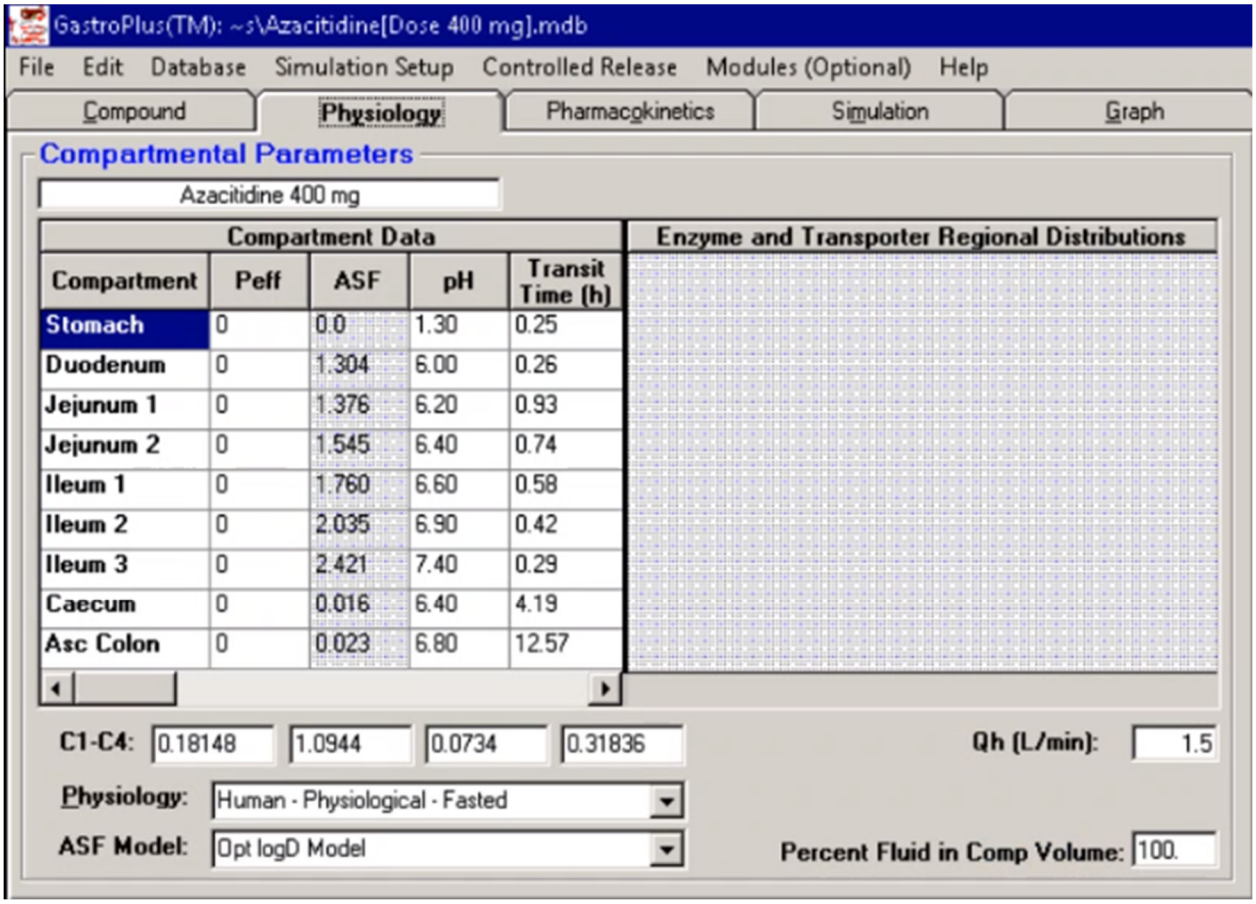


[10] As with the 200 mg dose model, the chemical degradation rate data file (EX-1057, Azacitidine 400mg.cdd) and the IV plasma concentration-time data file (EX-1058, Azacitidine 400mg.ipd) were loaded into GastroPlus to model the 400 mg dose.

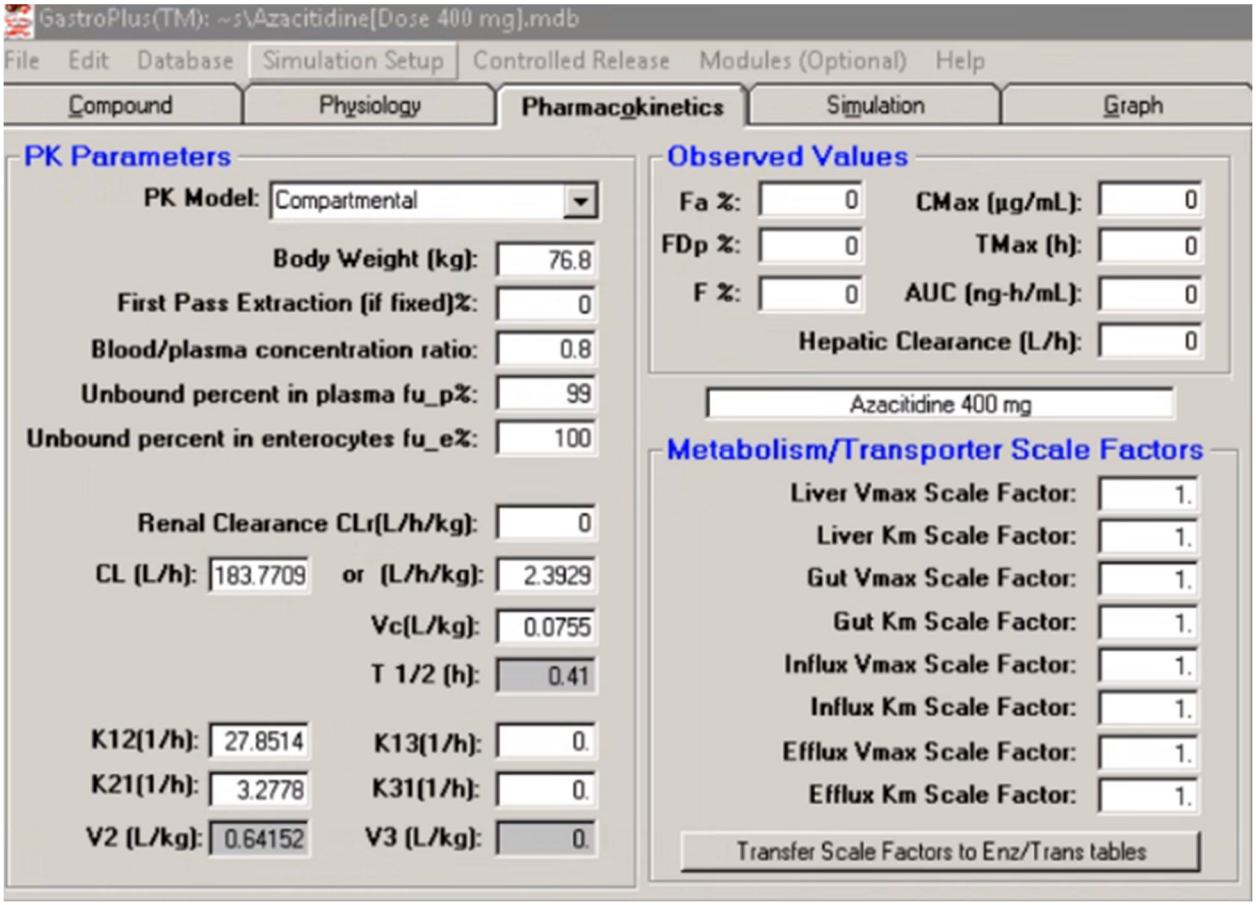
Appx III.A.1. pKa Table



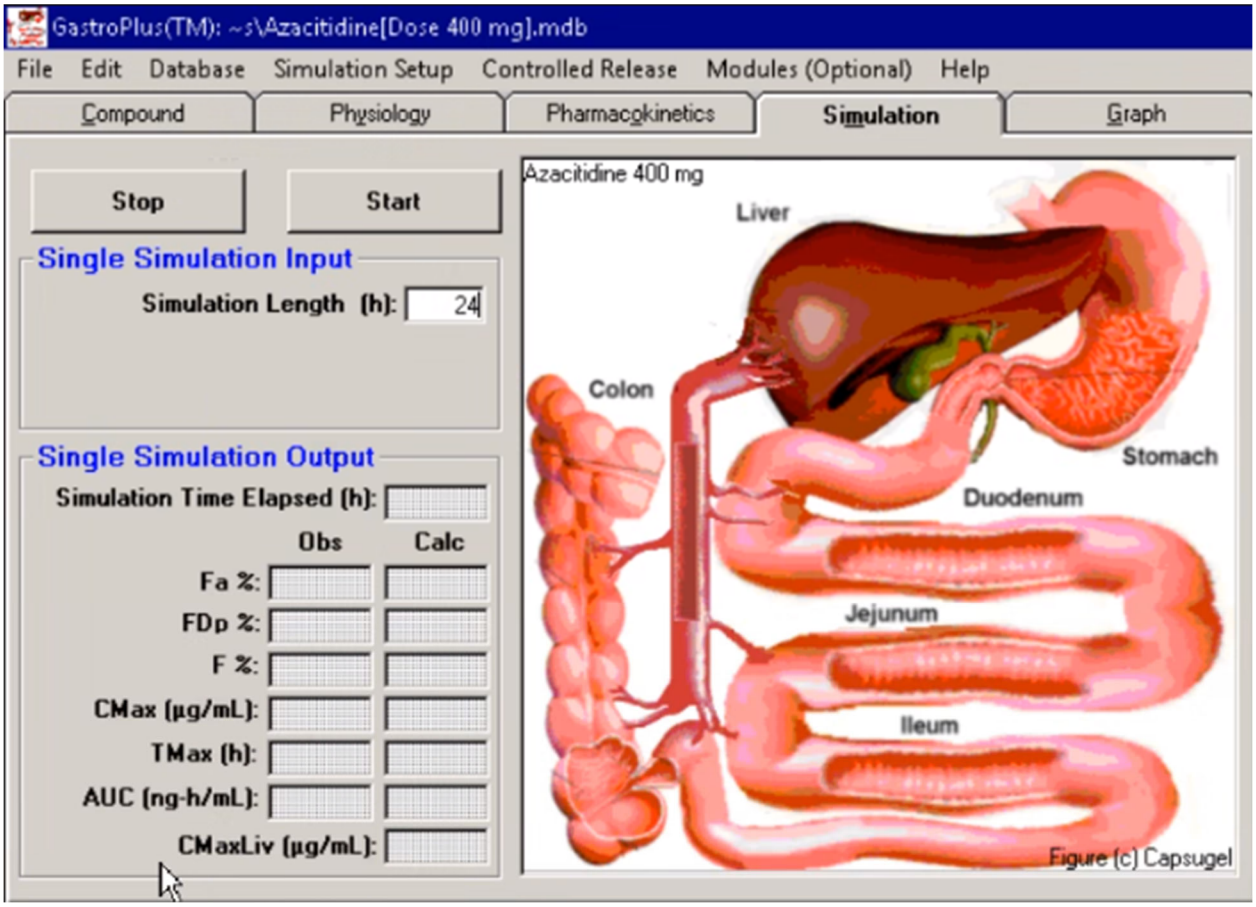
Appx III.B. Physiology Tab

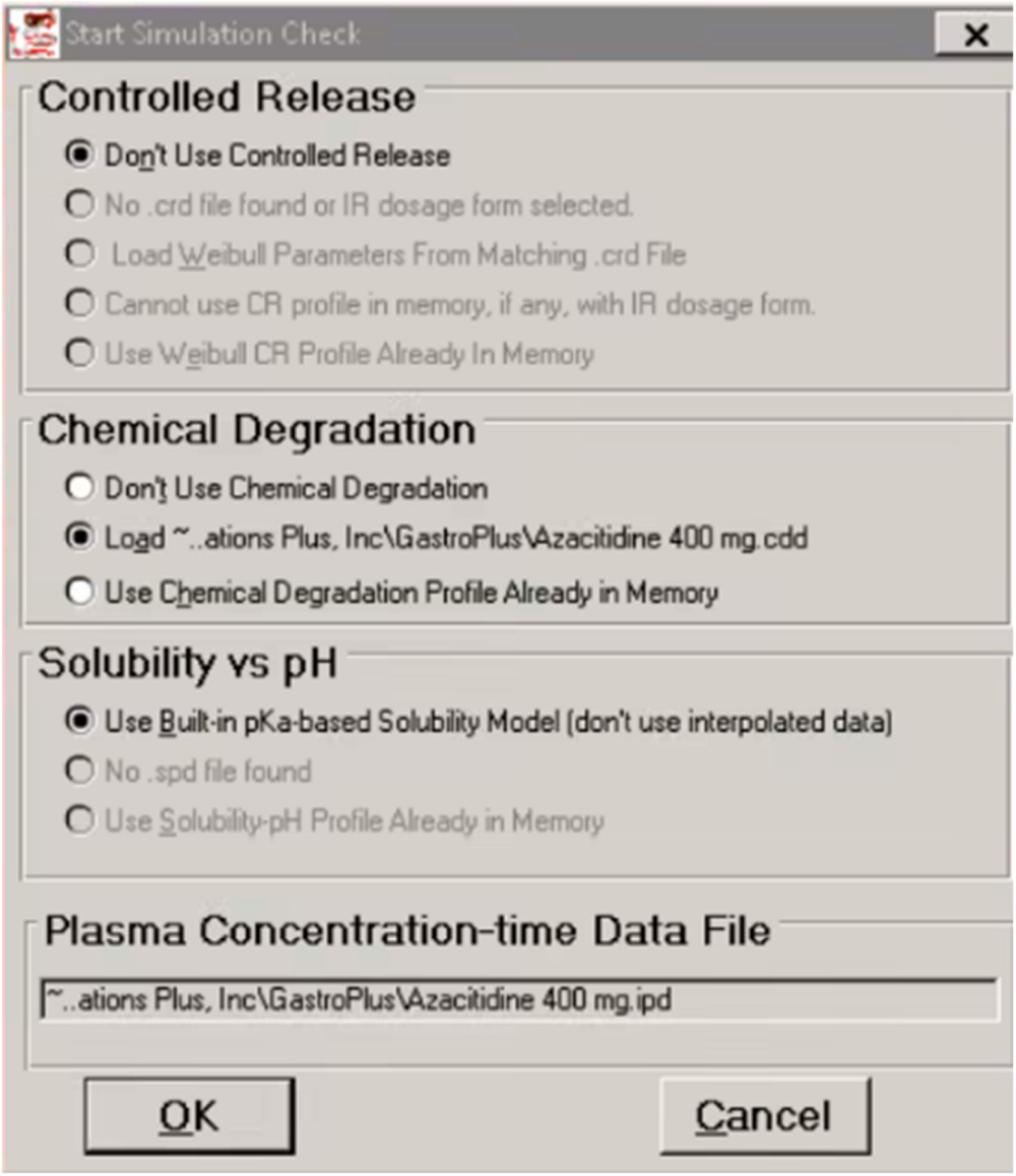


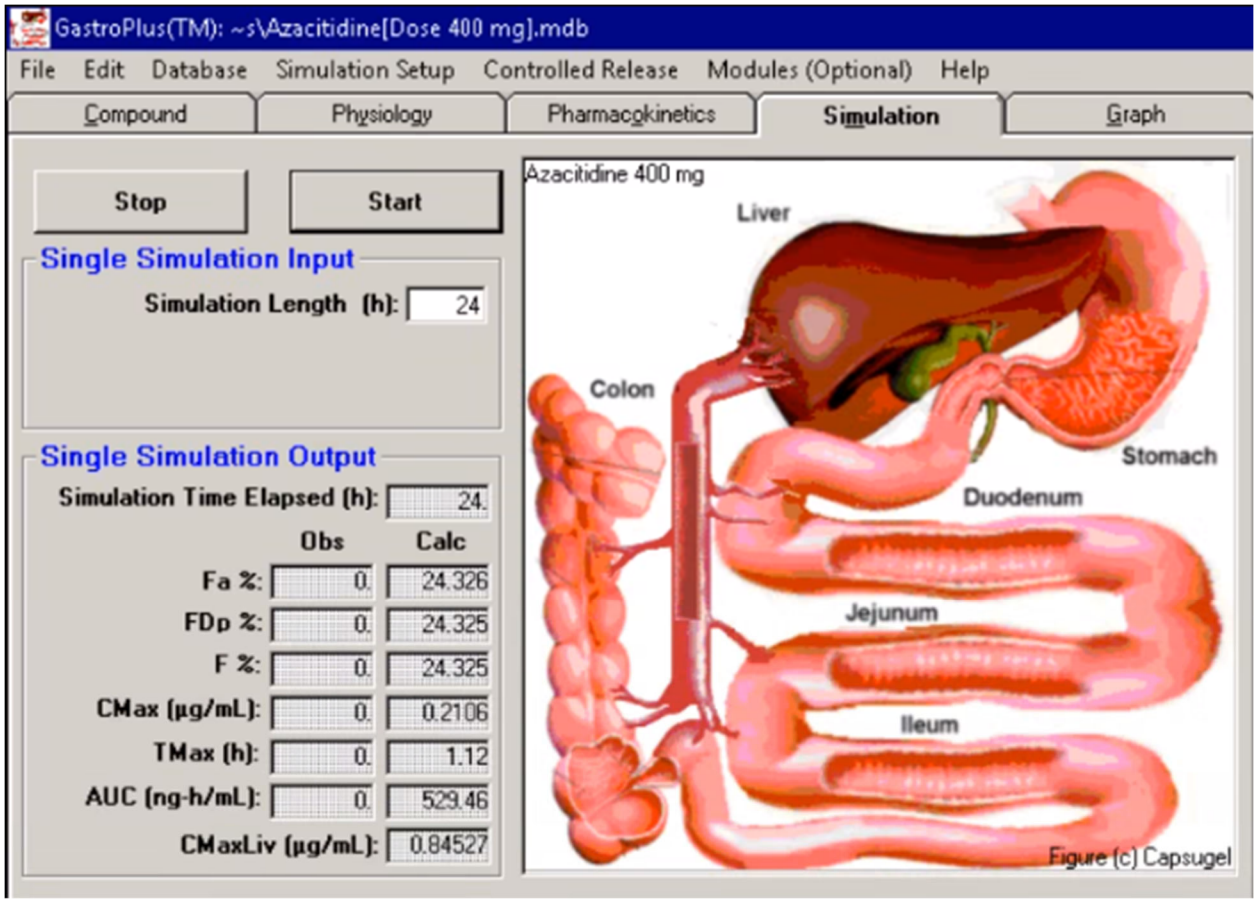
Appx III.C. Pharmacokinetics Tab



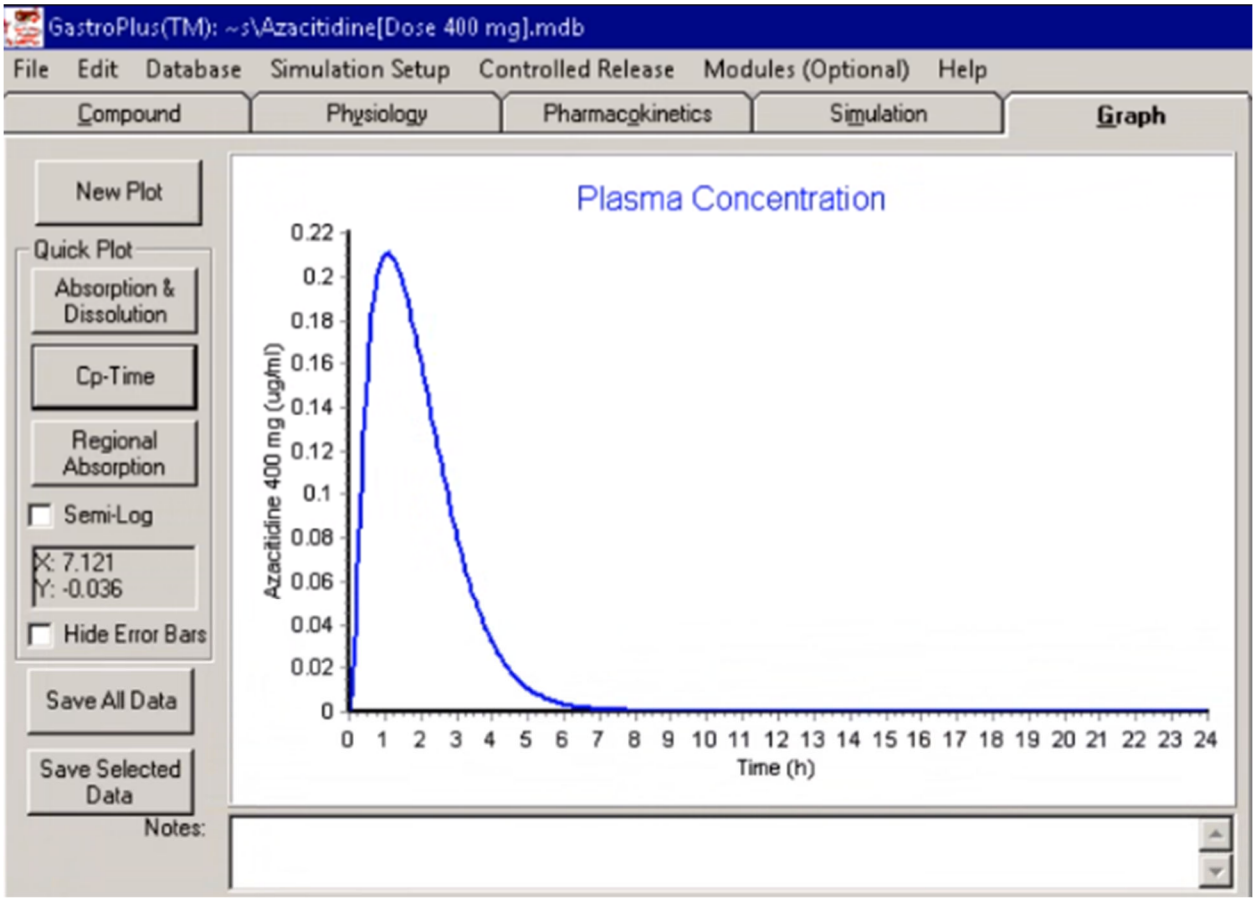
Appx III.D. Simulations Tab







Appx III.E. Graph Results Tab[11]



[11] The "Azacitidine 400 mg All Data.txt" file (EX-1059) was obtained by clicking the "Save All Data" button. The GastroPlus database file was also saved.

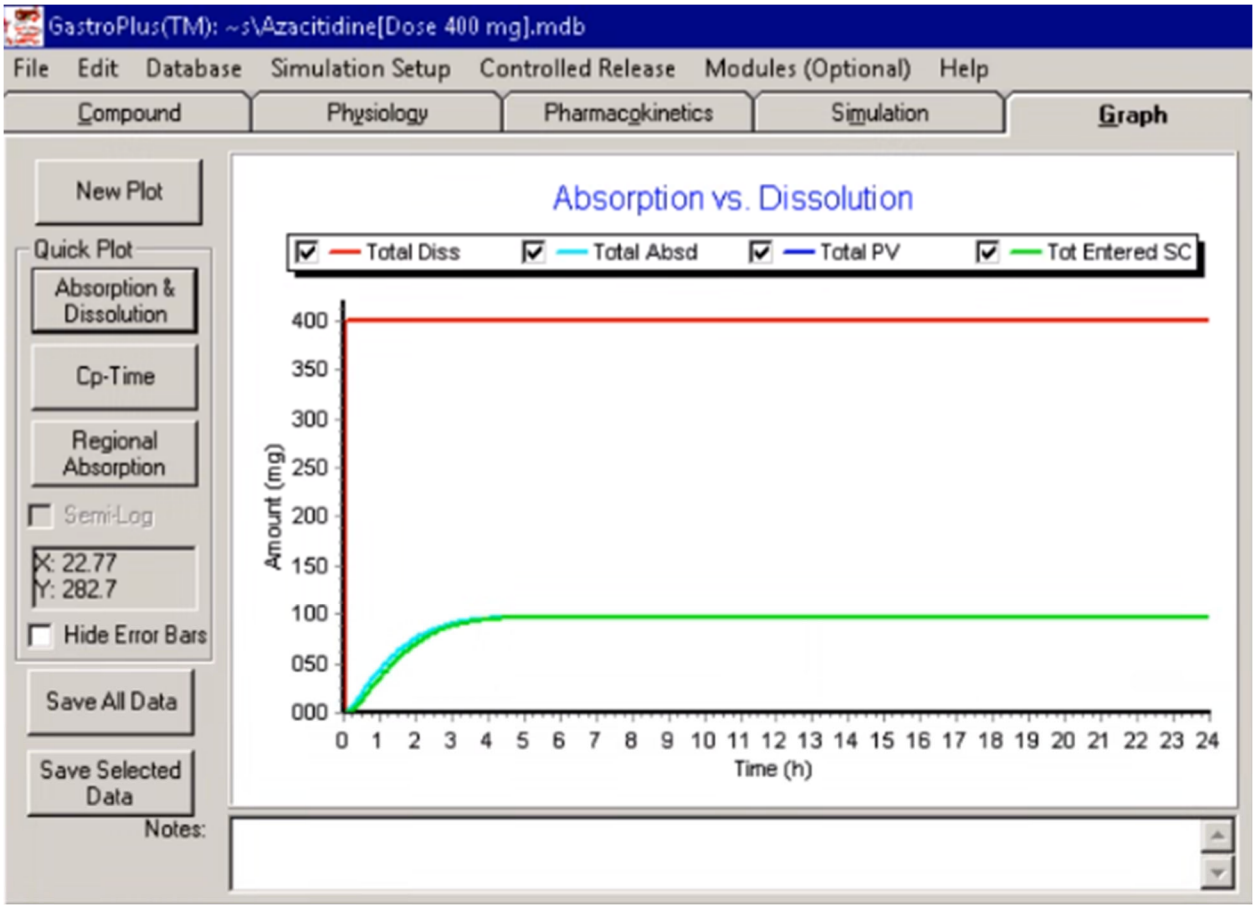


EXHIBIT A

Professor Hannah Batchelor

Professor in Pharmaceutics, Strathclyde Institute of Pharmacy and Biomedical Science, University of Strathclyde, 161 Cathedral Street, Glasgow G4 0RE

Hannah.batchelor@strath.ac.uk

SECTION 1: EDUCATIONAL SUMMARY

Sept 2010-Sept 2011	**Graduate Certificate in Statistics with Medical Applications, University of Sheffield (distance learning)** I undertook this course whilst working at AstraZeneca and Heart of England NHS Foundation Trust to strengthen my future research development and delivery. It was interesting to participate in a distance learning taught course to experience this teaching style as a student.
Sept 2001-June 2004	**Postgraduate Certificate in Learning and Teaching (SEDA accreditation as a Teacher in Higher Education).** This course was delivered by Aston University to ensure that teaching staff were appropriately trained. As part of my assessment I undertook an educational research project that resulted in two peer reviewed publications.
Sept 1997–Sept 2000	**PhD Drug Delivery, School of Pharmacy, University of London** My PhD research was investigating bioadhesive potential of alginate as a means of enhancing therapy for gastric reflux by forming a coat on the oesophagus. It was funded by Reckitt Benckiser and the EPSRC and resulted in four publications and influenced the advertising campaign for Gaviscon® showing the product coating the oesophagus.
Sept 1993-July 1996	**BSc Pharmacology and Chemistry, University of Sheffield** I did a combined honours undergraduate degree in pharmacology and chemistry which are the key scientific subject that underpin pharmacy. It provided an opportunity to experience a wide range of teaching styles. I undertook two final year projects, one of which resulted in a publication.

SECTION 2: CAREER TO DATE

July 2020-present	**Professor in Pharmaceutics, Strathclyde Institute of Pharmacy and Biomedical Science, University of Strathclyde** Specific research topics of interest include oral biopharmaceutics and development of appropriate *in vitro* and *in silico* testing strategies to predict *in vivo* performance. I have a particular interest in paediatric biopharmaceutics and I am actively involved in involvement of children and young people in research, particularly clinical research that impacts upon the treatment of this population.
Aug 2015 – July 2020	**Senior Lecturer in Pharmaceutics, Formulation and Drug Delivery** **Director of Research (2015-2018), School of Pharmacy, University of Birmingham** At the University of Birmingham I taught students on the following courses: Masters in Pharmacy (MPharm); Medicine and Surgery degree (MBChB); Masters in Chemical Engineering (MEng); Bachelor of Medical Sciences (BMedSci). Outside of the University of Birmingham I taught on the MSc in Paediatric Medicines Development and Evaluation awarded by the University of Rome Tor Vergata (Global Research in Paediatrics). I have also taught on a MOOC (Massive open online course) on "Drug Origins" which attracted 5500 participants. I was responsible for writing a module within the SCRIPT project on paediatric prescribing (www.safeprescriber.org). I supervised research scientists as both PhD students and overseas visiting researchers as well as numerous (undergraduate and Masters level) project students. My research was funded by the FDA; Certara; MRC; National Institute of Health Research (NIHR); Innovate UK; Janssen; AstraZeneca; Bristol Myers Squibb; Colorcon; GSK; Pfizer; Diurnal; Academy of Pharmaceutical Sciences; Cystic Fibrosis Trust; British Society of Paediatric Endocrinologists.
Apr 2012-Aug 2015	**Paediatric Formulations Research Fellow, University of Birmingham** The paediatric formulations fellow role was funded by the National Institute for Health Medicines for Children Research Network to support high quality clinical research into medicines for paediatric patients that are both safe and effective. This role involved both directing research into the design and development of age-appropriate medicines as well as supporting clinical research projects to ensure that formulation aspects are considered within their design.

Jan 2011 – Apr 2012	**Research Portfolio Manager, Heart of England NHS Foundation Trust** This was a strategic role to enhance the academic research conducted at HEFT. My activities included facilitating grant applications and assisting in the writing of high-quality grant submissions. During my time in the role more than £3.5m was secured for research funding.
Jan 2008 – Jan 2011	**Senior Scientist Biopharmaceutics, AstraZeneca R&D Charnwood.** This role required expert knowledge of pharmacokinetics and drug absorption and the application of this knowledge to drug development strategy. I was responsible for decisions that drove development and dictated the regulatory strategy. Although scientific knowledge is paramount, evaluation and communication of the impact of risks associated with biopharmaceutics was vital. Influencing skills and effective working in both cross functional and cross site teams were also key aspects of the role. I provided expertise to ten late stage development projects; authored regulatory submissions and answered questions from Regulatory Agencies. I directly impacted on projects by leading strategic in vitro work to minimise *in vivo* studies. Specifically, I have provided *in silico* modelling to optimally design a clinical study with reduced patient numbers and variants.
Sept 2000- Dec 2007	**Lecturer in Pharmaceutics, Aston University** I taught students on the following courses: Masters in Pharmacy (MPharm); Overseas diploma in Pharmacy; MSc in Drug Delivery; MSc in Pharmaceutics (all at Aston University) and MSc in Oncology (at Birmingham University). Whilst at Aston University I supervised over 18 scientists as both PhD students and overseas visiting researchers as well as numerous (>40 undergraduate and Masters level) project students. I generated income to support my research group from the following: BBSRC; EPSRC; MRC; ERASMUS; GlaxoSmithKline, Reckitt Benckiser, Bayer Healthcare, Wyeth, Technostics, Henderson Morley, Yarra Medica, CrossVet Pharma, BlueSky Botanics, PharmaKodex, and Verus Pharmaceuticals.
July 1996 – Sept 1997	**Formulation Scientist, Reckitt and Colman** *(now ReckittBenckiser)* As a formulation scientist my main role involved setting up and administering stability studies for medicines under review. I was also involved in the development of novel formulations including Gaviscon Advance and Fibrozest.

SECTION 3: RESEARCH

RESEARCH ACTIVITY

My research focuses on paediatric biopharmaceutics and development of age-appropriate medicines for children. I develop testing strategies to predict *in vivo* performance; undertake paediatric *in silico* modelling to optimise pharmacokinetic study design and work to understand the impact of drug-food interactions within paediatric populations.

To date I have received in excess of £2m in research funding and have supervised more than 20 PhD students to completion. My current live funding (>£800k) supports 5 PhD students and a research technician.

I have been invited to present my research as several relevant international conferences including: European Paediatric Formulation Initiative (EuPFI); American Association of Pharmaceutical Scientists (AAPS); Controlled Release Society and the Royal College of Paediatrics and Child Health annual meeting.

My research is highly interdisciplinary as I collaborate with Chemical Engineers, Dentists; Food Scientists; Mathematicians and Clinicians.

RESEARCH FUNDING (past 10 years)

Applications awarded	Dates	Value (£)
West Midlands Medicines for Children Research Network to support research activity conducted by Rebecca Venables to investigate paediatric preferences for tablets vs liquids and also preferences wrt tablet size and shape	January – June 2013	14,445
Medicines for Children Research Network to support research activity as a paediatric formulations research fellow	June 2013- March 2014	24,292
University of Birmingham and Birmingham Children's Hospital to support research activity for a pilot study to measure vancomycin concentrations in a paediatric population to validate an *in silico* model	July 2013- July 2014	4,800
From the TSB for a project "Accelerating paediatric formulation development through smart design and predictive science", with	Oct 2013-Oct 2016	999,842 (90,703 to UoB)

collaborators from AstraZeneca, Pfizer, Bristol Myers Squibb and GSK. Total value = **£999,842** to University of Birmingham is £90,703		
Medicines for Children Research Network to support research activity as a paediatric formulations research fellow (0.6WTE)	April 2014-March 2015	29,282
Birmingham-Nottingham Strategic Collaboration Fund	May 2014	850
Medicines for Children Research Network to support research activity as a paediatric formulations research fellow	April 2015-March 2016	32,383
British Inherited Diseases Metabolic Group. Mixing of sodium benzoate, sodium phenylbutyrate +/- arginine injection	December 2015 – April 2016	2,275
EPSRC Follow on fund: Active encapsulation and release technologies	March 2015 – December 2015	24,735
West Midlands Clinical Research Network: Children Strategic Funding, "Measuring adherence to medication in paediatric populations: making sense of the data"	December 2015- March 2016	20,455
Diurnal: Hydrocortisone and Congenital Hyperplasia: human factors in manipulation and their impact on dosing accuracy	July 2016-July 2017	20,800
CF START. PI = Kevin Southern. I am a CI. HTA Project: 14/22/23 - The cystic fibrosis (CF) anti-staphylococcal antibiotic prophylaxis trial (CF START); a randomised registry trial to assess the safety and efficacy of flucloxacillin as a long-term prophylaxis agent for infants with CF	August 2016	1,460,968 (27,850 to UoB)
APS Summer Student bursary: Coatings for taste-masking functionality	July 2016-August 2016	2290
Industrially funded PhD with Janssen looking at better understanding of the paediatric gastro-intestinal tract	April 2017-March 2020	121,000
British Society of Endocrinology Summer Studentship: Hydrocortisone tablets: Human factors in manipulation and their impact on dosing accuracy in paediatric populations	June 2017-September 2017	2725
Industrial contribution (from AstraZeneca) to a PhD project in the Doctoral Centre for Formulation Engineering, School of Chemical Engineering, University of Birmingham	September 2016-September 2020	57,000
Industrial contribution (from AstraZeneca) to a PhD project in the Doctoral Centre for Formulation Engineering, School of Chemical Engineering, University of Birmingham: Connor O'Farrell project on dynamic colon model	September 2018-September 2022	57,000
Industrial contribution (from GlaxoSmithKline) for a PhD project to understand the role of excipients in paediatric biopharmaceutics (external student located at GSK)	September 2018-September 2022	25,000
Colorcon funding to support a human study to assess the mouthfeel of coating for paediatric medicines	January 2018-December 2018	45,000
FDA funding to understand the risks associated with using generic medicines in paediatric populations	February 2019-July 2021	185,000
PhD funding from Certara SimCYP to better understand oral absorption of medicines in paediatric populations	September 2019-September 2022	90,000
Pfizer funding to support a human study to assess the acceptability of an oral syringe to dose multiparticulate paediatric medicines	May 2019-December 2019	43,000

MRC CiC Confidence in concept: Developing a translational tool to advance colonic drug targeting	January 2020-December 2020	46,735
EDCTP: Treatment for all: developing a paediatric formulation of moxidectin for neglected infectious diseases	January 2021-January 2024	£3.25m (£135k to Strathclyde)
UCB funding to support a PhD student to explore the impact of the microbiome on bile salt in the GI tract and the subsequent impact on drug absorption	September 2021-September 2024	90,000
GSK funding to support a PhD student to explore the impact of co-administration of food on the absorption of orally administered food in paediatric populations	September 2022-September 2025	90,000
EPSRC strategic equipment grant to support the purchase of an artificial GI tract to predict drug product performance (GIBio)	January 2023-December	675,340

PUBLICATIONS

Science Papers - published

1. Sakellari, G.I., Zafeiri, I., **Batchelor, H**., Spyropoulos, F., Solid lipid nanoparticles and nanostructured lipid carriers of dual functionality at emulsion interfaces. Part II: active carrying/delivery functionality (2023) Colloids and Surfaces A: Physicochemical and Engineering Aspects, 659, art. no. 130787, DOI: 10.1016/j.colsurfa.2022.130787
2. Sakellari, G.I., Zafeiri, I., **Batchelor, H**., Spyropoulos, F., Solid lipid nanoparticles and nanostructured lipid carriers of dual functionality at emulsion interfaces. Part I: Pickering stabilisation functionality (2022) Colloids and Surfaces A: Physicochemical and Engineering Aspects, 654, art. no. 130135. DOI: 10.1016/j.colsurfa.2022.130135
3. Al-Obaidi, I., Krome, A.K., Wagner, K.G., Pfarr, K., Kuesel, A.C., **Batchelor, H.K**., Drugs for neglected tropical diseases: availability of age-appropriate oral formulations for young children (2022) Parasites and Vectors, 15 (1), art. no. 462. DOI: 10.1186/s13071-022-05546-7
4. Schütt, M., Stamatopoulos, K., **Batchelor, H.K.,** Simmons, M.J.H., Alexiadis, A., Development of a digital twin of a tablet that mimics a real solid dosage form: Differences in the dissolution profile in conventional mini-USP II and a biorelevant colon model (2022) European Journal of Pharmaceutical Sciences, 179, art. no. 106310, DOI: 10.1016/j.ejps.2022.106310
5. O'Farrell, C., Simmons, M.J.H., **Batchelor, H.K**., Stamatopoulos, K. The Effect of Biorelevant Hydrodynamic Conditions on Drug Dissolution from Extended-Release Tablets in the Dynamic Colon Model (2022) Pharmaceutics, 14 (10), art. no. 2193, DOI: 10.3390/pharmaceutics14102193
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7. Matthias Van der Veken, Joachim Brouwers, Valérie Budts, Louis Lauwerys, Shriram M. Pathak, **Hannah Batchelor**, Patrick Augustijns, Practical and operational considerations related to paediatric oral drug formulation: An industry survey, International Journal of Pharmaceutics, Volume 618, 2022,
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Patent:
Topical Pharmaceutical formulations H K Batchelor and G Oladiran filed 23rd June 2006

Education Papers:
H K Batchelor, (2007) A constructivist method for teaching concentration calculations to pharmacy students. Pharmacy Education 7(1):69-76
H K Batchelor, (2004), The importance of a mathematics diagnostic test for incoming pharmacy undergraduates. Pharmacy Education. 4(2):69-74
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Book Chapters:
H K Batchelor and B R Conway. Drug delivery for infections of the GI tract. Within Advanced Formulation Design to Optimize Therapeutic Outcomes. Editors, J T McConville, D R Taft, R O Williams
H K Batchelor. Pediatric Development: Anatomy. Age, Weight, Body Surface and Stature, Organ Development; Within Pediatric Formulations – A Roadmap. Editors, Daniel Bar-Shalom & Klaus Rose. AAPS Advances in the Pharmaceutical Sciences Series, Vol. 11. 2014
H K Batchelor. Pediatric Development – Gastrointestinal; Within Pediatric Formulations – A Roadmap. Editors, Daniel Bar-Shalom & Klaus Rose. AAPS Advances in the Pharmaceutical Sciences Series, Vol. 11. 2014
H K Batchelor. Nasal, Ocular,and Otic Drug Delivery; Within Pediatric Formulations – A Roadmap. Editors, Daniel Bar-Shalom & Klaus Rose. AAPS Advances in the Pharmaceutical Sciences Series, Vol. 11. 2014

H K Batchelor. Rectal Drug Delivery; Within Pediatric Formulations – A Roadmap. Editors, Daniel Bar-Shalom & Klaus Rose. AAPS Advances in the Pharmaceutical Sciences Series, Vol. 11. 2014
D. Bar-Shalom, **H K Batchelor**, L. F. McElhiney, K. Rose. Concluding Remarks - The Future of Pediatric Formulations. The Dangerous Business Of Predicting The Future; Within Pediatric Formulations – A Roadmap. Editors, Daniel Bar-Shalom & Klaus Rose. AAPS Advances in the Pharmaceutical Sciences Series, Vol. 11. 2014

Edited Books
Biopharmaceutics: From Fundamentals to Industrial Practice
Hannah Batchelor (Editor).
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RESEARCH OUTPUTS (not publications)

Below is a list of **invited presentations** that I think are of most significance based on my research. Those below were selected as of greater importance based on the audience reach, evaluated both as the nature of the audience as well as their geographical location. The scope and reach of my research is highlighted by this list of external events.

Title of talk	Meeting	Date	Prestige
Generation and integration of paediatric gastrointestinal physiological data into PBPK software	4th International Symposium on BA/BE of Oral Drug Products	November 2022	Invited/Global
Oral PBPK to support bioequivalence evaluation for pediatric drugs	CRCG workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development	October 2022	Invited/Global
MiniMox -Treatment for all: Developing a paediatric formulation moxidectin for neglected infectious diseases	EuPFI 2022	September 2022	Invited/Global
A totally new treatment regime	Expo 2020 Dubai	January 2022	Invited/Global
Predicting product performance in patients	CMAC - the next 10 years	November 2021	Invited/National
Defining and Designing Patient-Centric Dosage Forms	CPhI Online	October 2021	Invited/Global
Innovative Techniques Toward Extrapolation and Efficient Drug Development	New Horizons in Pediatric Drug Development Symposium	October 2021	Invited/Global
Risk Assessment For Age-Appropriate medicines	Formulation & Drug Delivery Europe Congress	April 2021	Invited/Global
Unpacking the paediatric biopharmaceutics toolkit	Catalent Webinar	April 2021	Invited/European
Pediatric GI Biopharmaceutics - Important Learnings and Emerging Opportunities	Janssen Company meeting	September 2021	Invited/National
PharmSci Forum: Next Generation Multi-Particulate Delivery System	Pfizer Company meeting	September 2021	Invited/National
Quantification of gastrointestinal (GI) Luminal Water Volumes– A Step Towards Rational Pediatric Drug Product Development!	AAPS	November 2021	Invited/Global

Assessing the quality of paediatric oral drug products	4th International Symposium on BA/BE of Oral Drug Products. Commemorative Event to Honor the Retirement of Professor Gordon L. Amidon University of Michigan	July 2020	Invited/Global
Molecules to Man: Interactive game	FIP PSWC, Montreal, Canada	May 2020	Invited/ Global
Developing a dynamic colon model: biorelevant motion	EDAN, Ghent University, Belgium	March 2020	Invited/European
Age-appropriate sodium valproate formulations are associated with better clinical outcomes	Desitin Company meeting	October 2019	Invited/European
Virtual development of a medicines: a game for learning	EFPIA meeting, Brussels, Belgium	October 2019	Invited/European
Involving young people in research: a 10 year celebration	NIHR CRN West midlands meeting	Septemb er 2019	Invited/National
Acceptability of formulations in Paediatric Populations	CRS Annual Conference, Valencia, Spain	July 2019	Invited/Global
Collaborative working in paediatric medicines development	APS Industrial Insights	April 2019	Invited/National
Methodological approaches to measurement of medicines acceptability in special populations	University of Sydney, Australia	April 2019	Invited/Global
Using MRI data to measure intestinal volumes in children	Monash University, Melbourne	April 2019	Invited/Global
Improving Patient Experience & Adherence 'Swallowability'	Colorcon Webinar	March 2019	Invited/Global
Understanding the gastrointestinal environment of children helps to predict drug performance	China Pharmaceutical University, Nanjing	March 2019	Invited/Global
Measuring acceptability of medicines to children	Nanjing Children's Hospital Paediatric Pharmacy Department	March 2019	Invited/Global
Development of age appropriate medicines for children	Jinan National University, Guangzhou, China	March 2019	Invited/Global
Paediatric GI physiology and its importance for drug absorption	Guangzhou Women and Childrens Medical Centre	March 2019	Invited/Global
Administering oral drug products in specific populations	UNGAP Meeting, Sofia, Bulgaria	February 2019	Invited Keynote Lecture/Global
Patient-centered dosing: cradle to grave	Reckitt Benckiser	February 2019	Invited/National
A debate: this house believes that children with adrenal insufficiency (including CAH) need their own medicines	Diurnal Debate	Novemb er 2018	Invited/National
C+D gender equality in community pharmacy podcast	C&D Women in Pharmacy podcast	April 2018	Invited/National
Paediatric Formulations	Ninth Global Drug Delivery & Formulation Summit, Berlin, Germany	March 2018	Invited/Global

Update on paediatric biopharmaceutics	Juniper Pharmaceuticals Conference: A hard pill to swallow – challenges and advances in developing medicines for children	Dec 2017	Invited/Global
Is bioquivalence established in adults relevant for pediatrics?	AAPS, San Diego, USA	Nov 2017	Invited/Global
Patient centric products for paediatric populations	Colorcon Innovation Seminar - London	October 2017	Invited/National
PANDA Study: Manipulations of medicines for administration of paediatric dosing	Clinical Research Network: West Midlands	Sept 2017	Invited/National
Measuring acceptability of paediatric medicines	GSK internal seminar	June 2017	Invited/Global
A Dynamic Colon Model (DCM) of human proximal colon: Understanding fluid motion and mixing process in proximal human colon	International Symposium on Mixing in Industrial Processes	June 2017	Invited/Global
Gender diversity in academic pharmacy	Women in Healthcare leadership event, Royal Society of Pharmacists	May 2017	Invited/National
Using the Internet: What information is available for children and young people about their medicines?	RCPCH Royal College of Paediatrics and Child Health	May 2017	Selected from abstract/ National meeting of UK paediatricians
Using Simcyp to predict the likely change in phenytoin dosing to children: a comparison to audit data	7th Annual Simcyp Virtual Seminar on Applications of Population-based IVIVE and PBPK	Nov 2016	Invited/Global
Using tribology to understand the mouthfeel of medicines	Royal Society of Medicine. The RSM Wimpole Street London.	Sept 2016	Invited/ National meeting of medics
Food Effects in Pediatric Medicines Development for Products Co-administered with Food	Challenges and Strategies to Facilitate Formulation Development of Pediatric Drug Products Workshop, Washington, USA	June 2016	Invited/ Global
The Voice of the child in medicines research: Listen to or just heard?	44th Interpharm Conference	May 2016	Invited meeting of industry and regulators from the UK
Molecules to Man: Interactive game	FIP, Dusseldorf	October 2015	Invited/ Global
Current evidence for a paediatric biopharmaceutics classification system	Swedish Regulatory Network (Medicinal Products Agency)	Jan 2015	Invited/ overseas meeting of Swedish regulators

SECTION 4: RESEARCH SUPERVISION

Current supervision

Name	Post (pre-/post-doctoral clinician scientist/basic scientist)	From To (Year)	Source of Funding
Aljawhara Al-Subaie	Clinical PhD	2023-2026	NHS
Rana Abu-Rajab Tamimi	Basic scientist PhD	2022-2025	Jordan Government funding
Erin Campbell	Basic scientist PhD	2022-2025	GSK
Alison O'Prey	Clinical PhD	2022-2025	NHS
Zoe McKinnon	Basic scientist PhD	2021-2024	UCB

Abdullah Saggah	Basic scientist PhD	2020-2023	Saudi government funding
Alyaa Alsalhi	Basic scientist PhD	2018-2022	Saudi government funding
Connor O'Farrell	Basic scientist PhD	2018-2022	Astra Zeneca (part of Formulation engineering DTC)
Georgia Ioanna Sakellai	Basic scientist PhD	2019-2023	University of Birmingham
Jan Goelen	Basic scientist PhD	2019-2023	Certara
Anna Johnston	Basic scientist PhD	2019-2023	University of Birmingham

Past Supervision

Project	**Person**	**Dates**
PhD: Investigation into the mouthfeel of orodispersible tablets	Abdullah Asiri	2018-2022
Exploration of the sensory analysis of oral formulations designed for special populations	Justyna Hofmanova	2016- 2020
Characterisation of the composition and volume of fluids in the paediatric GI tract – funded by Janssen	Eleni Papadatou-Soulou	2017-2020
Formulations engineering CDT project funded by AstraZeneca to explore the use of twin screw granulation	Rachael Shinebaum	2017-2021
Understanding the impact of manipulation of medicines on dosage accuracy in paediatric populations	Ahmed Lahiq	2017-2020
Understanding prophylactic antibiotic dosing regimens fopr obese women undergoing Casearean section	Hanadi Alrammaal	2018-2022
PhD: Investigation of liquid sodium alginates as mucoadhesive bandages coating the oesophageal mucosa and protecting it from gastric reflux	Man Tang	2001-2004
PhD: Strategies for local drug delivery targeting the oesophagus	Liang Zhang	2005-2008
PhD: Solid oral dosage forms of sparingly soluble compounds: enhancement of their release profiles to predict bioavailability of dissolution rate limited drugs	Darren Matthews	2002-2006
PhD: Development of liquid formulations for targeted drug delivery to the oesophagus	Danielle Russell	2001-2006
PhD: Dissolution rate enhancement, in vitro evaluation and investigation of drug release kinetics of chloramphenicol and sulphamethoxazole solid dispersions	Sheraz Khan	2007-2011
PhD: Development and formulation of wax-based transdermal drug delivery systems	Oladiran Gbolohan	2004-2008
Post Docs		
Formulation development of oral BCG vaccine to treat badgers	Alan Smith	2006-2008
Investigation of childrens preferences for alternative pharmaceutical formulations (TabPIC and FormPIC studies)	Rebecca Venables	2013-2014
FDA Project to explore risk assessment of substitution of generic medicines in paediatric populations	Gopal Pawar	2019-2022
Exploration into the use of oral syringes to delivery multiparticulate formulations to children	Justyna Hofmanova	2019-2020
Visiting Researchers		
The use of microviscometry to study polymer dissolution from drug delivery systems	S. Esnaashari	2005
High speed DSC (Hyper-DSC) as a tool to measure the solubility of a drug within a solid or semi-solid matrix	Daniela Gramaglia	2005
Supervised a BMedSci project student for 10 weeks working on administration of flucloxacillin to children with CF	Claudia Rouse	2014

Supervised an MSc Research project (MSc Pharmaceutical Enterprise) "evaluation of emerging and existing taste masking technologies for paediatric drug development"	Eunice Afriyie	2015
Supervised an Erasmus exchange student from Italy for 6 months working on tribology of novel medicines for children	Benedetta Soldati	2016
Supervise an Erasmus exchange student from Italy (University of Bologna) for 6 months working on assessing the stability Pickering particle emulsions for flexible dosing of fixed dose combinations	Carlotta Imperia	September 2015-April 2016
Co-supervise an exchange student from the university of Sao Paolo (Brazil) working on extraction of essential oils from foods (Dr Fotios Spyropoulos , School of Chemical Engineering, UoB)	Luis Perez Cordoba	Apr 2016- Apr 2017
Supervise an Erasmus exchange student from Italy (University of Bologna) for 6 months working on assessing the stability of a combination product of sodium benzoate and sodium phenylbutyrate	Daniela Monti	Oct 16 – March 2017
Supervise an internship to work on a collaborative project with Tim Muntinga at Oxford University to establish the quality of medicines purchased online	Fanqing Xu	Oct 16 – Jan 2017
Erasmus student from the University of Pavia to work on a project joint with the dental school	Ciara Licchello	Jan 2018-July 2018
UNGAP project where the student visited from the University of Griefswald	Lisa Freeks	April 2019

I am also a mentor to PhD students outside of my institute to support students from a range of disciplines.

RESEARCH IMPACT

According to Scopus based on 96 documents.
My h-index is 23 I have 1890 citations and 234 co-authors.
There was a gap in publication history as I took a break from academia to work at AstraZeneca and then within the NHS (2007-2012).
(Google Scholar h-index = 26; i10-index = 51)

SECTION 5. TEACHING AND EDUCATION ACTIVITIES

I hold a Postgraduate Certificate in Learning and Teaching, awarded in 2004 from Aston University (SEDA accreditation as a Teacher in Higher Education).

At the University of Strathclyde I teach students on the MPharm and MSc in Advanced Drug Delivery.

At the University of Birmingham I taught students on the following courses: Masters in Pharmacy (MPharm); Medicine and Surgery degree (MBChB); Masters in Chemical Engineering (MEng); MSc in Pharmaceutical Enterprise; Bachelor of Medical Sciences (BMedSci). My total teaching contact hours for timetabled activity in 2019-20 was 163 hours.

I teach on the MSc in Paediatric Medicines Development and Evaluation awarded by the University of Rome Tor Vergata (Global Research in Paediatrics (http://www.grip-network.org/index.php/cms/en/master_paediatric_medicines)). I have also taught on a MOOC (Massive open online course) on "Drug Origins" (http://www.birmingham.ac.uk/postgraduate/courses/moocs/gbbb-drug-origins.aspx) which attracted 5500 participants in 2014. I was responsible for writing a module within the SCRIPT project on paediatric prescribing (www.safeprescriber.org).

TEACHING LEADERSHIP

I am the director for student experience at the University of Strathclyde.

SECTION 6: KNOWLEDGE EXCHANGE

- Editorial board for Nature Publishing Group: Scientific Reports (www.nature.com/srep)
- Editorial board for Journal of Applied Biopharmaceutics and Pharmacokinetics
- Editorial board for Biopharmaceutics and Drug Disposition
- EPSRC Peer Review Associate College
- Invited to be a reviewer for L'Oréal-UNESCO UK and Ireland Fellowships For Women In Science 2017, 2018, 2019
- Invited expert reviewer for the Research Foundation Flanders (FWO)
- Expert peer reviewer for Sparks Charity
- I am involved in consultancy for legal work with a range of parties in the UK and USA

Outreach Activities – Policymakers

- MHRA
  I have been a member of the MHRA British Pharmacopoeia Expert Advisory Group on Medicinal Chemistry since 2018. In August 2021 I was appointed to MHRA Chemistry, Pharmacy & Standards Expert Advisory Group. These groups provide advice to the UK government on matters relating to the regulation of medicines and medical devices, specifically on the quality in relation to safety and efficacy of medicinal products which are the subject of marketing authorisation applications.
- EMA meeting in London
  I was invited as an expert to attend an EMA workshop on how to better apply the Paediatric Regulation to boost development of medicines for children. I was able to input to this meeting and showcase work on formulations and age-appropriate medicines for children.
- Joint work with the FDA on bioequivalence of generic products in paediatric populations
  I was invited to present at the AAPS (American Academy of Pharmaceutical Sciences) within a session hosted by the FDA to look at risks associated with using generic products in children. This presentation led to an invitation to apply for funding from the FDA to support additional work in this area. If successful this grant offers a direct line to work with the FDA on the topic of children's medicines.
- MCersi meeting
  I was involved in the organisation of a workshop with the FDA on food effects in paediatric medicines. A paper has resulted from this workshop that has authors from the EMA and FDA as collaborators: Hannah Batchelor, Ann Marie Kaukonen, Sandra Klein, Barbara Davit, Rob Ju, Robert Ternik, Tycho Heimbach, Wen Lin, Jian Wang, David Storey, (2018) Food Effects in Paediatric Medicines Development for Products Co-administered with Food, International Journal of Pharmaceutics. 536(2): 530-535 https://doi.org/10.1016/j.ijpharm.2017.05.011.
- I am a member of the NSF Joint Committee on Pharmaceuticals Excipients. This is the American National Standard for GMP in Pharmaceutical Excipients and we are working to draft guidelines on the regulatory requirements for strengthening the safety and quality through the excipient supply chain. I work with industrial colleagues to revise the guidelines.
- I have contributed to writing a WHO document on assessment of acceptability for paediatric medicines and have been cited several times within this document.

SECTION 7: WIDENING PARTICIPATION

I have provided a summary of my outreach activities in the table below (note that there was a gap due to COVID):

Event	Activity	Audience	Venue	Dates
Explorathon	Raising awareness about the range of paediatric medicines	General public	Glasgow Science Centre	November 2022

College Outreach and Widening Participation Masterclass	Interaction session on virtual development of a drug product	Year 10 and 12 pupils	University of Birmingham	Novemb er 2019
University of Birmingham Public engagement	Evening showcase for the public. Tabletop demonstration on how to make tablets easier to swallow	General public	University of Birmingham	October 2019
Thinktank Lates	Evening showcase on making medicines acceptable	General public	Birmingham city centre	October 2019
Young persons steering group 10th Birthday	Why formulations matter in clinical trials	Healthcare professionals plus young people	Presentation at a conference	Septemb er 2019
Bring your family to work day	Showcase on how to make medicines acceptable to children and young people	Parents/carers and children	University of Birmingham	May 2019
ASE Annual Conference	Integration of pharmacy into the curriculum for Chemistry A level	Secondary science educators	Presentation at a conference	January 2019
Big Bang fair	Showcase on how to make medicines acceptable to children and young people	General public	Interactive display	March2 018
Twitter chat	The Pharmaceutical Journal hosted a Twitter chat on gender inequality in pharmacy. Using the tag #PJMindTheGap	General public	Twitter	April 2018
Chemist and Druggist Podcast	C+D gathered leading female community pharmacy figures for a discussion on equal pay and gender equality in the sector	General public	Podcast	April 2018
Exeter School	Interprofessional education talk	Year 9,10,11 and 12 students	Lesson delivery	Decemb er 2018
FindACure	Webinar presentation on the drug development process	General public	Webinar	April 2017
Child Growth Foundation annual meeting	How close is the dose? How accurate are doses of hydrocortisone for children that have been manipulated from a tablet	Parents/carers of children with a chronic illness	Presentation at a conference	October 2017
Local news channels	The ACCEPT multiparticulate study was featured on Midlands Today and also on BBC radio WM and BBC radio Coventry and Warwickshire	General Public	ThinkTank	February 2016
National Radio show	The dynamic colon model was featured on BBC radio's inside science programme	General Public	University of Birmingham	February 2016
TEDx Talk	A talk on why children should be leading research https://www.youtube.com/watch?v=DGbqLsY5J4c.	General public (adults only)	University of Birmingham	March 2015
Public engagement video	Why children don't like their medicines https://www.youtube.com/watch?v=IrrFiDjq9P4	General public		Decemb er 2015

Work on gender balance in pharmacy

I ran an MPharm project that specifically explored gender diversity within the Pharmacy profession. This has generated interest in a wide range of outlets that include:

- The Pharmacist http://www.thepharmacist.co.uk/lack-women-senior-pharmacy-roles-report-shows/

- C&D https://www.chemistanddruggist.co.uk/news/gender-inequality-higher-senior-level-pharmacy-bodies-and-chains
- P3 http://www.p3pharmacy.co.uk/pharmacy-lacks-women-in-senior-roles
- P3 Sasa's article http://www.p3pharmacy.co.uk/why-we-need-more-female-pharmacists-at-the-table
- PJ online https://www.pharmaceutical-journal.com/news-and-analysis/news/women-underrepresented-in-senior-pharmacy-and-nhs-roles/20204515.article
- Pharmacy Magazine http://www.pharmacymagazine.co.uk/283015-pharmacy-lacks-women-in-senior-roles
- Pf magazine https://www.pharmafield.co.uk/Pf-Fox-News/News/2018/03/Women-still-absent-from-senior-pharmacy-roles
- Independent Community Pharmacist http://www.independentpharmacist.co.uk/women-still-absent-from-senior-pharmacy-roles
- RPS blog http://blog.rpharms.com/england/2017/03/08/inspiring-women-in-pharmacy/

I am passionate about diversity in pharmacy leadership and ensuring that all students have an equal opportunity to achieve their goals. This has been a really interesting project and I believe that additional work is required to generate additional data to better understand the diversity in pharmacy leadership.

SECTION 8: CITIZENSHIP

MEMBERSHIPS/AFFILIATIONS

- Current chair of the Academy of Pharmaceutical Scientists
    - (APS) member (Board member 2018-present)
    - Responsible for communications and Editor of the newsletter
- Committee member of the Biopharmaceutics focus group within the APS (2012- present); Chair of this focus group 2019 - present
    - Organised and presented at a Biopharmaceutics Basic Workshop, June 2019, London
- Committee member of New Scientists Focus Group (within APS) 2003-present
    - Managed organisation of the 2010 Industrial Insights meeting at AstraZeneca with responsibility for the agenda driving the meeting
- Workstream leader of the biopharmaceutics theme within the European Paediatric Formulation Initiative (EuPFI). A consortium with members from academia, hospital pharmacies, pharmaceutical industry and the European Medicine Agency (EMA) as an observer working in a pre-competitive way on paediatric drug formulations. (2012 – present). This role has enabled me to direct and participate in a meeting with the FDA to direct the future development of paediatric biopharmaceutics in the USA.
- Member of UNGAP (The European Network on Understanding Gastrointestinal Absorption-related Processes (UNGAP) is a multidisciplinary Network of scientists aiming to advance the field of intestinal drug absorption) 2018-present
- Member of the Expert Advisory group on medicinal chemistry to the British Pharmacopoeia. 2019-present
- Member of standards committee for IPEC (International Pharmaceutical Excipients Committee)
- Formulations expert within the https://conect4children.org/network/
- Founding member of the Drug Delivery Research Network (DDRN) 2004-2007
- Member of the Young Academic Network for Chemical Engineers (YANCE) (2003-2007)

EDITORIAL BOARD FOR THE FOLLOWING JOURNALS

Biopharmaceutics and Drug Disposition
Nature Scientific Reports

PEER REVIEW FOR THE FOLLOWING PUBLICATIONS

AAPS PharmSciTech

Acta Biomaterialia
Acta Paediatrica
Advanced Drug Delivery Reviews
Archives of Disease in Childhood
BMJ Paediatrics Open
British Journal of Clinical Pharmacology
European Journal of Hospital Pharmacy.
European Journal of Pharmaceutical and Biopharmaceutics
European Journal of Pharmaceutical Science
Expert Opinion on Drug Delivery
International Journal of Pharmaceutics
Journal of Asthma
Journal of Controlled Release
Journal of Drug Targeting
Journal of Pharmacy and Pharmacology
Molecular Pharmaceutics
Nanomedicine
Pharmaceutica Analytica Acta
Pharmaceutical Research
Pharmaceutical Sciences
PLOSOne
The Journal of Pediatrics

EXAMINING AT UNDERGRADUATE LEVEL

Liverpool John Moores University: I am the external examiner on the following programmes:

- 20771 MPH Pharmacy
- 23170 SBSH Applied Chemical and Pharmaceutical Science
- 25577 MPH Pharmacy
- 35577 MPH Pharmacy
- 35649 BSH Pharmaceutical Science

Manchester University
I am external examiner for the PIAT programme: Industrial Pharmacy MSc programme (2017-2021)

University of Nottingham
I am external examiner for their MPharm programme and the Pharmaceutical and Health Sciences Programme (2019-2023).

University College London
I am external examiner for their MPharm programme (2021-2025)

EXAMINING AT POSTGRADUATE LEVEL

External examiner for PhD:
1. School of Pharmacy, Portsmouth University, UK (2005)
2. School of Pharmacy, University of Brighton, UK (2006)
3. School of Pharmacy, Queens University Belfast, UK (2006, 2017)
4. School of Pharmacy, University of London, UK (2007)
5. School of Pharmacy, Huddersfield University, UK (2016)
6. School of Pharmacy, University College London, UK (2016, 2017, 2021)
7. School of Pharmacy, University of Nottingham, UK (2016, 2018, 2019)
8. School of Social Sciences, University College London, UK (2018)

9. School of Pharmacy, Greenwich University, Kent, UK (2019)
10. School of Pharmacy, University of Hertfordshire, UK (2019)
11. School of Pharmacy, University College Cork, Ireland (2020)
12. School of Pharmacy, Kings College London, UK (2020)
13. School of Nursing, Edge Hill University, UK (2020)
14. School of Pharmacy, Kings College London (2021)
15. School of Pharmacy, University of Bath (2021)
16. School of Pharmacy, University of Reading (2022)
17. Karolinska Institute, Stockholm, Sweden (2023)

Internal examiner for PhD:
Aston University (2003-2007)
University of Birmingham (2015-2020)
University of Strathclyde (2022-present)