CURRICULUM VITAE

Name: Rodrigo Cristofoletti

Date of Birth: 03rd March 1981
Place of Birth: Rio Claro, Sao Paulo, Brazil
Marital status: Divorced
Nationality: Brazilian
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Academic Profile

2000-2004: BSc Pharmaceutical Sciences, University of Sao Paulo, FCFRP, Ribeirao Preto, SP, Brazil

This included four-year experience in a Pharmacology laboratory, working on antipyretic and pain relief models. The final year was dedicated to industrial pharmacy, including a 6-month placement at the CIMED Indústria Farmaceutica Ltda, Brazil (drug product development).

2010-2013: MSc Applied Toxicology to Health Surveillance, State University of Londrina, PR, Brazil

The qualification was based on a thesis which aimed at analyzing the predictive capacity of BCS and BDDCS on bioequivalence outcome.

Advisor: Prof. Dr. Silvia Storpirtis

2015-2017: PhD, *summa cum laude*, School of Biochemistry, Chemistry and Pharmacy of the Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany

The qualification was based on a dissertation which aimed at exploring the utilization of *in vitro and in silico* tools to improve the assessment and extrapolation of therapeutic equivalence. In vitro to in vivo extrapolation using PBPK models was the core of the dissertation. The feasibility of extrapolating bioequivalence results from the traditional healthy adults model to special populations as well as an integrative approach combining *in vitro* predictive dissolution, PBPK and PK/PD models for decision making about generic drug BE standards were also addressed.

Committee: Prof. Dr. Jennifer B. Dressman, Prof. Dr. Cristos Reppas, Prof. Dr. Dieter Steinhilber and Prof. Dr. Achim Schmidtko.

2017-current: Guest professor at the State University of Maringá (UEM), University of São Paulo (USP), Federal University of Rio Grande do Sul (UFRGS) and Federal University of Goiás (UFG)

I have been responsible for PhD coursework on *in vitro* to *in vivo* extrapolation (IVIVE) approaches and Quantitative Clinical Pharmacology (QCP) at four different Universities in Brazil:

- ✓ State University of Maringá, together with Prof. Dr. Andrea Diniz;
- ✓ University of São Paulo, together with Prof. Dr. Vera Lanchote;
- ✓ Federal University of Rio Grande do Sul, together with Prof. Dra Bibiana Verlindo and,
- ✓ Federal University of Goiás, together with Prof. Dr. Kênnia Rocha Rezende.

Employment Profile

2004-2005: CIMED Industria Farmaceutica Ltda, Pouso Alegre, MG, Brazil

Projects included the development of oral generic formulations.

2005-2019: Brazilian Health Regulatory Agency (Anvisa), Brasilia, DF, Brazil

From 2005 on I have been working at the Therapeutic Equivalence Department of Anvisa where I am responsible for carrying out inspections under the scope of GCP and GLP as well as for reviewing

clinical pharmacology reports and bioequivalence studies submitted to support generic and new drug applications as well as biosimilars. I have been a member of the Brazilian Pharmacopoeia since 2010. I was given a leave of absence to work on my Ph.D.

2008-2010: Head of the Therapeutic Equivalence Department at Anvisa, Brasilia, DF, Brazil

From 2008 to 2010 I was the head of the Therapeutic Equivalence Department at Anvisa, leading the development of the still current legal framework on bioequivalence and bioavailability studies within the Brazilian jurisdiction. In addition, I have been an internal advocate for using quantitative methods and modeling to modernize drug development and regulatory decisions. In 2010 I renounced to this position to pursue my academic career (*i.e.* MSc and PhD).

2019-current: Research Assistant Professor at the Center for Pharmacometrics and Systems Pharmacology in Lake Nona (Orlando), University of Florida.

In June of 2019 I joined the CPSP in Lake Nona in a full-time position at the Research Assistant Professor level to develop state-of-the-art physiologically-based and disease-based pharmacokinetic models to investigate the impact of intrinsic and extrinsic factors on systemic and tissue drug distribution as potential sources of variability in the time course of pharmacological effect. From July 1st on I will assume a tenure-track Assistant Professor position at the University of Florida.

Research Interests

- Development of brain-targeted drug delivery systems
- Biopanning phage display library to investigate blood-brain barrier shuttle peptides
- Development and validation of low cost 3D microfluidic BBB-on-a-chip systems
- Physiological and pathophysiological microfluidic Systems of the brain
- Exploring integrated frameworks combining with *in vitro* to *in vivo* extrapolation techniques, mechanistic PBPK modeling, pharmacometrics and big data to support regulatory decision-making;
- Translational modeling strategies (e.g., PBPK, PK/PD and quantitative systems pharmacology) to support drug product development;

Awards

Simcyp Academic Award for the Most Informative and Scientific Report 2017:

Cristofoletti R, Patel N, Dressman JB. 2017. Assessment of Bioequivalence of Weak Base Formulations Under Various Dosing Conditions Using Physiologically Based Pharmacokinetic Simulations in Virtual Populations. Case Examples: Ketoconazole and Posaconazole. *J Pharm Sci* 106(2):560-569.

In recognition of scientific research which is leading the field of IVIVE, ADME, PBPK, Pharmaceutics, Biologics, Safety Pharmacology, Systems Pharmacology and Modeling and Simulation.

Memberships

2010-current: member of the Brazilian Pharmacopoeia

I am the Anvisa's representative on the Brazilian Pharmacopoeia for issues related to drug dissolution and bioequivalence.

2014-current: FIP Biopharmaceutics classification system and biowaiver focus group

I am the only Latin American representative on the Biopharmaceutics Classification System (BCS) and Biowaivers Focus Group is part of FIP's Special Interest Group on Regulatory Sciences. The major goals of this group are: a) provide a global, independent platform for scientific discussion among academia, industry and regulators on the possibilities and the limitations of biowaivers for *in vivo* bioequivalence studies; b) stimulate optimisation of biowaiver methods; c) contribute to harmonisation of the application of BCS-based biowaivers and d) provide leadership in educating scientists worldwide about the BCS Biowaiver and how it fits into the determination of bioequivalence.

2017-current: Brazilian representative on the recently founded Iberoamerican Pharmacometrics Network (RedIF)

The RedIF aims to promote and develop pharmacometrics and quantitative systems pharmacology in Latin America, where both disciplines are still emergent. This international society involved groups from Mexico, Cuba, Panama, Colombia, Chile, Brazil, Argentina, Uruguay and Spain.

2019-current: member of the American Society for Clinical Pharmacology and Therapeutics (ASCPT)

I was appointed as a member of the Webinar Committee for the American Society for Clinical Pharmacology and Therapeutics (ASCPT). This appointment term begins on March 16, 2019, and will be for a 1-year period (through the 2020 Annual Meeting).

2019-current: member of the International Society of Pharmacometrics (ISoP)

Publications (papers and book chapters)

1. Farhan N, Cristofoletti R, Basu S, Fang L, Lesko L, Schmidt S. 2020. Physiologically Based Pharmacokinetics Modeling to Investigate Formulation Factors Influencing the Generic Substitution of Dabigatran Etexilate. *CPT Pharmacometrics Syst Pharmacol.* Submitted.
2. Hens B, Bermejo M, Cristofoletti R, Amidon GE, Amidon GL. 2020. Application of the Gastrointestinal Simulator (GIS) coupled with in silico modeling to measure the impact of Coca-Cola® on the luminal and systemic behavior of loratadine (BCS class 2b). *Pharmaceutics*. Submitted.
3. Jesus SM, Pinto L, Perin L, Fonseca K, Cristofoletti R, Carneiro CM. 2020. Influence of experimental chronic Trypanosoma cruzi infection on the pharmacokinetics of benznidazole in mice. *Journal of Antimicrobial Chemotherapy*. Submitted.
4. Cristofoletti R, et al. 2020. Using physiologically-based pharmacokinetic modeling to assess the risks of failing bioequivalence criteria: a tale of two ibuprofen products. *AAPS J*. Submitted.
5. Cicali B, Long T, Kim S, Cristofoletti R. 2020. Assessing the impact of cystic fibrosis on the antipyretic response of ibuprofen in children: Physiologically-based modeling as a candle in the dark. *Br J Clin Pharmacol*. 2020 Apr 25. doi: 10.1111/bcp.14326. Online ahead of print.

6. Plöger GF, Quizon PM, Abrahamsson B, Cristofoletti R, Groot DW, Parr A, Langguth P, Polli JE, Shah VP, Tajiri T, Mehta MU, Dressman J. 2020. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Cephalexin Monohydrate. *J Pharm Sci* 109(6):1846-1862.
7. Loisios-Konstantinidis I, Cristofoletti R, Fotaki N, Turner DB, Dressman J. 2020. Establishing virtual bioequivalence and clinically relevant specifications using in vitro biorelevant dissolution testing and physiologically-based population pharmacokinetic modeling. case example: Naproxen. *Eur J Pharm Sci* 143:105170. doi: 10.1016/j.ejps.2019.105170. Epub 2019 Nov 27.
8. Cristofoletti R, Hens B, Patel N, Esteban VV, Schmidt S, Dressman J. 2019. Integrating Drug- and Formulation-Related Properties With Gastrointestinal Tract Variability Using a Product-Specific Particle Size Approach: Case Example Ibuprofen. *J Pharm Sci* 108(12):3842-3847.
9. Rajawat GS, Belubbi T, Nagarsenker MS, Abrahamsson B, Cristofoletti R, Groot DW, Langguth P, Parr A, Polli JE, Mehta M, Shah VP, Tajiri T, Dressman J. 2019. Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Ondansetron. *J Pharm Sci*. doi: 10.1016/j.xphs.2019.05.033. [Epub ahead of print]
10. Schmidt S, Kim S, Vozmediano V, Cristofoletti R, Winterstein AG, Brown JD. 2019. Pharmacometrics, Physiologically Based Pharmacokinetics, Quantitative Systems Pharmacology-What's Next?-Joining Mechanistic and Epidemiological Approaches. *CPT Pharmacometrics Syst Pharmacol*. doi: 10.1002/psp4.12425. [Epub ahead of print]
11. Kim S, Sharma VD, Lingineni K, Farhan N, Fang L, Zhao L, Brown JD, Cristofoletti R, Vozmediano V, Ait-Oudhia S, Lesko LJ, Trame MN, Schmidt S. 2019. Evaluating the Clinical Impact of Formulation Variability: A Metoprolol Extended-Release Case Study. *J Clin Pharmacol*. doi: 10.1002/jcph.1433. [Epub ahead of print]
12. Loisios-Konstantinidis I, Paraiso RLM, Fotaki N, McAllister M, Cristofoletti R, Dressman J. 2019. Application of the relationship between pharmacokinetics and pharmacodynamics in drug development and therapeutic equivalence: a PEARRL review. *J Pharm Pharmacol* 71(4):699-723.
13. Ibarra M, Dalla Costa T, Schaiquevich P, Cristofoletti R, Hernández González I, Fajardo-Robledo NS, Aragón Novoa M, Pecchio M, Cortinez I, Trocóniz IF, Romero-Tejeda EM. 2019. Iberoamerican Pharmacometrics Network Congress 2018 Report: Fostering Modeling and Simulation Approaches for Drug Development and Regulatory and Clinical Applications in Latin America. *CPT Pharmacometrics Syst Pharmacol*. doi: 10.1002/psp4.12387.
14. Cristofoletti R, Schmidt S, Diniz A. 2018. Non-Procrustean pathways for complex generic drugs development. *Ther Deliv* 9(9):605-607.

15. Cristofoletti R, Rowland M, Lesko LJ, Blume H, Rostami-Hodjegan A, Dressman JB. 2018. Past, Present, and Future of Bioequivalence: Improving Assessment and Extrapolation of Therapeutic Equivalence for Oral Drug Products. *J Pharm Sci* 107(10):2519-2530.
16. Plöger GF, Abrahamsson B, Cristofoletti R, Groot DW, Langguth P, Mehta MU, Parr A, Polli JE, Shah VP, Tajiri T, Dressman JB. 2018. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Proguanil Hydrochloride. *J Pharm Sci* 107(7):1761-1772.
17. Cristofoletti R, Marques M, Storpirtis S. 2017. Brazil. In: Bioequivalence Requirements in Various Global Jurisdictions (p.1-20). Springer International Publishing. doi. 10.1007/978-3-319-68078-1.
18. Hofsäss MA, Souza J, Silva-Barcellos NM, Bellavinha KR, Abrahamsson B, Cristofoletti R, Groot DW, Parr A, Langguth P, Polli JE, Shah VP, Tajiri T, Mehta MU, Dressman JB. 2017. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Folic acid. *J Pharm Sci* 106(12):3421-3430.
19. Thambavita D, Galappatthy P, Mannapperuma U, Jayakody L, Cristofoletti R, Abrahamsson B, Groot DW, Langguth P, Mehta M, Parr A, Polli JE, Shah VP, Dressman J. 2017. Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Amoxicillin Trihydrate. J Pharm Sci. DOI: 10.1016/j.xphs.2017.04.068. [Epub ahead of print]
20. Verbeeck RK, Kanfer I, Löbenberg R, Abrahamsson B, Cristofoletti R, Groot DW, Langguth P, Polli JE, Parr A, Shah VP, Mehta M, Dressman JB. 2017. Biowaiver Monographs for Immediate-Release Solid Oral Dosage Forms: Enalapril. J Pharm Sci 106(8):1933-1943.
21. Charoo NA, Cristofoletti R, Kim SK. 2017. Integrating biopharmaceutics risk assessment and in vivo absorption model in formulation development of BCS class I drug using the QbD approach. Drug Dev Ind Pharm 43(4):668-677.
22. Cristofoletti R, Patel N, Dressman JB. 2017. Assessment of Bioequivalence of Weak Base Formulations Under Various Dosing Conditions Using Physiologically Based Pharmacokinetic Simulations in Virtual Populations. Case Examples: Ketoconazole and Posaconazole. J Pharm Sci 106(2):560-569.
23. Cristofoletti R, Dressman JB. 2016. Bridging the gap between in vitro dissolution and the time course of ibuprofen-mediating pain relief. J Pharm Sci 105(12):3658-3667.
24. Cristofoletti R, Dressman JB. 2016. Dissolution Methods to Increasing Discriminatory Power of In Vitro Dissolution Testing for Ibuprofen Free Acid and Its Salts. J Pharm Sci 106(1):92-99.
25. Cristofoletti R, Dressman JB. 2016. FaSSIF-V3, but not compendial media, appropriately detects differences in the peak and extent of exposure between reference and test formulations of ibuprofen. Eur J Pharm Biopharm 105:134-140.

26. Cristofoletti R, Dressman JB. 2016. Matching phosphate and maleate buffer systems for dissolution of weak acids: Equivalence in terms of buffer capacity of bulk solution or surface pH? Eur J Pharm Biopharm 103:104-108.
27. Cristofoletti R, Charoo NA, Dressman JB. 2016. Exploratory Investigation of the Limiting Steps of Oral Absorption of Fluconazole and Ketoconazole in Children Using an In Silico Pediatric Absorption Model. J Pharm Sci 105(9):2794-2803.
28. Goodarzi N, Barazesh Morgani A, Abrahamsson B, Cristofoletti R, Groot DW, Langguth P, Mehta MU, Polli JE, Shah VP, Dressman JB. 2016. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Ribavirin. J Pharm Sci 105(4):1362-1369.
29. Cristofoletti R, Patel N, Dressman JB. 2016. Differences in Food Effects for 2 Weak Bases With Similar BCS Drug-Related Properties: What Is Happening in the Intestinal Lumen? J Pharm Sci 105(9):2712-2722.
30. Gajendran J, Krämer J, Shah VP, Langguth P, Polli J, Mehta M, Groot DW, Cristofoletti R, Abrahamsson B, Dressman JB. 2015. Biowaiver Monographs for Immediate-Release Solid Oral Dosage Forms: Nifedipine. *J Pharm Sci* 104(10):3289-3298.
31. Cristofoletti R, et al. 2015. Meeting Report: International Workshop on Implementation of Biowaivers Based on the Biopharmaceutics Classification System (BCS). *Dissolution Technologies* 22(2):77-81
32. Charoo NA, Cristofoletti R, Dressman JB. 2015. Risk assessment for extending the Biopharmaceutics Classification System-based biowaiver of immediate release dosage forms of fluconazole in adults to the paediatric population. *J Pharm Pharmacol* 67(8):1156-1169.
33. Petruševska M, Berglez S, Krisch I, Legen I, Megušar K, Peternel L, Abrahamsson B, Cristofoletti R, Groot DW, Kopp S, Langguth P, Mehta M, Polli JE, Shah VP, Dressman J. 2015. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Levetiracetam. *J Pharm Sci* 104(9):2676-2687.
34. Charoo N, Cristofoletti R, Graham A, Lartey P, Abrahamsson B, Groot DW, Kopp S, Langguth P, Polli J, Shah VP, Dressman J. 2014. Biowaiver monograph for immediate-release solid oral dosage forms: fluconazole. *J Pharm Sci* 103(12):3843-3858.
35. Cristofoletti R, Dressman JB. 2014. Use of physiologically based pharmacokinetic models coupled with pharmacodynamic models to assess the clinical relevance of current bioequivalence criteria for generic drug products containing Ibuprofen. *J Pharm Sci* 103(10):3263-3275.
36. Dahan A, Wolk O, Zur M, Amidon GL, Abrahamsson B, Cristofoletti R, Groot DW, Kopp S, Langguth P, Polli JE, Shah VP, Dressman JB. 2014. Biowaiver monographs for immediate-release solid oral dosage forms: codeine phosphate. *J Pharm Sci* 103(6):1592-1600.

37. Charoo NA, Cristofoletti R, Khatri AR, Ali AA. 2014. Significance of metabolites in bioequivalence: losartan potassium as a case study. *J Pharm Sci* 103(6):1584-1591.
38. Rediguieri CF, Cristofoletti R, Soares KC, Tavares-Neto J. 2014. Similarities and differences of international guidelines for bioequivalence: an update of the Brazilian requirements. *AAPS J* 16(2):350-351.
39. Charoo NA, Shamsher AA, Lian LY, Abrahamsson B, Cristofoletti R, Groot DW, Kopp S, Langguth P, Polli J, Shah VP, Dressman J. 2014. Biowaiver monograph for immediate-release solid oral dosage forms: bisoprolol fumarate. *J Pharm Sci* 103(2):378-391.
40. Storpirtis S, Gai NM, Cristofoletti R. 2014. Generic and similar products in Latin American countries: Current aspects and perspectives on bioequivalence and biowaivers. *Pharmaceuticals Policy and Law* 16(3):225-248.
41. Cristofoletti R, Chiann C, Dressman JB, Storpirtis S. 2013. A comparative analysis of biopharmaceutics classification system and biopharmaceutics drug disposition classification system: a cross-sectional survey with 500 bioequivalence studies. *J Pharm Sci* 102(9):3136-3144.
42. Cristofoletti R, Nair A, Abrahamsson B, Groot DW, Kopp S, Langguth P, Polli JE, Shah VP, Dressman JB. 2013. Biowaiver monographs for immediate release solid oral dosage forms: efavirenz. *J Pharm Sci* 102(2):318-329.
43. Silva AL, Cristofoletti R, Storpirtis S, Sousa VD, Junginger HE, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2012. Biowaiver monographs for immediate-release solid oral dosage forms: stavudine. *J Pharm Sci* 101(1):10-16.
44. Koeppe MO, Cristofoletti R, Fernandes EF, Storpirtis S, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2011. Biowaiver monographs for immediate release solid oral dosage forms: levofloxacin. *J Pharm Sci* 100(5):1628-1636.
45. Soares DM, Cristofoletti R, Melo MC, Lindsey CJ, Veiga-Souza FH, Fabricio AS, Souza GE. 2011. Cyclooxygenase-independent mechanism of ibuprofen-induced antipyresis: the role of central vasopressin V_1 receptors. *Fundam Clin Pharmacol* 25(6):670-681.
46. Cristofoletti R, Rama EM, Chiann C. 2011. Técnicas Computacionais em Farmacocinética. In: Storpirtis S, Gai MN, Campos DR, Gonçalves JE (Eds.), *Farmacocinética Básica e Aplicada* (pp.174-188). Rio de Janeiro, RJ: Editora Guanabara Koogan.
47. Cristofoletti R, Rama EM, Chiann C. 2011. Relação entre Farmacocinética e Farmacodinâmica (PK/PD). In: Storpirtis S, Gai MN, Campos DR, Gonçalves JE (Eds.), *Farmacocinética Básica e Aplicada* (pp.162-172). Rio de Janeiro, RJ: Editora Guanabara Koogan.

48. Cristofoletti R, Chiann C. 2009. Introdução à simulação bootstrap. In: Storpirtis S, Gai MN, Chiann C, Gonçalves JE (Eds.), *Biofarmacotécnica* (pp.302-307). Rio de Janeiro, RJ: Editora Guanabara Koogan.
49. Cristofoletti R, Chiann C. 2009. Inspeção em centros de Equivalência Farmacêutica e Bioequivalência. In: Storpirtis S, Gai MN, Chiann C, Gonçalves JE (Eds.), *Biofarmacotécnica* (pp.244-250). Rio de Janeiro, RJ: Editora Guanabara Koogan.
50. Fabricio AS, Veiga FH, Cristofoletti R, Navarra P, Souza GE. 2005. The effects of selective and nonselective cyclooxygenase inhibitors on endothelin-1-induced fever in rats. *Am J Physiol Regul Integr Comp Physiol* 288(3):R671-677.

Ad hoc reviewer for

Journal Pharmaceutical Sciences
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European Journal of Pharmaceutical Sciences
American Association of Pharmaceutical Scientists Journal (AAPS J)
AAPS PharmSciTech
Pharmaceutical Research
CPT: Pharmacometrics & System Pharmacology
Drugs in R&D
Biopharmaceutics & Drug Disposition
Therapeutic Delivery
Brazilian Journal of Pharmaceutical Sciences
Scientific Reports (Nature)
Journal Pharmacy and Pharmacology

Language competencies

Fluent in Portuguese (native) and English (oral and written). Advanced skills in Spanish (oral and written). Basic skills in German.