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Project Title: Science-based statistical comparison of dissolution profiles
Project Faculty: Drazer, Cuitino, Androulakis, Ierapetritou

Problem Statement: The ability to compare dissolution profiles for tablets and other oral products is extremely important to the pharmaceutical industry. Typical situations are: (i) Product release decisions, in which dissolution profiles are one of the criteria used to make product release decision during manufacturing. (ii) Equivalence decisions, in which similarity of *in vitro* dissolution profiles between the reference product and its generic or modified version are one of the key requirements for regulatory approval decisions. (iii) Optimization decisions, in which dissolution performance is a critical quality attribute and both the product formulation and the manufacturing process are optimized based on achieving specific dissolution targets. Therefore, it is essential to have science-based reliable methods for comparison of dissolution profiles, assessing the statistical significance of observations. However, comparisons are almost always carried out using the "f2" test, a largely arbitrary criterion that has a weak theoretical basis and is limited to pairwise comparisons.

Objectives: The objective of this project is to develop specific methodologies for the product *release, equivalence* and *optimization decision* tests discussed above, by implementing multivariate statistical methods that allow for the comparison of different dissolution profiles simultaneously. For each case, we will not only develop the statistical procedures but also implement a "tool box" of useful methodologies. In addition, we shall write a tutorial that illustrates the methodologies, interprets the results, points out the limitations of current practices, and highlights the advantages of the proposed methods.

Methods and Materials: Our group has recently introduced the idea of using *level* and *shape* to describe and compare dissolution curves by means of a modified Principal Component Analysis (PCA). This method showed great potential to discriminate between similar dissolution curves, something that proved impossible with traditional methods. In this project, we will continue introducing simple yet rigorous methodologies for the determination of statistical significance of observed multivariate effects in dissolution testing.

Anticipated Impact: The intended deliverables and impact on technology/industry are listed below:

- Specific statistical methods and procedures to follow for *release, equivalence* and *optimization decision* tests.
- Implementation of multivariate statistical methods that allow for multiple comparisons simultaneously, compared to current methods limited to pairwise comparisons.
- For each situation, appropriate analysis methodologies will be determined, illustrated, results interpreted, and the strengths and limitations of the method identified
- A detailed tutorial for the implementation of the different statistical methods and procedures developed, including specific guideline elements for *release, equivalence* and *optimization decision tests.*
- A "tool box" of methodologies that are useful for the analysis of dissolution profile studies along with illustrations of how the methods are to be applied and interpreted
- Dissemination of results and education to the scientific and industrial communities.

Timeline:

1st trimester						**2nd trimester**		**3rd trimester**		**4th trimester**			
Recruit-ment		Multivariate Analysis for *Release decision*				Multivariate Analysis for *Equivalence decision*		Multivariate Analysis for *Optimization decision*					
				Develop case studies for Release decision			Develop case studies for *Equivalence* decision		Develop case studies for *Optimization* decision				
						Develop Tutorial and Toolbox Release Decision		Develop Tutorial and Toolbox *Equivalence* Decision		Develop Tutorial and Toolbox *Optimization* Decision			
						Secure external funding; NIH – FDA; NIPTE; Disseminate results; Internal seminars and workshops for ERC students. Industrial partners for toolbox development;							