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Survey Results for In Vitro-In Vivo Correlations (IVIVC): Critical Variables for Success

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ABSTRACT

This report summarizes the results of the "In Vitro–In Vivo Correlations (IVIVC): Critical Variables for Success" survey organized by the In Vitro Release and Dissolution Testing (IVRDT) and the QbD and Product Performance AAPS Focus Groups. This was a web-based survey conducted over a 26-day period from Wednesday, June 29, 2011, to Sunday, July 24, 2011, and results were initially presented at the 2011 AAPS Annual Meeting and Exposition. The goal was to describe the current views from scientists across academia, industry, and regulatory agencies on the adoption, utility, and benefits of IVIVCs and to begin identifying potentially critical variables for their success. Questions in the survey cover their development, use, and success.

INTRODUCTION

One of the challenges of pharmaceutical research is correlating in vitro drug release information of various drug formulations to their in vivo drug profiles (IVIVC). Some of the common objectives of developing and evaluating an IVIVC include but are not limited to:

- Assist in early formulation development and study critical quality attributes (CQAs).
- Reduce the number of bioequivalence studies performed during the initial approval process and for certain scale-up and post-approval changes (use of dissolution testing as a surrogate for in vivo studies).
- Support or validate the use of dissolution methods and set clinically relevant dissolution specifications.

Within the wider Quality by Design (QbD) framework, IVIVC can bring additional value by facilitating a mechanistic understanding of formulation in vivo performance and development of more in vivo predictive in vitro methodologies. This can lead to improved product quality, interpretation of product-related clinical outcomes, and prediction of the impact of future product or process changes on a drug's in vivo performance via the surrogate measurement of in vitro dissolution.

The In Vitro Release and Dissolution Testing and the QbD and Product Performance Focus Groups decided to organize this survey to obtain a clearer picture of the current status of the adoption and expectations on IVIVC and to identify the perceived critical variables for their development.

In total, 57 completed survey responses were received. The full text of the questions is provided in the Appendix. A strict definition of IVIVC was not provided as part of the survey; therefore, it is possible that some of the responses also reflect different interpretations of the term IVIVC by the responders. The interpretation of the survey results and the assignment of statistical significance are not addressed in this report but may be the subject of a future joint communication by the two AAPS focus groups involved in this survey.

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SURVEY RESULTS

IVIVC: Use and Success Rates

The IVIVC approach is used in early and late development (87.7%; Figure 1). Success rates, as revealed by Question 3 (Figure 1), cover a wide range of responses with the majority of responders indicating fair success, and 8.8% corresponds to poor and very poor success rates. The majority of respondents indicated that the IVIVC approach is used to set dissolution specifications (71.4%) and for the development of ER formulations (70.0%). In contrast to the ER dosage forms, the use of the IVIVC approach for immediate-release formulations is much more limited (23% for BCS Class 2 compounds and 12% for BCS Class 4). Furthermore, it seems that the IVIVC approach in non-oral formulations is currently limited—18% of the respondents declared that they use the IVIVC approach for other than oral formulations. However, it is possible that this represents only the lower prevalence of non-oral dosage forms as development formulations within the survey responders. Animal data for an IVIVC in development is used to a good extent (42%), whereas the use of these data for an IVIVC in approval is very limited (11%).

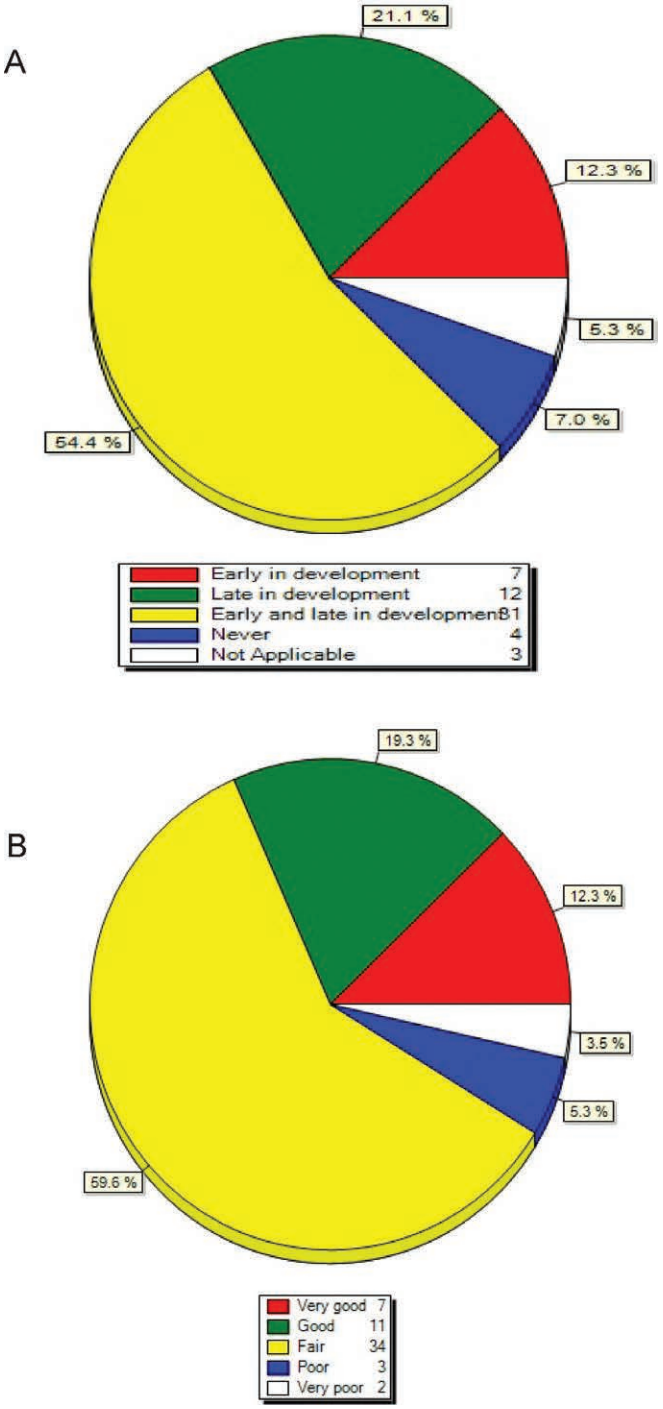

Figure 1. (A) IVIVC use (Question 2) and (B) success rates (Question 3).

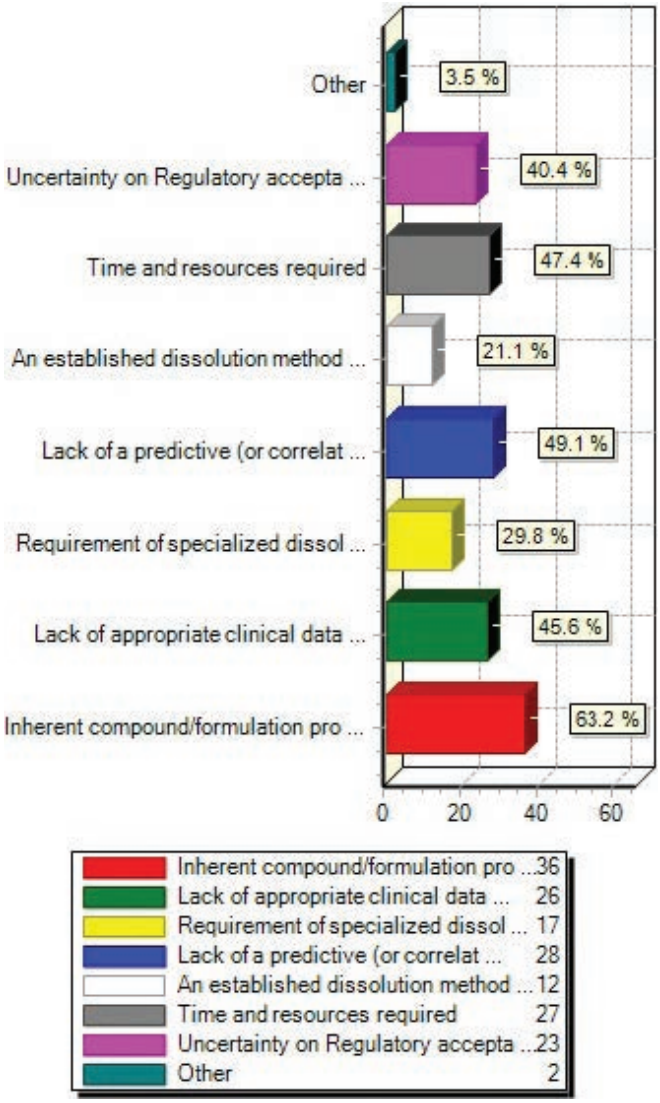

Figure 2. Main difficulties for pursuing an IVIVC (Question 4).

Main Difficulties in Pursuing an IVIVC

In an effort to understand the issues in pursuing an IVIVC, we decided to list a variety of reasons that could be defined as possible difficulties for pursuing an IVIVC. The responses can be seen in Figure 2.

Development of Level A Correlations

For the development of Level A correlations, the de-convolution–convolution technique and the simple linear

Table 1. Evaluation of IVIVC Approach

Question	Strongly Agree and Agree	Neither Agree nor Disagree	Disagree/ Strongly Disagree
IVIVC saves money	77%	19%	4%
Two dissolution methods: one for regulatory, one for IVIVC	50%	29%	21%
Need Level A at filing	32%	33%	35%

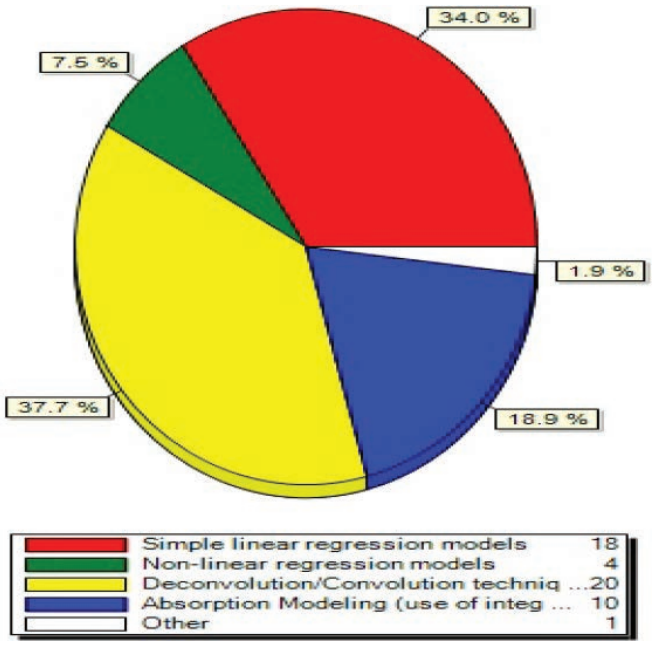

Figure 3. Development of Level A correlations (Question 10).

regression models are the predominant ones (71.7%), as shown in Figure 3. Alternate or novel methods were also indicated from the respondents (34%); responses include both alternate dissolution methods (e.g., USP Apparatus 3 and 4 or the Dynamic Gastric Model) and alternate computational methods (e.g., mechanistic deconvolution). It should be noted that the majority of respondents (83%) acknowledged the importance of simulations in the development of an IVIVC (Question 9).

Evaluation of IVIVC Impact on Return on Investment and Regulatory Submissions

Table 1 presents an evaluation of the IVIVC approach based on Questions 5, 8, and 11. The large majority of responders felt that IVIVCs do eventually provide a return on investment (i.e., save money). Half of the responders favored the utilization of a different dissolution method for filing (QC method) versus IVIVC development, while there appeared to be no clear consensus on the requirement of Level A IVIVCs.

CONCLUSIONS

This survey represents the first step in understanding the views of scientists on IVIVC based on their hands-on experience in the area. The In Vitro Release and Dissolution Testing (IVRDT) and the QbD and Product Performance AAPS Focus Groups will continue to monitor this space and help identify the key aspects that will facilitate utilization of IVIVC in drug development.

APPENDIX

Survey Questions:

1) Employment area.
2) We use the IVIVC approach: Early in development; Late in development; Early and late in development; Never; N/A.
3) Success rates for IVIVCs are: very poor, poor, fair, good, very good.
4) What are the main difficulties for pursuing an IVIVC? (Pick all that apply):
   Inherent compound/formulation properties (e.g., difficult to pursue for IR products, complex PK);
   Lack of appropriate clinical data or difficulty in justifying generation of appropriate clinical data;
   Requirement of specialized dissolution method/assay;
   Lack of a predictive (or correlating) dissolution method;
   An established dissolution method exists and value of developing an IVIVC is unclear; Time and resources required;
   Uncertainty on Regulatory acceptability/benefit;
   Other.
5) Having an IVIVC truly saves money in the long run.
6) How is Return on Investment defined? (Pick all that apply):
   Obtaining formal biowaiver;
   Help with QbD arguments and specification settings in filing documents;
   Facilitating internal decision to eliminate a clinical study;
   Facilitating internal formulation development efforts;
   Facilitating line extensions by leveraging existing knowledge;
   Other.
7) We use IVIVC to set dissolution specifications for a product.
8) We have two dissolution methods: one for regulatory and one for IVIVC.
9) Simulations play an important role in developing an IVIVC.
10) For the development of Level A correlations we typically use:
    Simple linear regression models;
    Non-linear regression models;
    Deconvolution/Convolution techniques;
    Absorption Modeling (use of integrated software).
11) It is absolutely necessary to have only Level A correlations in a filing.
12) We use the IVIVC approach for the development of ER formulations.
13) We have examples of IVIVC with BCS 2 immediate release compounds.
14) We have examples of IVIVC with BCS 4 immediate release compounds.
15) Have you tried alternate/novel methods/approaches for building correlations and/or relationships?
16) Have you developed IVIVCs for non oral formulations?
17) Do you use a biorelevant dissolution method to assist in the development of bio-equivalent formulations for generic drugs?
18) We use animal data for an IVIVC in development.
19) We use animal data for an IVIVC in approval.
20) Are there cases where you would expect a correlation but the results were inconclusive or not supportive? What changes might have improved the correlation?