ISSUES IMPORTANT TO IN VITRO–IN VIVO CORRELATION

IVIVR Workshop Open Discussion

Although this book addresses numerous topics in the area of in vitro-in vivo correlation (IVIVC), this chapter summarizes some of the scientific and regulatory issues important to IVIVC and the Draft FDA Guidelines on IVIVC. This chapter was based on the open discussion sessions at the IVIVR Workshop in Baltimore, Maryland on September 4–6, 1996. The chapter represents a compilation of comments and the consensus of the attendees at the meeting. This chapter is organized into five major topics with each issue listed under the topic and the consensus response from the attendees. For those few times that a consensus could not be reached, the different points of view are provided.

GASTROINTESTINAL PHYSIOLOGY

1. Our knowledge about GI physiology is greater than ever before but more research is needed.

   The consensus was that this statement is true and a better understanding of GI physiology would provide a better understanding as to the limits of developing and applying IVIVCs.

2. The use of animal models for IVIVC investigation needs to be considered.

   The consensus was that animal models should not be used in the regulatory decision process for oral or extended release products. However, they may be a useful tool for product development.

3. In vitro and in situ animal and human systems are important to IVIVC.

   The consensus was that these systems, in principal, have a role in IVIVC research but the role is not well defined except for permeability.

4. New in vitro and in situ animal and human models need to be developed and correlated to man.

   The consensus was that additional research on permeability and regional permeability will be valuable for the development of ER products.
5. Investigation of factors affecting BA.

This is an important area to investigate but the consensus was that it is outside the realm of this conference on IVIVC.

**Dissolution**

1. *In vitro* dissolution can be used for QC and as a surrogate for *in vivo* (IVIVC).

   It was agreed that *in vitro* dissolution can be used for both QC and as a surrogate for *in vivo*. More importantly, however, was the agreement that the systems are not required to be the same. If they are not the same, a major concern was that the QC dissolution specifications would be based on batch history and not the anticipated *in vivo* consequences to the formulations.

   A concern by a number of individuals was the appropriateness of using a different dissolution test for QC release vs. IVIVC. The problem is that the QC specifications from a dissolution system different from the IVIVC system does not ensure comparable *in vivo* response for different formulations.

   In a similar vein, a number of attendees stated, “how can the dissolution specifications be developed from a different system than the IVIVC dissolution system which is a surrogate for the *in vivo*, if we are concerned about *in vivo* response to the product?” It was agreed that there may be financial and/or logistical reasons why a company would not be able to use the dissolution system from the IVIVC, in this case the ideal situation would be to relate the two dissolution systems in some manner (e.g., mapping the formulations from one dissolution system to another).

2. We must define and further investigate the methodology needed to determine differences in dissolution.

   It was agreed that further research in this area is appropriate.

3. We must define what is an acceptable vs. unacceptable difference.

   For biowavers which require IVIVC, the acceptance criteria for the comparison of curves should be based on *in vivo* consequences not just the *in vitro* curves.

4. The guidance states “*If in vitro* dissolution is shown to be independent of dissolution conditions such as pH and agitation...”. We must define independent.

   The consensus was that the variables and range of variables to be investigated need to consider the characteristics of the product. The variables one might consider are: pH, agitation, ionic strength, lipids/surfactants, apparatus.

5. Optimization of dissolution systems to obtain IVIVC is important.

   The attendees agreed that the optimization process can go to the extreme. A better approach would be to describe the IVIVC by more complex mathematical/statistical models without making heroic efforts to change dissolution. This assumes that the existing dissolution system is discriminating.