

**FDA's ACPS Meeting, October 2005**  
**Awareness Topic: Mitigating the Risks of Ethanol Induced Dose Dumping from Oral Sustained/Controlled Release Dosage Forms**

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**Background Information**

Unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified release dosage form is often referred to as “dose dumping”. Depending on the therapeutic indication and the therapeutic index of a drug, dose-dumping can pose a significant risk to patients, either due to safety issues or diminished efficacy or both. Generally dose-dumping is observed due to a compromise of the release-rate-controlling mechanism. The likelihood of dose-dumping for certain modified release products when administered with food has been recognized for about twenty years and a regulatory process established to address it (1-2).

Some modified-release oral dosage forms contain drugs and excipients that exhibit higher solubility in ethanolic solutions compared to water. Such products can be expected to exhibit a more rapid drug dissolution and release rate in the presence of ethanol. Therefore, in theory, concomitant consumption of alcoholic beverages along with these products might be expected to have the potential to induce dose dumping. This potential mechanism leading to dose-dumping from an oral modified-release dosage form has not previously attracted attention in the pharmaceutical science literature or in regulatory assessment process. There are many reasons this may not have previously been considered, amongst these reasons is that there may have existed a general assumption that a clinically insignificant difference in drug release rate would be expected with concomitant ethanol consumption *in vivo*. A study conducted over twenty years ago (3) and the absence of a clear post-marketing signal pointing to alcohol inducing dose dumping may have reinforced the latter assumption.

However, a recent observation of alcohol-induced dose dumping and the potential risk it posed (4) necessitates a reexamination of this issue. In July 2005, FDA concluded that the overall risk versus benefit profile of a hydromorphone modified-release drug product was unfavorable due to alcohol induced dose dumping. This decision was based, in part, on an a pharmacokinetic study in healthy subjects (utilizing a naltrexone block), which demonstrated that co-ingestion of this product with 240 mL (8 ounces) of 40% (80 proof) alcohol resulted in an average peak hydromorphone concentration approximately six times greater than when taken with water. Furthermore, one subject in this study experienced a 16-fold increase when the drug was ingested with 40% alcohol compared with water. This study also showed that 8 ounces of 4% alcohol (equivalent to 2/3 of a typical serving of beer) could in some subjects result in almost twice the peak plasma hydromorphone concentration than when the drug was ingested with water (4).

Concomitant alcohol use is warned against or contraindicated for many drugs due to the potential for pharmacokinetic (e.g., altered clearance) or pharmacodynamic interactions (e.g., effects on the central nervous system). In these cases, product labels warn physicians and patients on the adverse consequence of alcohol consumption while on a drug regimen. For other drugs moieties, those that do not have a pharmacokinetic or pharmacodynamic interaction with alcohol, a warning on the adverse consequence of alcohol consumption due to potential for dose dumping may not be included in the product label. However, especially for certain narrow therapeutic index drugs (including hydromorphone), it may be prudent to consider the consequences of concomitant alcohol use, even in the face of significant alcohol warnings in product labeling because alcohol use would still be likely. For instance, with regard to the consideration for the consequences implied by the alcohol-drug interaction study with the hydromorphone product, the following data were considered:

- Data from the Behavioral Risk Factor Surveillance System indicates that 1 in 3 drinkers in the U.S. reported binge drinking, defined as 5 drinks in a short period of time (4 drinks for women)] (5)
- Survey data in chronic low back pain show no reduction in opiate use in heavy drinkers, despite current warnings about concomitant use of alcohol and opiates based on known pharmacodynamic interactions. (6)

## **Topic Introduction**

The FDA's recent finding (4) of an unfavorable risk versus benefit profile of a hydromorphone product due to alcohol-induced dose dumping necessitates development of a general regulatory approach to address the issue of whether alcohol undermines the release characteristics of the drug for new drug applications and currently marketed products that utilize a controlled-release mechanism. The goal of the regulatory approach should be to minimize the risk of alcohol-induced dose dumping from modified-release dosage forms, irrespective of any warnings on product labeling and instructions by health care providers.

A regulatory decisional framework to minimize the risk of alcohol-induced dose dumping could be modeled on existing regulatory decision criteria for food-drug or drug-drug interactions. However, unlike the guidance provided for these interactions, a routine recommendation for a pharmacokinetic study examining whether there is an alcohol-formulation interaction may not be the preferred approach for a number of reasons. Pharmacokinetic studies in healthy subjects that involve co-administration of high alcohol loads (to emulate a "worst case" scenario) and a modified-release product may pose a risk, either due to the alcohol load itself and because of the potential for dose dumping in cases where the high exposure itself may be dangerous. For some drugs a pharmacologic antagonist can be used to reduce risks posed by dose dumping (e.g., for opiates, a naltrexone or naloxone block), however this approach may not be feasible or provide an adequate protection for most drugs. In case of food-induced dose dumping, the FDA guidance clearly recognizes that (unless the product is well designed) food effect studies can pose a risk to study subjects - "co-administration with food can result in

*dose dumping*, in which the complete dose may be more rapidly released from the dosage form than intended, creating a potential safety risk for the study subjects” (2). One can, therefore, argue that the current food-effect study requirements for modified release dosage forms are not primarily intended to assess dose-dumping; these studies have much broader utility in terms of how the information generated is used for clinical study design and dosing regimen recommendations. To be consistent with these FDA principles - intended to minimize risk to subjects – reliable alternate approaches to an *in vivo* evaluation are preferred.

The underlying principle in risk minimization efforts is to prevent the occurrence of undesirable outcomes. Since regulatory experience suggests labeling and other means of informing patients about potential interactions with alcohol may be incompletely effective, to minimize risks of alcohol leading to dose-dumping, the regulatory goal should be to promote the design of rugged modified-release dosage forms that are not sensitive to alcohol. To achieve this goal, it is necessary to have an objective means to evaluate the dose dumping potential of a product design early in the product development phase so that only “rugged” product designs are developed and progressed in the clinical development program, and this generalized, risk-based regulatory approach needs to be developed for both new and generic drug products. In fact, if the reference listed product is rugged and no labeling cautions are therefore warranted, it would be highly desirable for any generic products to be similarly rugged, even if their modified-release mechanism was different from the innovator products.

A regulatory decision framework that facilitates a risk-based “quality by design” would need to integrate these principles into the assessment of dose dumping potential and the criteria for defining the regulatory consequence of developing a “vulnerable” product. A regulatory approach to gauge the potential for dose dumping from formulation and manufacturing process information and to classify products into “vulnerable” and “rugged” categories is being developed. The proposed classification approach identifies product and process failure modes based on the mechanism of drug release and the class membership verified using a suitable *in vitro* test of alcohol induced dose dumping potential. A reliable classification system based on mechanism of drug release may be sufficient in some cases, or in case of class uncertainty, this may need to be supplemented with a suitable *in vitro* test. It is anticipated that in most cases an *in vivo* pharmacokinetic study may not be necessary. The choice of tools for assessing dose dumping potential and the regulatory consequence of developing a “vulnerable” product would be guided by clinical risk-benefit assessment criteria. At the October 2005 ACPS meeting our efforts on developing this regulatory decision system will be outlined.

## References

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