Reply to: assessing physico-chemical compatibility of concomitantly diluted antiemetics including palonosetron-HCl and fosaprepitant dimeglumine

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Dear Editor,

We are grateful that the author of the commentary finds our product helpful. It took many years to make fosaprepitant available to patients, and we are grateful that it is of value to patients during a challenging time in their lives.

We wish to respond to the two key issues Dr. Lipp discusses the difference between the behavior of palonosetron and granisetron in fosaprepitant solutions and second the proposed degradate growth limit of <0.2 %.

The reason palonosetron and granisetron behave differently in the admixture is that when mixed with fosaprepitant, the resultant solutions have different final pH. One observation can be drawn from the data in Sun et al. that there is a strong dependence of final solution pH on degradate formation. We have observed that the transition from acceptable stability to unacceptable stability occurs around pH 7 with higher pH having greater stability. The palonosetron solutions all fall below pH 7, conditions which favor more rapid hydrolysis to aprepitant, hence the different behavior in the admixture solutions.

The larger issue, in our opinion, is the authors suggestion that a limit of 0.2 % degradate growth is too conservative, given that the “degradate” is actually the active

pharmaceutical agent aprepitant (fosaprepitant is quantitatively converted to aprepitant in the body). We would like to comment that the reason the limit is in place is due to the risk of precipitation. As the author notes:

...a slow release of low amounts of the active compound aprepitant by hydrolysis over time can be observed ... which results in a precipitation after several days when a critical concentration level is exceeded.

It is the phenomenon, precipitation of aprepitant, which the limit of <0.2 % aprepitant growth is designed to prevent. Our internal shelf-life models which are based on the true aqueous solubility of aprepitant and include maximum levels of degradate growth in the drug substance as well as degradate growth rates in the drug product only allow 0.2 % aprepitant growth during the reconstituted in-use period. Given these data and the unpredictable nature of the onset precipitation from a supersaturated solution, we are not able to support a widening limit of acceptable degradate growth to more than that proposed by Sun et al. should be considered the definitive source for the degradate growth limit.

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