

Hope this helps.

Jeff

Subject: Content of Herceptin vials
Date: Wed, 25 Sep 2002 11:52:19 -0700
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Genentech's Herceptin Production Engineer

The following data should correct the misconception of the pharmacy department at US Oncology that we are not filling 440 mg of Herceptin in our vials. Their assumption is based on the package insert statement that the concentration of Herceptin in the vial is 21 mg/ml and it is reconstituted with 20 ml of diluent.

$$(21 \times 20 + 0.5 \text{ ml} = 409.5 \text{ to } 430.5 \text{mg})$$

In actuality we fill 18 ml of bulk solution at a concentration of 25

mg/ml into the vial and lyophilize. We therefore target 450 mg in a vial (and nominally state 440 mg). $(18 \times 25 = 450 \text{ mg})$

Our technical report supporting the IND Studies of Lyophilized Multi-dose Her2 Formulation written in 1996 states that the reconstituted volume after adding 20 ml of diluent is actually about 20.6 ml due to the volume expansion of the solids present in the vial. Hence the theoretical concentration of the reconstituted product is actually 21.8 mg/ml. $(450 \text{ mg}/20.6 \text{ ml} = 21.8 \text{mg})$ After internal discussion in 1996, it was decided to round down the concentration in the insert to the nearest whole number rather than round up to a concentration we in fact do not achieve (ie. 22mg/ml). I believe this is the source of the confusion.

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Whereas we actually have between 440 and 450 mg in our vials they calculate that it is less.

$$(21.8 \text{ mg/ml} \times 20.6 \text{ ml}) \text{ vs } (21 \text{ mg/ml} \times 20 \text{ ml})$$

Let me know if this fully addresses their concern or if further explanation is necessary.