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Note

Comment to "The pharmacopeial evolution of Intralipid injectable emulsion in plastic containers: From a coarse to a fine emulsion"

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ABSTRACT

The droplet size distribution of 50 batches of multi-chamber bags containing the parenteral nutrition emulsions Intralipid (Kabiven and Kabiven Peripheral) or Structolipid (StructoKabiven and StructoKabiven Peripheral), respectively, has been investigated. The results show that the non-compounded lipid emulsions analysed are in compliance with the *United States Pharmacopeia* (*USP*) chapter 729, Method II limit for the droplet size distribution, $PFAT_5 < 0.05\%$.

In a recent publication, droplet size measurements determined mainly with the Single Particle Optical Sensing (SPOS) technique in Intralipid and other fat emulsions were reviewed (Driscoll, 2009). The chapter 729, Method II of the *United States Pharmacopeia* (*USP*) refers to the droplet size distribution as determined with SPOS, stating an upper limit of the volume percentage of droplets larger than 5 μm ($PFAT_5$) for parenteral fat emulsions, which must be less than 0.05%. It was demonstrated that Intralipid since October 2006 complies with the limit (Driscoll, 2009), well in advance of the introduction of the droplet size monograph in the *USP* in December 2007. The adherence of Intralipid in plastic packaging to the *USP* limit has previously also been addressed and verified by other authors (Gallegos et al., 2009).

Driscoll (Driscoll, 2009; Driscoll et al., 2009) included data demonstrating that the non-compounded emulsion in the multi-chamber bags (MCB's) Kabiven, StructoKabiven Peripheral and StructoKabiven 1100 respectively, were above the limits in Method II of the *USP* chapter 729 (described as "recent failures"). However, in his recent investigation Gallegos et al. (2009) claimed that also Kabiven shows $PFAT_5 < 0.05\%$.

In order to comprehensively resolve the issue, we have performed measurements of the droplet size distribution of the emulsion in recently produced MCB's, according to Method II in the *USP* chapter 729. The measurements were performed directly on the non-compounded emulsion, i.e. on the emulsion filled and stored in the emulsion compartment of the multi-chamber bag. Analyses were performed approximately 3–12 months after manufacturing and the samples were stored under reference storage conditions (15–25 °C). Droplet size analysis was performed on a total of 50 commercial batches of the products Kabiven, Kabiven Peripheral, StructoKabiven and StructoKabiven Peripheral manufactured by Fresenius Kabi. The measurements included the products tested by Driscoll et al. (2009). Kabiven and Kabiven Peripheral contain the soybean oil emulsion Intralipid as lipid component, whereas StructoKabiven and StructoKabiven Peripheral contain an emulsion based on an interesterified mixture of soybean oil and MCT-oil, Structolipid, as the lipid phase. The $PFAT_5$ levels were determined using the AccuSizer model 780APS (Particle Sizing Systems, Santa Barbara, CA) equipped with an automatic dilution system and utilizing an LE 400 sensor in extinction mode previously calibrated with polystyrene latex spheres. The emulsion samples were removed from each container and transferred to the dilution system. The applied dilution factor was set according to the oil concentration of each product to achieve an acceptable level of cumulative particles counts, which was approximately 1/3 of the coincidence limit of the sensor (9000 particles/ml). Samples were run in triplicate and the mean value is reported.

The complete set of droplet size determinations is presented in Table 1. All batches of the tested multi-chamber bags comply with the criterion listed in *USP* chapter 729 (Method II), i.e. $PFAT_5 < 0.05\%$. The mean $PFAT_5$ value for each emulsion, averaged over all batches, is reported in Table 2. The mean $PFAT_5$ value for the lipid emulsions

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Table 1
Batches of multi-chamber bags characterized using Method II according to the *USP* chapter 729.

Product	Batch number	Expiry date	$PFAT_5$ [%]
MCBs containing Intralipid			
Kabiven	10BF4801	2010-06-01	0.004
Kabiven	10BG5565	2010-07-01	0.016
Kabiven	10BH5594	2010-07-31	0.019
Kabiven	10BH6154	2010-07-31	0.007
Kabiven	10BH5807	2010-08-01	0.008
Kabiven	10BG5664	2010-08-09	0.010
Kabiven	10BK7129	2010-09-30	0.004
Kabiven	10BK7125	2010-10-01	0.009
Kabiven	10BK7133	2010-10-01	0.007
Kabiven	10BM8428	2010-11-30	0.019
Kabiven Peripheral	10BD3406	2010-03-31	0.004
Kabiven Peripheral	10BD3460	2010-04-01	0.005
Kabiven Peripheral	10BF4942	2010-05-31	0.004
Kabiven Peripheral	10BF4642	2010-06-01	0.011
Kabiven Peripheral	10BF4750	2010-06-01	0.014
Kabiven Peripheral	10BF5361	2010-06-30	0.010
Kabiven Peripheral	10BG5269	2010-06-30	0.009
Kabiven Peripheral	10BG5519	2010-07-28	0.012
Kabiven Peripheral	10BH5602	2010-07-31	0.020
Kabiven Peripheral	10BH5606	2010-07-31	0.004
Kabiven Peripheral	10BH5679	2010-08-01	0.012
Kabiven Peripheral	10BH5683	2010-08-01	0.009
Kabiven Peripheral	10BH5695	2010-08-01	0.010
Kabiven Peripheral	10BH5709	2010-08-01	0.019
Kabiven Peripheral	10BG5621	2010-08-05	0.013
Kabiven Peripheral	10BG5667	2010-08-06	0.011
Kabiven Peripheral	10BK7308	2010-10-01	0.010
Kabiven Peripheral	10BK7312	2010-10-01	0.005
Kabiven Peripheral	10BK7316	2010-10-01	0.018
MCBs containing Structolipid			
StructoKabiven	10CC1826	2011-02-28	0.019
StructoKabiven	10CC1830	2011-02-28	0.018
StructoKabiven	10BF4946	2010-06-01	0.017
StructoKabiven	10BH5973	2010-08-22	0.026
StructoKabiven	10BH5981	2010-08-01	0.023
StructoKabiven	10BH6050	2010-08-01	0.024
StructoKabiven	10BI6289	2010-08-31	0.022
StructoKabiven	10BI6888	2010-08-31	0.011
StructoKabiven	10BI6889	2010-08-31	0.007
StructoKabiven	10BI6289	2010-08-31	0.022
StructoKabiven	10BL6559	2010-09-01	0.025
StructoKabiven	10BL7631	2010-10-31	0.017
StructoKabiven	10BL8044	2010-10-31	0.014
StructoKabiven	10BL8029	2010-11-01	0.016
StructoKabiven	10BM8883	2010-11-30	0.015
StructoKabiven	10BM8879	2010-11-30	0.019
StructoKabiven Peripheral	10BL7793	2010-10-31	0.019
StructoKabiven Peripheral	10BL7797	2010-10-31	0.022
StructoKabiven Peripheral	10BL7801	2010-10-31	0.022
StructoKabiven Peripheral	10BL7805	2010-10-31	0.024
StructoKabiven Peripheral	10BL7842	2010-11-01	0.037

Table 2
Mean $PFAT_5$ values for multi-chamber bags characterized using Method II according to the *USP* chapter 729.

Product	$PFAT_5 \pm SD$ (%)
Intralipid in Kabiven/Kabiven Peripheral	0.010 ± 0.005
Structolipid in StructoKabiven/StructoKabiven Peripheral	0.020 ± 0.006

in the lipid chamber of the multi-chamber bag is determined to 0.010% for Intralipid (Kabiven and Kabiven Peripheral) and 0.020% for Structolipid (StructoKabiven and StructoKabiven Peripheral). All data are presented as the mean ± standard deviation (SD). The $PFAT_5$ values are in agreement with the previously reported data by Gallegos et al. (2009).

It should be recognized that the data reported by Driscoll et al. (2009), showing the opposite result, pertain to a smaller data set of 3 batches of multi-chamber bags. In addition, the 3 batches examined by Driscoll have expiry dates ranging from May 2007 to January 2008, (corresponding to manufacturing dates May 2005–Jan 2006), in spite of the recent publication date. The data set presented in Table 1 is based on batches with expiry dates March 2010–2011 (corresponding to manufacturing dates March 2008–March 2009). Thus, the more recent data show $PFAT_5$ values consistently and with significant margin below the USP limit 0.05. Moreover, continuous improvement and optimization of manufacturing processes are regularly taking place in the pharmaceutical industry and this is also the case for multi-chamber bags (MCB's). We therefore regard the present data set as more conclusive and representative with respect to the current status of droplet size

distribution in the multi-chamber bags Kabiven and StructoKabiven.

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