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The pharmacopeial evolution of intralipid injectable emulsion in plastic containers: From a coarse to a fine dispersion

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ABSTRACT

On December 1, 2007, the United States Pharmacopeia (USP) adopted Chapter ⟨729⟩ entitled Globule Size Distribution in Lipid Injectable Emulsions that contains two globule sizing methods and criteria to measure the mean droplet diameter (MDD) and the large-diameter tail of the globule size distribution to meet pharmacopeial specifications. The first of these measures, as the intensity-weighted MDD expressed in nanometers, must be less than 500 nm. The second measure, as the volume-weighted percentage of fat greater than 5 μm or $PFAT_5$, must be less than 0.05%. These limits were first suggested in 2001 based on an analysis of 16 lipid injectable emulsions available worldwide. In 2004, the packaging of the innovator lipid emulsion product Intralipid™ was changed from conventional glass bottles to plastic containers in the U.S. A subsequent analysis of the emulsion in its new container showed it to be more coarse than its previous glass counterpart and now failed the $PFAT_5$ limit. In 2007, it was announced that Intralipid™ in plastic containers was reformulated to meet the pharmacopeial limits. To track the time course of its transition from a coarse to a fine dispersion, 31 lots of Intralipid with expiration dates spanning five years were investigated.

1. Introduction

Between 1945 and 1960, the experimental and clinical experience with the intravenous administration of long-chain triglyceride oil-in-water emulsions was marginally acceptable (Geyer, 1960). Dr. Robert P. Geyer was a 20th century pioneer in the field and conducted his research in the Department of Nutrition at the Harvard School of Public Health in Boston. The Nutrition Division, created from a generous 5-year grant from the Rockefeller Foundation, was founded and led by Dr. Frederick Stare, and he, Geyer and colleagues conducted a significant amount of work on intravenous fat emulsions during this time. Additional support for this work also came from the U.S. Army, and later from the Upjohn Company of Kalamazoo, MI, USA, using a product named Lipomul™ I.V., which was also marketed in Europe under the name of Infonutrol™ (Wretlind, 1981). This formulation was composed of 15% (w/v) cottonseed oil, 1.2% naturally occurring soybean lecithin, along with 0.3% of the synthetic emulsifier known as Pluronic F68, and 4% dextrose in sterile water for injection. Unfortunately, this well-studied product was plagued by a myriad of severe and potentially fatal adverse reactions that posed significant safety issues, with lipid droplet size being clearly recognized by Geyer as a potentially significant factor given "the particulate nature of the emulsion" when he said "*A simple means of determining the particle size distribution throughout the entire range would be of considerable aid in all such studies*" (Geyer, 1960). Clinical manifestations of adverse reactions, such as nausea and vomiting, chest or back pain, dyspnea, blood dyscrasias and liver dysfunction occurred and could be acute, i.e., after a single infusion of the lipid emulsion referred to as a "colloid reaction", or develop chronically, after several infusions, and termed simply "fat overload syndrome".

Also during this period of research on lipid inectable emulsions, a Swedish surgeon named Arvid Wretlind, was a guest researcher in the lab of Drs. Stare and Geyer (Stare, 1987). Dr. Wretlind subsequently returned to the Karolinska Institute in Stockholm, Sweden, and continued work on developing a clinically acceptable intravenous fat emulsion. One of the key breakthroughs in this research was devising a relevant preclinical animal model (Wretlind, 1981). Once the dose of fat in the animal model was appropriately adjusted for its energy expenditure or EE (e.g., dogs: fat dose, up to 9 g/kg; EE: 80–100 kcal/kg) vs. the average human EE (fat dose, up to 3 g/kg, 25–30 kcal/kg), the adverse events seen in the clinical setting were reproduced in the experimental setting. In other words, correctly lowering the dose (amount and infusion rate) of lipid emulsion

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in humans significantly reduced adverse infusion events, allowing broad clinical application of intravenous fat emulsions that could not be achieved in earlier clinical trials with Lipomul I.V. In 1961, Dr. Wretlind, along with Dr. Schuberth, succeeded in developing a suitable emulsion that appeared safe in humans with the introduction of a commercial product known as Intralipid™ by the Swedish pharmaceutical firm, Vitrum (Vinnars and Wilmore, 2003). Its main components (%w/v) included 10% soybean oil, 1.2% egg lecithin, 2.5% glycerol, and sterile water for injection. Over the next several years, other similar lipid injectable emulsions were introduced including, for example, Liposyn™, Lipofundin™, Travamulsion™, Lipiphysan™, Soyacal™, etc. Dr. Wretlind, writing a similar review as Geyer, but approximately 20 years later, also recognized the importance of a fine homogenous emulsion where droplet size was an important safety issue when he stated: "*A very rapid elimination occurs with fat emulsions that are unstable when mixed with blood, resulting in aggregates of the fat particles. The aggregates are then removed very rapidly or trapped in the lungs, liver and reticuloendothelial system*" (Wretlind, 1981).

Today, there are numerous lipid injectable emulsions of varying oil concentrations (i.e., 10, 20 and 30%, w/v) and composition (i.e., soybean, safflower, MCT, olive and fish oils). In 2001, a comparative report on the globule size distribution (GSD) of 16 different lipid emulsion formulations employing globule sizing techniques that focused on the mean droplet size and the large-diameter tail of the GSD, was published (Driscoll et al., 2001). From this work, potential pharmacopeial limits were recommended in reference to the most recent (at that time) United States Pharmacopeia (USP) in-process revision of Chapter ⟨729⟩ entitled "Globule Size Distribution in Intravenous Emulsions" (Globule Size Distribution in Intravenous Emulsions, 1998). Two sizing methods with specific limits were recommended and included: (1) using light scattering, the mean droplet size should not exceed 450 nm and (2) using light obscuration, the large-diameter tail, defined as the volume-weighted percent of fat greater than 5 μm or $PFAT_5$ must be <0.05% of the total dispersed phase. A review and critique of the various globule sizing techniques for lipid injectable emulsions followed (Driscoll, 2002). A table of the common lipid injectable emulsions was also provided in support of the above recommendations. An updated and expanded version now appears in Table 1.

In 2003, the USP began a new effort to revise Chapter ⟨729⟩ that would now include specific pharmacopeial limits on the globule size distribution of lipid injectable emulsions. Subsequently in 2004, a completely revised version of Chapter ⟨729⟩ was published (Globule Size Distribution in Lipid Injectable Emulsions, 2004) along with an accompanying Stimuli Article (Driscoll, 2004) to explain the rationale for the selection of the proposed globule sizing techniques and limits. A second revision of USP ⟨729⟩ was published in 2005 and slightly refined the limits further, identifying a two-step procedure with Method I via light scattering, to limit the intensity-weighted mean droplet size to <500 nm, and Method II via light obscuration, which limits the volume-weighted $PFAT_5$ of <0.05% (Globule Size Distribution in Lipid Injectable Emulsions, 2005). These globule size limits applied to all lipid emulsions in the U.S., irrespective of the concentration or the composition of the lipid phase of the dispersion, and were intended to achieve pharmaceutical equivalence amongst all commercially available lipid emulsion formulations.

During this time, the packaging and distribution of Intralipid™ in conventional glass bottles in the U.S. was stopped, and importation of a newly introduced Intralipid™ product in plastic

Table 1
Physical characteristics of commercially available lipid injectable emulsions[a].

Product	Lot number	Months to ED[b]	GN_5/mL[c]	$PFAT_5$[d]	MDD[e]
Soybean oil only					
Intralipid 10%	12202-51	9	75,148	0.009%	286
Intralipid 20%	10776-71	6	8,645	0.005%	340
Intralipid 30%	16115-51	17	12,504	0.007%	420
Kabiven (P)[f]	**UB10891**	**6**	**2,440,123**	**0.133%**	**298**
Liposyn III 10%	45-351-DE	18	75,456	0.013%	263
Liposyn III 20%	43-440-DE	12	73,822	0.005%	307
Liposyn III 30%	41-395-DE	10	340,158	0.029%	301
Lipofundin-N 10%	8085A83	15	3,856	0.001%	272
Lipofundin-N 20%	8082A84	15	67,508	0.005%	332
Soybean oil mixtures					
Liposyn II 20%	47-412-DE	16	45,637	0.004%	278
ClinOleic 20%	9801376	16	11,598	0.001%	276
Structolipid 20%	18417-51	5	123,661	0.009%	276
Lipoplus 20%	9235A32	15	83,642	0.008%	263
SMOFlipid 20%	U61566	6	359,420	0.019%	312
Lipofundin MCT 10%	8042A81	13	44,930	0.008%	266
Lipofundin MCT 20%	8075A81	15	114,299	0.009%	287
Lipovenous MCT 20%	KK1569	20	15,483	0.001%	275
Critilip 20%	KV1249B	17	205,183	0.012%	330
ClinOleic 20% (P)	06F23A90	9	92,915	0.006%	284
Nutriflex peri (P)	5422A150	18	133,998	0.009%	310
Nutriflex special (P)	5404A159	17	112,927	0.008%	308
StructoKabiven peri (P)	**1032674**	**16**	**3,649,600**	**0.226%**	**313**
StructoKabiven 1100 (P)	**1033521**	**18**	**2,869,770**	**0.180%**	**318**

Boldface are recent failures, excluding current study emulsions (Driscoll et al., in press).

[a] Adapted and expanded from Driscoll et al. (2001, 2006b, in press, 2008b).

[b] Months to ED = months to expiration date at time of test.

[c] GN_5/mL = globule number > 5 μm per mL.

[d] $PFAT_5$ = percentage (volume-weighted) of fat > 5 μm determined by LE/SPOS.

[e] MDD = mean droplet diameter in nanometers determined by DLS.

[f] (P) plastic container.

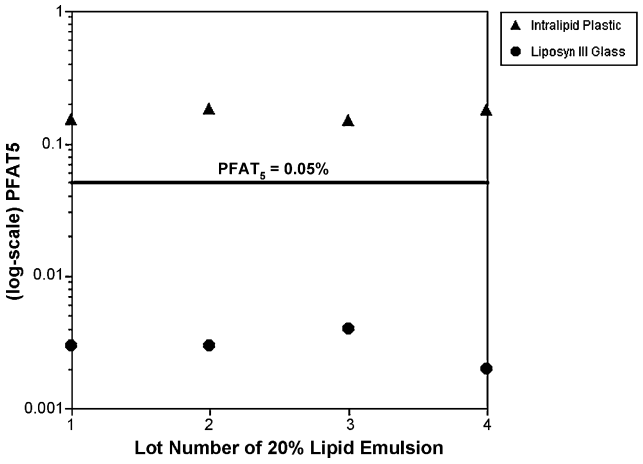

Fig. 1. Comparison of newly introduced 20% soybean oil emulsions as Intralipid™ in plastic containers vs. conventional glass bottles (Driscoll, 2006b).

containers, made exclusively in Uppsala, Sweden, was announced by its U.S. distributor (Baxter Communication, 2004). A subsequent investigation of four separate lots of the newly introduced product, Intralipid™ 20% in plastic containers was compared to an equal number of a comparable soybean oil-in-water emulsion (Liposyn™ 20%) in glass bottles, revealed all those in glass passed ($PFAT_5$: 0.005 ± 0.001%) Method II of proposed USP ⟨729⟩ as shown previously (Driscoll et al., 2001), but now all Intralipid™ lots in plastic were more coarse and all failed, with an average $PFAT_5$ of 0.166 ± 0.016% as shown in Fig. 1 (Driscoll and Bistrian, 2005a). A follow-up investigation of the role of the plastic container in causing the observed failure to meet Method II of USP ⟨729⟩ suggested the defect in the globule size distribution (GSD) was more likely a manufacturing issue (Driscoll et al., 2005b), which was later confirmed to be specific to a single manufacturer and not the plastic container involving two of their lipid emulsion products, Intralipid™ and Structolipid™ (Driscoll, 2007a). Further investigation of the abnormal GSD seen with Intralipid™ in plastic when applied as a parenteral nutrition additive in adult all-in-one (AIO) or total nutrient admixtures (TNA) (Driscoll et al., 2007b), or as an extemporaneously prepared syringe of undiluted 20% lipid injectable emulsion during a simulated neonatal infusion (Driscoll et al., 2007c), showed the plastic-based Intralipid™ was less stable under both conditions of typical clinical use.

On January 15, 2007 officials at Baxter Healthcare Corporation sent a Letter to the Editor regarding a 2006 paper reviewing the current status of lipid injectable emulsions in nutrition support (Driscoll, 2006a), and specifically criticized the value of Method II in assessing the stability and/or safety implications for lipid injectable emulsions (Zaloga et al., 2007). On February 21, 2007, nonetheless, Baxter announced to its U.S. customers that Intralipid™ was now in compliance with USP ⟨729⟩, and that the re-formulation of the product to meet USP limits was completed by September of 2006 (Baxter Communication, 2007). Finally, on June 1, 2007, the USP announced the adoption of Chapter ⟨729⟩, with an effective date of December 1, 2007 (USP 2nd Supplement, 2007) and it now appears in the official 2008 compendium (Globule Size Distribution in Lipid Injectable Emulsions, 2008).

In an attempt to chart a time line of the formulation changes affecting the GSD of Intralipid™ in plastic containers from its introduction in the U.S. in 2004 to the present, data on available lots were collated in chronological manufacturing order and analyzed for this investigation.

2. Materials and methods

Thirty-one lots of 20% Intralipid™ injectable emulsion[2] retrieved from hospital inventory were evaluated for their compliance with the globule size methods outlined in Chapter ⟨729⟩ of the USP The "20%" formulation was chosen as it is the most commonly used concentration in both adults and in premature and full-term infants. All lots of Intralipid™ 20% in plastic containers that were studied had expiration dates varying from May of 2006 to January of 2010. According to the 18-month FDA-approved expiration date of this dosage form, these products were therefore manufactured between November of 2004 to July of 2008. These are important dates considering the 2007 announcement of full compliance of Intralipid™ with USP ⟨729⟩ that specifically stated the following: "*During the course of implementing ongoing process improvements, Fresenius Kabi now manufactures INTRALIPID I.V. Fat Emulsion in plastic containers with a $PFAT_5$ < 0.05%. INTRALIPID 20% customers began receiving this product in the September 2006 timeframe. All INTRALIPID I.V. Fat Emulsion products were transitioned by the end of 2006*" (Baxter Communication, 2007). Of the 31 individual lots evaluated for compliance with USP ⟨729⟩ as described above and given the approximate 5 year range of expiration dates, it was anticipated that a specific time point would be identified when the Intralipid products crossed over from the period when the product was coarse and failed, to when it returned to a fine emulsion and passed pharmacopeial globule size limits, coincident with the aforementioned public announcement. Two distinct groups based on a $PFAT_5$ designation of >0.05% or <0.05% were therefore expected in this assessment, given the broad base of representative emulsions available for study. Thus, the final analysis will include Group 1, representing the early lots of Intralipid™ that failed the limits of USP ⟨729⟩ and Group 2, comprising the later formulations that passed.

The GSDs of the emulsions were assessed according to USP Chapter ⟨729⟩ (Globule Size Distribution in Lipid Injectable Emulsions, 2008). The intensity-weighted mean droplet diameter (MDD), as per Method I of USP ⟨729⟩ that cannot exceed 500 nm, was determined via dynamic light scattering[3] for 24/31 lots of Intralipid™ 20%. The principal focus of this investigation was compliance with Method II of USP ⟨729⟩. As such, the volume-weighted percent of fat greater than 5 μm or $PFAT_5$, that cannot exceed 0.05% of the dispersed oil phase, was determined using light obscuration employing a single-particle optical sensing optical sensing technique (LE/SPOS[4]) for all lots. The starting size threshold for these analyses was set a 1.8 μm, and the globule size data from the large-diameter tail is reported at ≥5 μm (USP limit), and are expressed as either the volume-weighted PFAT or number per mL.

The detailed application of these globule sizing procedures were recently described (Driscoll et al., 2006b). All samples (bags) were analyzed in triplicate. Ideally, three separate bags per lot were desirable, but not possible in every case. The data were grouped by year of manufacture (18 months before expiration date or ED). This was done to show the extent of the tail of the distribution over time, particularly during the reformulation of the product in its transition from a coarse to a fine dispersion. All pharmacopeial data are expressed at the mean ± SD.

[2] INTRALIPID I.V. Fat Emulsion, lot numbers: 1019065, 1021723, 1022373, 1022700, 1022848, 1023285, 1023538, 1031218, 1031220, UC11201, UC11569, UC11572, UC11678, UC11851, UE12534, UE12818, UE13022, UK15909, UK15776, UL16319, UL16323, UL17048, UM17257, UM17696, UM17698, WA10662, WA10664, WL17366, 10BA1008, 10BA1015, 10BB2174, manufactured by Fresenius Kabi, Uppsala, Sweden and distributed in the U.S. by Baxter Healthcare, Deerfield, IL, USA.

[3] Nicomp 370 Submicron Analyzer, Particle Sizing Systems, Santa Barbara, CA, USA.

[4] AccuSizer 780/APS, Particle Sizing Systems, Santa Barbara, CA, USA.

Based on separating the GSD data into two groups statistical assessments were made. A one-way analysis of variance (ANOVA) was performed on the globule size data for plastic Intralipid™ with those in Group 1 (pre-compliant) and in Group 2 (compliant) with USP ⟨729⟩, with Group as the independent variable, and MDD and $PFAT_5$ as the dependent variable(s). Statistical significance was set at $p < 0.05$.

3. Results

The data on the emulsions included in this report were collected in three stages: (1) Pre-compliant (with ⟨729⟩) period, Lots 1–9; (2) Transition period, Lots 10–21; and (3) Compliant period, Lots 22–31. Of the 31 individual lots tested, 15 were identified as pre-compliant and were assigned to Group 1, while 16 were compliant and assigned to Group 2. The lots assessed in Group 1 represented products manufactured during May 2004 to October of 2006 (corresponding to expiration dates o November of 2006 to April of 2008) and those in Group 2 were made during October of 2006 to July of 2008 (corresponding to expiration dates of April of 2008 to January of 2010). The data obtained from the globule size measurements for the 31 lots of Intralipid™ tested appears in Table 2. With respect to Method I of USP ⟨729⟩, the MDD for both groups met the limit of <500 nm. Group 1 had an overall average MDD of 331 ± 8 nm (range: 313–344 nm) compared to Group 2 at 318 ± 8 nm (range: 302–331 nm), and was significantly higher in Group 1 vs. 2 ($p < 0.001$). For Method II of USP ⟨729⟩, the $PFAT_5$ limit was also significantly higher in Group 1 (0.117 ± 0.034%; range: 0.073–0.184%) vs. Group 2 (0.018 ± 0.006%; range: 0.001–0.030%), $p < 0.001$.

A specific cross-over or "breakpoint" in formulations failing to pass $PFAT_5$ limits was identified between lots 15 and 16 in this study, which were actually manufactured in the same month based on their identical expiration dates. In fact, a reduction in the $PFAT_5$ level of >70% was noted between these two lots, and the fineness in the emulsion continued to improve with subsequent lots manufactured. From the available samples for analysis, all Intralipid™ products met the limits of Method I irrespective of time period or grouping, but compliance with Method II of USP ⟨729⟩ was not achieved until approximately 30 months after its introduction into the U.S, occurring in the September–October 2006 time frame as noted in Fig. 2, and as indicated by the distributor/manufacturer (Baxter Communication, 2007). Fig. 3 plots the same data, but now expressed as the number of globules/mL vs. lot no. by year of manufacture.

4. Discussion

The application of light obscuration in assessing the stability of lipid injectable emulsions was initially focused on lipid-based parenteral nutrition (PN) therapy (Sayeed et al., 1986, 1987a,b; Tripp et al., 1990; Bullock et al., 1992; Mehta et al., 1992) into a

Table 2
Intralipid in plastic—$PFAT_5$ values over time, 2004 to present.

	Lot number	Exp. date	Manuf. Date[a]	Months to ED[b]	GN_5 per mL[c]	$PFAT_5$ (%)[d]	MDD (nm)[e]
1 (1)[f]	1019065	11/2006	05/2004	17	2,428,633	0.131 ± 0.005	–
2 (1)	1021723	02/2006	08/2004	14	2,625,140	0.153 ± 0.006	–
3 (1)	1022373	03/2006	09/2004	15	3,028,001	0.184 ± 0.001	–
4 (1)	1022700	03/2006	09/2004	15	2,952,563	0.179 ± 0.001	–
5 (1)	1022848	04/2006	10/2004	12	2,868,348	0.166 ± 0.003	–
6 (1)	1023285	04/2006	10/2004	12	1,205,634	0.126 ± 0.008	–
7 (1)	1023538	05/2006	11/2004	17	2,641,176	0.149 ± 0.004	–
8 (2)	1031218	04/2007	10/2005	16	2,390,704	0.135 ± 0.009	327 ± 9
9 (2)	1031220	04/2007	10/2005	16	2,595,298	0.140 ± 0.010	319 ± 4
10 (2)	UC11201	02/2008	08/2006	10	1,644,106	0.093 ± 0.009	335 ± 5
11 (2)	UC11569	02/2008	08/2006	10	1,489,175	0.081 ± 0.004	338 ± 5
12 (3)	UC11572	02/2008	08/2006	10	1,490,834	0.081 ± 0.004	338 ± 3
13 (2)	UC11678	02/2008	08/2006	10	2,146,244	0.117 ± 0.008	333 ± 8
14 (1)	UC11851	02/2008	08/2006	10	1,909,149	0.109 ± 0.008	325 ± 2
15 (3)	UE12534	04/2008	10/2006	12	1,504,976	0.082 ± 0.005	332 ± 2
Breakpoint: All subsequent emulsions tested meet Method II of USP ⟨729⟩							
16 (2)	UE12818	04/2008	10/2006	12	328,910	0.023 ± 0.007	319 ± 4
17 (3)	UE13022	04/2008	10/2006	12	284,956	0.018 ± 0.002	330 ± 2
18 (3)	UK15909	09/2008	03/2007	17	272,880	0.017 ± 0.001	312 ± 8
19 (3)	UK15776	09/2008	03/2007	17	217,712	0.014 ± 0.003	319 ± 6
20 (3)	UL16319	10/2008	04/2007	18	230,333	0.013 ± 0.002	313 ± 3
21 (3)	UL16323	10/2008	04/2007	18	220,748	0.013 ± 0.001	320 ± 3
22 (3)	UL17048	10/2008	04/2007	3	53,711	0.005 ± 0.001	313 ± 4
23 (3)	UM17257	10/2008	04/2007	3	53,462	0.005 ± 0.001	310 ± 2
24 (3)	UM17696	11/2008	05/2007	4	40,490	0.004 ± 0.001	320 ± 2
25 (3)	UM17698	11/2008	05/2007	4	36,022	0.003 ± 0.001	315 ± 5
26 (3)	WA10662	12/2008	06/2007	5	40,091	0.004 ± 0.001	323 ± 2
27 (3)	WA10664	12/2008	06/2007	5	35,830	0.003 ± 0.000	319 ± 5
28 (3)	WL17366	10/2009	04/2008	15	34,718	0.003 ± 0.001	322 ± 1
29 (3)	10BA1008	12/2009	06/2008	17	32,022	0.003 ± 0.001	320 ± 2
30 (3)	10BA1015	12/2009	06/2008	17	18,286	0.002 ± 0.001	323 ± 2
31 (3)	10BB2174	01/2010	07/2008	18	19,149	0.002 ± 0.000	324 ± 2

[a] Manufacture date: assumes 18 months before expiration date.
[b] Months to expiration date at time of test
[c] GN_5 = globule numbers per mL greater than 5 μm.
[d] $PFAT_5$ = volume-weighted percent fat greater than 5 μm; *according to Method II of USP Chapter* ⟨729⟩*, it must be less than 0.05%.*
[e] MDD = intensity-weighted mean droplet diameter in nanometers (nm); *according to Method I of USP Chapter* ⟨729⟩*, it must be less than 500 nm.*
[f] (1, 2 or 3) = the number of bags tested per lot; all bags in triplicate.

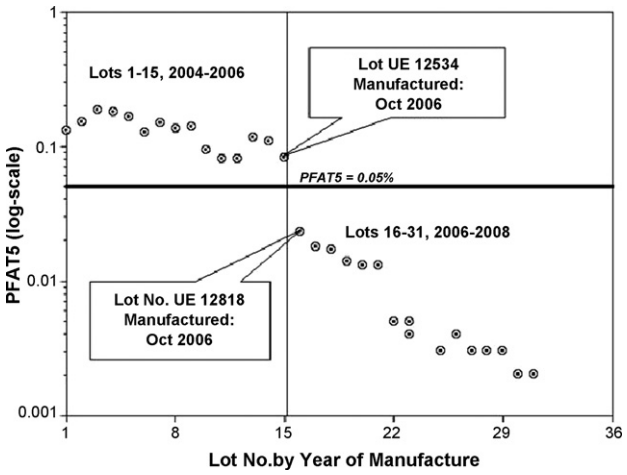

Fig. 2. Plot of the varying globule size distributions as $PFAT_5$ levels of intralipid in plastic (2004–2008).

single bag (i.e., AIO or TNA formulations) for intravenous administration in patients with a dysfunctional gastrointestinal tract. In each of these reports, the results from light obscuration on the large-diameter tail of the GSD were presented, but without limits, and stability, per se, was ultimately determined on the basis of visually evident separation of the dispersed oil phase from the continuous water phase, or not. Then, in 1995, a large study of 90 lipid-based AIO or TNA formulations explored a possible quantitative relationship between the population of large-diameter (>5 μm) fat globules (as the volume-weighted percent of fat determined via light obscuration) and the emergence of visually obvious phase separation. When $PFAT_5$ was >0.4%, visibly evident phase separation was noted. In contrast, MDD measurements taken by DLS bore no relation to these changes in emulsion stability (Driscoll et al., 1995). At the time of this study, the USP had just published an "in process" revision of what was then known as Chapter <728> (Globule Size Distribution in Intravenous Emulsions, 1995), which, like previous versions (Globule Size Distribution in Intravenous Emulsions, 1991, 1994), was devoid of globule size limits. In fact, it was a stated purpose in the above study (Driscoll et al., 1995) that the work was undertaken: "*. . .because light obscuration is now the preferred method of determining the number of particulates in large-volume (aqueous) injections, we hope to provide evidence to support its application to intravenous fat emulsions and TNA* [total nutrient admixture] *formulations*". Thus, USP <788> (Particulate Matter in Injections, 1994) served as a template for the eventual pharmacopeial development of maximum tolerable particle/globule sizing limits for lipid injectable emulsions.

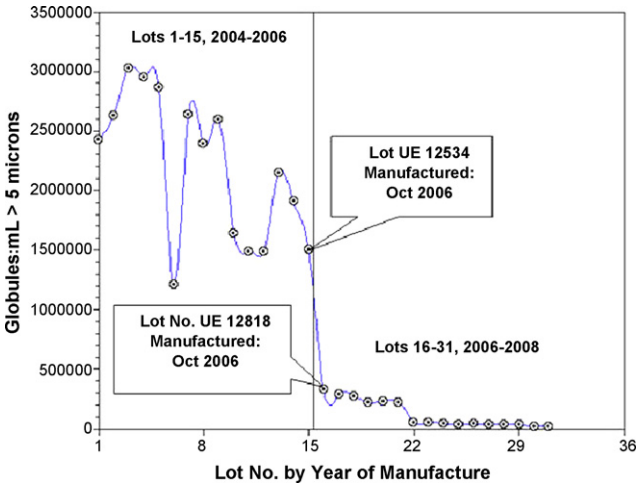

Fig. 3. Plot of the varying globule size distributions as globule number/mL >5 μm of intralipid in plastic (2004–2008).

Presently, USP ⟨729⟩ stipulates GSD limits on the MDD as no >500 nm (Method I) and the large-diameter tail as $PFAT_5$ <0.05% (Globule Size Distribution in Lipid Injectable Emulsions, 2008). Until the introduction of Intralipid™ in plastic containers in the U.S. in 2004, all previous commercial lipid injectable emulsions (including Intralipid in *glass* containers) was within these pharmacopeial limits (Driscoll et al., 2001). The current study confirms the insensitivity of light scattering to large-diameter fat globules described previously (Driscoll et al., 1995) showing all Intralipid™ products would pass Method I of USP ⟨729⟩, despite the obvious differences detected in the coarseness of the large-diameter tails between formulations tested in Group 1 (pre-compliance with Method II) vs. Group 2 (compliant). Of note, the MDD of Group 1 (331 ± 8 nm) was significantly larger ($p < 0.001$) than Group 2 (318 ± 8 nm), but importantly, both were compliant with Method I of USP ⟨729⟩. This difference most likely represents the consequences of actions taken to reduce the large-diameter tail to meet $PFAT_5$ <0.05% during its reformulation.

With respect to Method II of USP ⟨729⟩ ($PFAT_5 < 0.05\%$), the introduction of Intralipid™ in plastic containers into the United States in March or April of 2004 which were found to be more significantly coarse than their glass counterparts, now failed to meet pharmacopeial specifications (proposed at the time) for $PFAT_5$ levels. According to a recent company communication to its customers (Baxter Communication, 2007), Intralipid™ in plastic appears to have been distributed in its "coarse state" until September or October of 2006 or for approximately 30 months in the U.S. following its introduction in the spring of 2004. In Europe, Intralipid™ in plastic was introduced a couple of years earlier, so clinical exposure to this coarse formulation may have continued for up to five years. During this time in the U.S., the $PFAT_5$ levels from 15 separate lots tested in Group 1, were, on average, more than two times the upper limit of Method II ($0.117 \pm 0.034\%$). In addition to the data that coarse Intralipid™ products produce less stable extemporaneously prepared dosage forms (all-in-one admixtures or AIOs, prefilled lipid syringes for neonates) than those that pass USP ⟨729⟩ limits as discussed earlier, more recent evidence has shown that these products have additional disadvantages. For example, the stability of pre-mixed AIOs from the manufacturer in multi-compartment bags are also less stable after mixing compared to lipid emulsions that comply with USP ⟨729⟩ (Driscoll et al., in press). Moreover, infusion of coarse ($PFAT_5 > 0.05\%$) vs. fine AIOs ($PFAT_5 < 0.05\%$) to adult laboratory animals showed the coarse AIOs had significant alterations in the clearance of plasma triglycerides, as well as significantly worsened hepatic injury compared to those receiving fine AIOs (Driscoll et al., 2008a). Finally, in premature critically ill infants where parenteral lipid therapy is necessary in the absence of enteral intake (Driscoll et al., 2008b), coarse Intralipid in plastic vs. fine Intralipid in glass containers was associated with significantly higher incidence of hypertriglyceridemia (Martin et al., 2008).

The subsequent 16 lots tested in this investigation from Group 2 met pharmacopeial specifications of Method II of USP ⟨729⟩ ($0.018 \pm 0.006\%$). In fact, the data shows a significant improvement in the fineness of the emulsion over time, and the current data from Group 2 suggests that Intralipid™ in plastic can be considered pharmaceutically equivalent to existing formulations that meet pharmacopeial specifications.

5. Conclusions

In summary, the initial change from glass to plastic containers for Intralipid™ resulted in a uniquely coarse formulation that failed pharmacopeial limits. There is laboratory and clinical evidence suggesting this coarse formulation could be problematic under conditions of patient use. At present, it appears the abnormal GSD of Intralipid™ in plastic containers has been corrected to meet pharmacopeial specifications. Nonetheless, compliance with the $PFAT_5$ parameter of Method II of USP ⟨729⟩, appears to be an important measure of the stability and safety of these dispersions, a factor previously recognized by the modern pioneers in this field.

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