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Evaluation of Quantitative Capsule Rupture Test Methods and Data Variability in Generic Omega-3 Capsule Applications

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PURPOSE

LOVAZA® (Omega-3-Acid Ethyl Esters Oral Capsule) was approved in 2004 as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. The current product-specific guidance (PSG) from the Agency recommends the use of quantitative capsule rupture test (QCRT) to compare three batches of reference and test products for in vitro demonstration of bioequivalence. The release of eicosapentaenoic acid ethyl ester (EPAee) and docosahexaenoic acid ethyl ester (DHAee) in three batches of reference and test products was measured and compared. The challenge that many generic drug developers faced when demonstrating in vitro bioequivalence of an omega-3 generic capsule product is the high variability (%RSD is greater than 20) in the early time points of the capsule's release profiles that makes it difficult to establish bioequivalence between the generic test product and the reference product. This work seeks to understand where the observed variability comes from by examining data and methods submitted in Abbreviated New Drug Applications (ANDAs).

METHOD

We analyzed QCRT data and methods from Omega-3-Acid Ethyl Esters ANDA applications (both approved and those under review). The release of EPAee and DHAee in QCRT at early time points (i.e., time points less than 30 mins) is summarized and compared across applications. We compared the drug release average, range, and relative standard deviation between different ANDAs and the reference product. We also analyzed the method optimization and validation process of QCRT and evaluated the effect of method conditions on drug release profile.

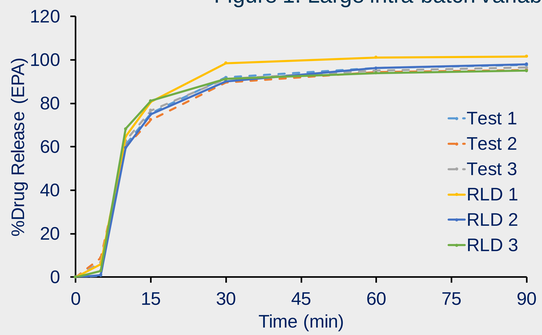
RESULTS

High variability at early release time of QCRT was observed in most of the applications, which may lead to failure of subsequent assessment on bioequivalence between the generic and reference drug products. In addition, inadequate method optimization was identified as another major issue, which led to insufficient discrimination power of the test method.

Table 1. Major deficiencies identified in BE assessments

Deficiencies	%ANDAs affected
High variability in early time points	~90%
Rapid release - not discriminatory	~20%
Insufficient optimizations for QCRT method	~50%

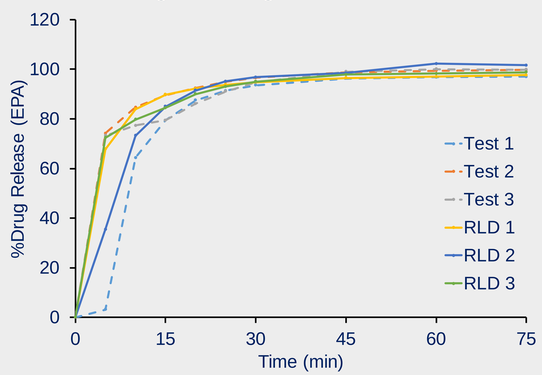
Figure 1. Large intra-batch variability in both a proposed ANDA and RLD



	Variability (%RSD) at Various Collection Times (min)							
	5	10	15	20	25	30	60	90
Test 1	245	10	6.2	3.7	2.8	2.3	1.7	1.6
Test 2	193.7	9.7	3.9	2.5	2.2	1.9	1.5	1.3
Test 3	135.8	11.7	5	3.2	2.5	2.1	1.2	0.9
RLD 1	150.2	10	5.3	2.9	2.4	2.1	1.6	1.3
RLD 2	217.1	11.3	6.4	3.3	2.3	2.1	1.8	1.7
RLD 3	171.3	15.3	11.3	7.1	5.7	4.8	3.1	2.5

Figure 1. Drug release of an ANDA and the RLD where the drug release profiles (left figure) between the test and reference is comparable, but the intra-batch variability (in %RSD) is high (greater than 20%) at early time point (at 5 mins, right table).

Figure 2. Large inter-batch and intra-batch variability in both a proposed ANDA and RLD



	Variability (%RSD) at Various Collection Times (min)								
	5	10	15	20	25	30	45	60	75
Test 1	81.4	36.9	23.7	16.8	12.7	8.8	4.1	2.2	1.5
Test 2	116.4	28.1	12.5	6	3.6	2.5	1.1	1.1	1.1
Test 3	17.6	4.6	5.5	5.1	3.1	2	1.4	0.8	0.9
RLD 1	30.7	10.8	6.6	4.5	3.6	3.1	1.9	1.7	1.6
RLD 2	62.9	18.2	11.8	4.8	3.9	2.7	2.3	2.7	2.4
RLD 3	29.3	21.1	15	11.8	8.7	6.7	2.9	1.3	1.1

Figure 2. Drug release of an ANDA and the RLD where the drug release profile (left figure) of the test is within the reference's release profile range, but the inter-batch variability and intra-batch variability are high at early time points (less than 15 mins, right table).

CONCLUSION

The most challenging BE issue with many Omega-3 capsule ANDAs is the large variability at early time points of the release, as observed in most of the applications. By examining the variability within the affected ANDA applications, we believe the causes of this observed variability could be within the QCRT method or due to issues within the drug products.

Both the RLD and the proposed generics can exhibit large variation because the gelatin capsules can cross-link, during storage and aging, which would result in delaying in the capsule rupture and slow down the release of the active pharmaceutical ingredient (API). Therefore, to minimize the variability, QCRT should be conducted on batches made during similar time periods.

QCRT method conditions may also contribute to the variability. For example, the inclusion of enzyme and surfactant can facilitate the rupture of capsules and release of EPAee and DHAee that would result in the rapid release of the drug. The lack of optimization in these parameters would result in the QCRT not being sufficiently discriminating for differences between formulations and process changes. In order to develop a generic Omega-3 capsule having the equivalent QCRT profile as the RLD's, it is critical for applicants to have tight controls over both method and product conditions.

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DISCLAIMER

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