Current Thinking and Rationale for When an In Vitro Approach to Establish Bioequivalence May be Recommended for an Injectable Suspension

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Introduction

An in vivo pharmacokinetic (PK) study is typically recommended to demonstrate BE for systemically acting injectable suspension products. However, in vitro BE approaches have recently been recommended in the product-specific guidances (PSGs) for certain injectable suspension products. These are generally for injectable drug substance suspensions, in which the drug substance is the only insoluble component in the formulation. This work provides an overview of the current thinking on how and when an in vitro bioequivalence (BE) approach may be recommended for injectable suspension products.

Materials and Methods

A comprehensive review of the scientific literature and FDA database was conducted on injectable drug substance suspension products. Special attention was paid to the scientific understanding of the drug release mechanism, critical quality attributes (CQAs) that could affect bioavailability and the formulation design space for drug product performance and pharmacokinetic property.

Table 1. Categories and examples of injectable drug substance suspension and the recommended BE study in PSGs

Examples / Category	NDA#	Drug substance	Route; Dosing interval	Indication	PSG recommendation
Group I **Immediate release suspensions**	050794	Azacitidine	IV, SC; Daily for 7 days (a cycle), repeat cycles every 4 weeks; 4-6 cycles	Treatment of patients with specific FAB myelodysplastic syndrome subtypes	In vitro only
	210583	Meloxicam	IV; Once daily	Management of moderate-to-severe pain	In vitro only
	205579	Dantrolene sodium	IV; Single dose; 75 mins prior to surgery	Treatment or prevention of malignant hyperthermia	In vitro only
Group II **Extended release suspensions for short-term use**	011757	Methylprednisolone acetate	Injection; Not specified	Anti-inflammatory glucocorticoid	In vitro or in vivo
	012041	Triamcinolone acetonide	Intra-articular or intralesional; Not specified	Anti-inflammatory glucocorticoid	In vitro or in vivo
	022048	Triamcinolone acetonide	Intravitreal; Not specified	Ophthalmic diseases, visualization during vitrectomy	In vitro
	050141	Penicillin G Benzathine	IM; Single injection or 7 days interval for three doses or once a month or biweekly	Treat or prevent infections caused by bacteria	In vitro or in vivo
	14602	Betamethasone acetate and betamethasone sodium phosphate	Injection; Not specified	Anti-inflammatory glucocorticoid	In vitro or in vivo
Group III **Extended release suspensions for long-term use**	202971	Aripiprazole	IM; Monthly	Schizophrenia, bipolar I disorder	In vivo
	207533	Aripiprazole lauroxil	IM; Monthly, monthly or every 6 weeks, every 2 month	Schizophrenia	In vivo
	022264, 207946	Paliperidone palmitate	IM; Monthly, 3 months	Schizophrenia, Schizoaffective disorder	In vivo
	022173	Olanzapine pamoate	IM; 2 weeks, 4 weeks	Schizophrenia	In vivo
	212888	Cabotegravir; Rilpivirine	IM; 2 months	HIV-1 infection treatment	In vivo
	215499	Cabotegravir	IM ; 2 months	Reduce the risk of sexually acquired HIV-1 infection	In vivo
	020246	Medroxyprogesterone Acetate (MPA)	IM ; 3 months (not for >2 years use)	Prevent pregnancy	In vitro or in vivo

Main Finding

In vitro BE approaches rely on a totality of evidence approach and are developed based on the understanding of the critical quality attributes and performance tests that may affect BE. The underlying foundation of the approach is that the generic injectable product should be formulated qualitative (Q1) and quantitative (Q2) the same to the reference listed drug (RLD). When an injectable drug substance suspension product is Q1/Q2 the same, the only possible differences are in the arrangement of matter, i.e., the physiochemical properties of the product. Differences in the arrangement of matter for these complex products can arise from differences in manufacture, processing, or excipients used. Therefore, studies to demonstrate comparable physiochemical properties of Q1/Q2 formulated generic drug product and reference standard products ensures similar product performance and thus BE.

For injectable drug substance suspension products, the dissolution rate of drug, and thus bioavailability of the drug, is governed by particle size distribution (PSD) and solubility of the drug substance. Population bioequivalence (PBE) statistical analysis of PSD is therefore recommended to demonstrate comparable PSD between test and reference standard (RS). In vitro drug release testing (IVRT) serves as another pivotal study to ensure sameness between test and RS.

- **F1**: API was used as received
- **F2**: The API was recrystallized using acetone-water (1:1) system (water as anti-solvent). Following drying under vacuum at 40° C, the API was passed through a 45 µm sieve. The API was added to the suspending media to achieve suspension F1.
- **F3**: processing based on F1 using probe sonication for 5 mins with 10% of pulse. The formulation underwent 10 s sonication, stop 1s.
- **F4**: Same as F1 except using different vendor of PEG3350 (Spectrum Chemical for F1 and BASF for F4)

Formulation	Dv10	Dv50	Dv90	Span
F1	7.21±0.42	13.40±0.54	24.09±0.74	1.26±0.04
F2	8.73±0.31	21.73±0.28	41.08±0.53	1.49±0.04
F3	0.69±0.33	3.67±0.43	10.13±0.99	2.61±0.44
F4	7.00±0.13	13.03±0.23	23.44±0.37	1.26±0.01
RLD	10.37±0.99	18.23±1.36	30.61±1.78	1.11±0.05

Figure 1. Compositionally equivalent MPA suspensions prepared with different particle sizes

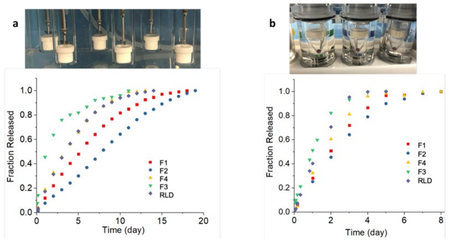

Figure 2. In vitro release profiles of the RLD and Q1/Q2 equivalent suspensions (with different particle sizes) obtained using: a) the USP apparatus 2 with enhancer cells; and b) USP apparatus 4 with semisolid adapters at 37 ± 0.5 ◦C (mean ± SD, n = 3)

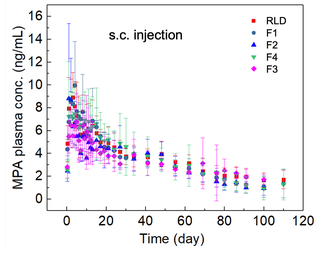

Figure 3. The in vivo release of the prepared suspensions and the RLD Depo-SubQ Provera 104 were investigated in female New Zealand White rabbits (n=6, mean ± SD)

Results and Discussion

With the scientific understanding of the critical quality performance for injectable drug substance suspension, in vitro BE approaches have been recommended for immediate release as well as short term use drug substance suspension products. However, the application of the in vitro BE approaches to long-term use suspension products remains limited because of the higher perceived risk and concerns of the potential accumulation of any differences in long-term use products. Current efforts are focused on addressing these concerns by gaining a comprehensive understanding of the clinically allowed pharmacokinetic formulation design space for long-term use suspension products . Outcomes from GDUFA-funded research #HHSF223201710135C (Figures 1, 2 and 3) [1,2] as well as FDA's knowledge have been leveraged to recommend the first in vitro BE study in the PSG for a long-term use product, medroxyprogesterone acetate (MPA) injection[3].

As discussed, PBE analysis is recommended to demonstrate comparable PSD between test and RS. Formulation for injectable drug substance suspension in micron size range may be designed to be flocculated for desired physical stability. Flocculation is a process where small primary particles in suspension collide to form loosely held larger particles that can be redispersed (Figure 4)[4]. The flocculation behavior is impacted by the primary particle and the excipients (e.g., surfactant). In general, the finished product is a mixture of flocculated and primary particle while the flocculated particle is very sensitive to the shear in PSD measurement. Therefore, both comparable flocculated and primary particles should be captured for PSD study. The most scientific and robust approach is to conduct PBE analysis under conditions that capture the majority of primary particles.

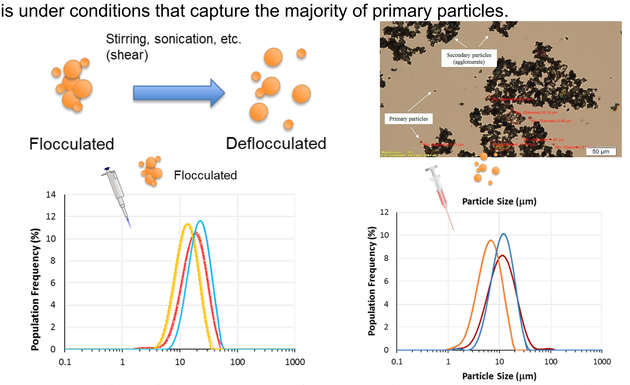

Figure 4. Flocculation behavior of triamcinolone acetonide injectable suspension

Conclusion

An in vitro BE approach is based on the understanding of the critical quality attributes of the product that affect bioequivalence and relies on totality of evidence. It has been readily applied in immediate release suspension products and extended release suspension product for short-term use. Ongoing efforts are collecting evidence to support the use of in vitro alternative BE approaches for long-term use suspension products.

Disclaimer

The poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

Reference

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