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Evaluation of U.S. FDA Approved Generic Oral Solution Products

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PURPOSE/OBJECTIVE

For oral solution products, according to 21 CFR 320.22, the in vivo bioequivalence study may be waived if the generic (i) contains the same active drug ingredient in the same concentration and dosage form as the reference listed drug (RLD); and (ii) contains no inactive ingredient or other change in formulation from the RLD that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed. Most U.S. generic versions of oral solution products are approved based on biowaiver if the above conditions are met.

This study aims to 1) systematically compare different regulatory agencies' requirements regarding bioequivalence demonstration of oral solution products (e.g., when a biowaiver may be granted), and 2) evaluate the approval basis of U.S. generic oral solution products, especially the ones which contain poorly soluble active pharmaceutical ingredients (API).

METHODS

We reviewed U.S. Food and Drug Administration (FDA) and six other regulatory agencies' guidance and practice regarding bioequivalence demonstration of oral solution products. For all U.S. approved generic oral solution products, we compared the formulation composition of the generic products to that of the RLDs and evaluated conditions that biowaiver were granted or denied for these approved generic drug products.

RESULTS

REGULATION AND GUIDANCE REVIEW

U.S. FDA	For oral solution products, according to 21 CFR 320.22, the in vivo bioequivalence study may be waived if the generic (i) contains the same active drug ingredient in the same concentration and dosage form as the reference listed drug (RLD); and (ii) contains no inactive ingredient or other change in formulation from the RLD that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.22
Health Canada	To support the request for a waiver of the requirement to demonstrate *in vivo* bioequivalence for other aqueous solutions (e.g., oral, dermatological, ophthalmic, otic), the non-medicinal ingredients in the formulation of the test product, when compared to the reference product, should be qualitatively *the same* and quantitatively *essentially the same*. For the purposes of this document, *essentially the same* would be interpreted as the amount (or concentration) of each excipient in the test product to be within ±10% of the amount (or concentration) of each excipient in the reference product. A side-by-side comparison of the qualitative and quantitative formulations for the test and reference products should be provided. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/notice-guidance-industry-pharmaceutical-quality-aqueous-solutions.html#a5
European Medicines Agency (EMA)	If the product in an aqueous oral solution at time of administration and contains an active substance in the same concentration as an oral solution currently approved as a medicinal product, no bioequivalence study is required, provided the excipients contained in it do not affect gastrointestinal transit, absorption or in vivo stability of the active substance. **https://www.ema.europa.eu/en/documents/scientific-guideline/draft-note-guidance-investigation-bioavailability-bioequivalence_en.pdf**
Therapeutic Goods Administration (TGA Australia)	15.3 Medicines that do not require biopharmaceutic data We do not require biopharmaceutic data or a justification for not providing this data for: Oral solutions that both (1) contain the same drug substance(s) in the same concentration as a currently registered oral solution (2) do not contain excipients that may significantly affect: gastric passage or absorption of the drug substance(s) *in vivo* solubility or *in vivo* stability of the drug substance. https://www.tga.gov.au/book/export/html/4158
South African Development Community (SADC)	5.1.1 Bioavailability and Bioequivalence Requirements - Orally administered medicinal products with systemic action Solutions: A bioequivalence waiver may be granted for oral solutions containing the same APIs in the same concentration as the reference product, and containing no ingredient known to significantly affect absorption in the medicinal ingredient. http://apps.who.int/medicinedocs/documents/s19283en/s19283en.pdf
Health Sciences Authority (HSA Singapore)	In general BE data or justification for not providing such data are not required for the following products: Oral solutions containing the same active ingredient(s) in the same concentration as a currently registered oral solution and which does not contain excipients that may significantly affect the gastric passage or absorption of the active ingredient(s) **https://www.hsa.gov.sg/content/dam/HSA/HPRG/Western_Medicine/Overview_Framework_Policies/Guidelines_on_Drug_Registration/DR_Guide_update_2018/Appendix%2010_Product%20Interchangeability%20and%20Biowaiver%20Request%20for%20Chemical%20Generic%20Drug%20Applications.pdf**
Medsafe Guideline on the Regulation of Therapeutic Product (New Zealand)	1.4. Bioequivalence is required, unless otherwise justified (see section 1.6), for the following types of new generic prescription medicines. Orally administered suspensions and solutions (including oral powders for reconstitution). Under some circumstances, bioequivalence may be waived for orally administered aqueous solutions (refer to the CHMP *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr)). https://www.medsafe.govt.nz/regulatory/Guideline/GRTPNZ/bioequivalence-of-medicines.pdf

Figure 1. Different types of Oral Solutions

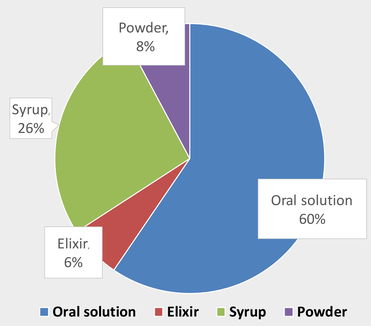
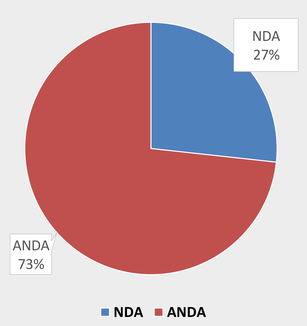


Figure 2. NDA vs. ANDA Product Distribution



COMMON FORMULATION COMPOSITION OF ORAL SOLUTION PRODUCTS WITH WATER SOLUBLE APIs

COMMON EXCIPIENTS
• Sweetener • Preservative • Buffer • Flavor • Solvents: oPropylene Glycol as stabilizer/co-solvent oWater oSometimes alcohol as solvent

COMMON FORMULATION COMPOSITION OF ORAL SOLUTION PRODUCTS WITH POORLY SOLUBLE APIs

COMMON EXCIPIENTS	SOLUBILIZATION APPROACH
• Sweetener • Stabilizer • Preservative • Buffer • Flavor • Solvents	• pH adjustment • Co-solvent o Propylene glycol o Polyethylene glycol o Glycerol/Glycerin • Complexation • Oil- Based

COMMON FORMULATION COMPOSITION OF ORAL SOLUTION PRODUCTS WITH POORLY SOLUBLE API USING NON-AQUEOUS APPROACH

SOLVENTS	SURFACTANTS	ANTIOXIDANTS
• Medium chain triglycerides • Alcohol • Propylene glycol • Phosal 50 PG (Propylene Glycol-Lecithin)	• PEG castor oil • SPAN 80 • PEG caprylic/capric glycerides • Tween 80	• Dl-alpha-tocopherol • Butylated hydroxyanisole

ORAL SOLUTION WAIVER SUMMARY

- Overall, most ANDAs have formulation compositions similar to those of the RLDs, thus a low risk of therapeutic inequivalence.
- For some ANDAs with different formulations from that of the RLD, requests for waivers of in vivo bioequivalence studies were denied due to certain excipients exceeding the maximum allowed quantity or threshold difference between ANDA and NDA formulations.
- These ANDAs were either reformulated or in vivo bioequivalence studies were conducted.

CONCLUSIONS

- Review of seven regulatory agencies showed that biowaivers can be granted for generic oral solution products if specific conditions are met. However, slightly different requirements exist among regulatory agencies.
- Our evaluation indicates that there is minimal therapeutic inequivalence risk of U.S. approved generic oral solution products based on biowaiver, as their formulations are very similar to the RLD.
- When formulation differences were noted between generics and RLDs, they were carefully evaluated during the review process to determine whether the differences were significant enough to preclude approval without additional data.
- This study provides a summary about the approval basis of U.S. generic oral solution products and identifies potential areas for specific guideline development and global harmonization regarding the waiver of oral solution products.

ACKNOWLEDGEMENT

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DISCLAIMER

The contents in this poster reflect the views of the authors and should not be construed to represent FDA's views or policies.

REFERENCES

"Criteria for Waiver of Evidence of in vivo Bioavailability or Bioequivalence." *Code of Federal Regulations,* title 21.

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