A Scientific and Regulatory Overview of IVRT: Current Considerations and Challenges

FDA-CRCG Workshop on In Vitro Release Test and In Vitro In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted products

Virtual Public Workshop

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IVRT Considerations and Challenges

- The current status of In Vitro Release Testing (IVRT) for complex generic ophthalmic, injectable, implantable, and inserted product development
  - A product performance test, method development and standardization, selecting evaluation criteria
- Where we want to be: IVRT gaps and needs
  - Desire for more sensitive and standardized methods/procedures, more biorelevant and in vivo predictive measurements, in vitro-in vivo correlations
- Addressing IVRT needs: the Generic Drug User Fee Amendments (GDUFA) research program
  - Examples of GDUFA funded IVRT research on new analytical approaches, novel methods, and developing more biorelevant apparatuses

Benefit of IVRT

- An appropriately designed and validated IVRT method can significantly expediate the development and approval of complex generic drug products by identifying potential differences in drug substance bioavailability and thus mitigate a potentially major bioequivalence failure mode.

Current Status of IVRT: A Product Property

- IVRT is currently a performance test that measures a product's response to a change in the local environment (e.g., upon administration).
- IVRT is a measure of the drug product properties.
  - The rate and extent of drug release depends on the chemical composition and physical properties of the drug substance and drug product (e.g., polymorphic form, particle/globule size distribution, viscosity).
- Although desirable, an IVRT does not need to be biorelevant or predictive of in vivo performance to support a product equivalence determination.
  - "A product that meets Q1/Q2 sameness, comparability of physicochemical properties, and an acceptable comparative in vitro release rate should become available at the site of action at a rate and to an extent that is not significantly different from that of the RLD, thus meeting the requirement for demonstrating bioequivalence." FDA-2014-P-2301, FDA-2016-P-2781, FDA-2016-P-2782

Current Status of IVRT: Method Development

- In general, there is not a compendial IVRT method for complex (e.g., suspension, emulsion, liposomal, polymeric insert) products. This is due in part to the complex diversity of these products and associated challenges of developing methods that accurately measure drug released.
- Therefore, generic applicants should develop an IVRT method that is reproducible and discriminatory to potential formulation or manufacturing changes to the product.
  - Information on the IVRT method helps characterize the mechanism of drug release from the drug product formulation and how this may relate to the in vivo mechanism of drug release can further support the importance of IVRT data in an equivalence assessment.

Current Status of IVRT: Evaluation

- Setting appropriate evaluation conditions is critical to demonstrating comparable drug release.
- The evaluation conditions selected should be based on the mechanism and associated profile of release from the formulation, data variability, and appropriate comparison assumptions and criteria to ensure sameness.
  - Currently FDA does not have recommended statistical approaches for evaluating the equivalence of IVRT profiles for complex ophthalmic, injectable, implantable, and inserted products. A 90% confidence interval of for the ratio of the median IVRT rate or model independent similarity factor (f2) are often used.[1] An applicant should not feel limited to these approaches and instead should select and justify why an evaluation approach is appropriate.

1. FDA's guidance for industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms (Aug 1997) https://www.fda.gov/media/70936/download

IVRT: Where We Want to Be

- Provide specific IVRT recommendations for complex ophthalmic, injectable, implantable, and inserted products including:
  - Experimental design, media, and conditions
  - Statistical analysis
  - Expectations for method validation, if any
- Develop better understanding of the relationship between a product's critical quality attributes and its drug release profile
- Establish in vitro-in vivo correlations

Examples of Current Gaps and Hurdles

- IVRT Method Development And Validation
  - Standardized IVRT Apparatuses (i.e., USP I and II) are not readily applicable for complex ophthalmic, parenteral, and implantable products, such as emulsions, suspensions, ointments, intrauterine systems
  - Need for separating the released free drug from the formulation introduces additional complexity
  - The sensitivity and precision of an IVRT method can be highly dependent on the IVRT method conditions
  - Understanding of product critical quality attributes (CQAs) that can affect drug release and selective IVRT methods that can discriminate differences in these product CQAs
- Data Analysis
  - Need for guidance on appropriate statistical models to evaluate drugs that rapidly or only partially release
- In Vitro-In Vivo Correlations
  - Understanding of in vitro and in vivo drug release mechanism
  - Media (composition or volume) required to enable in vitro drug release is often not biorelevant which may give rise to a change in release mechanism compared to in vivo
  - Need for accelerated IVRT methods that correlated with real time condition and in vivo for long-acting drug products

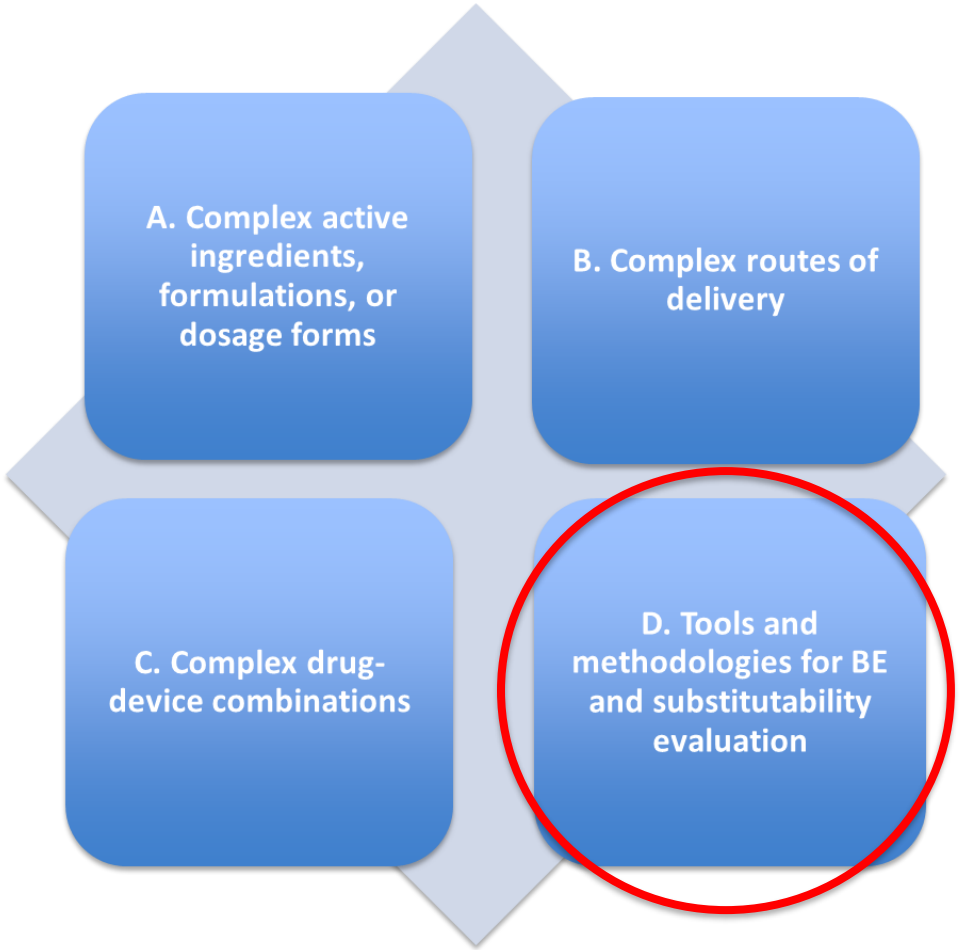
Addressing These Challenges: GDUFA Regulatory Science Program

- The Generic Drug User Fee Amendments (GDUFA) Research Program provides resources for FDA to fund research to advance the development and assessment of generic drug products.
  - Since 2013, FDA has awarded 188 external research contracts and grants as well as numerous projects conducted by FDA staff.[1]
  - This program provides new tools for FDA and industry to evaluate generic drug equivalence. This enables more efficient development and assessment of generic drugs, including the development of FDA guidance recommendations.
  - Results from GDUFA research are presented at scientific and public meetings as well as published in peer-reviewed scientific journals.

1. https://www.fda.gov/drugs/generic-drugs/generic-drug-research-collaboration-opportunities

GDUFA Regulatory Science Priorities

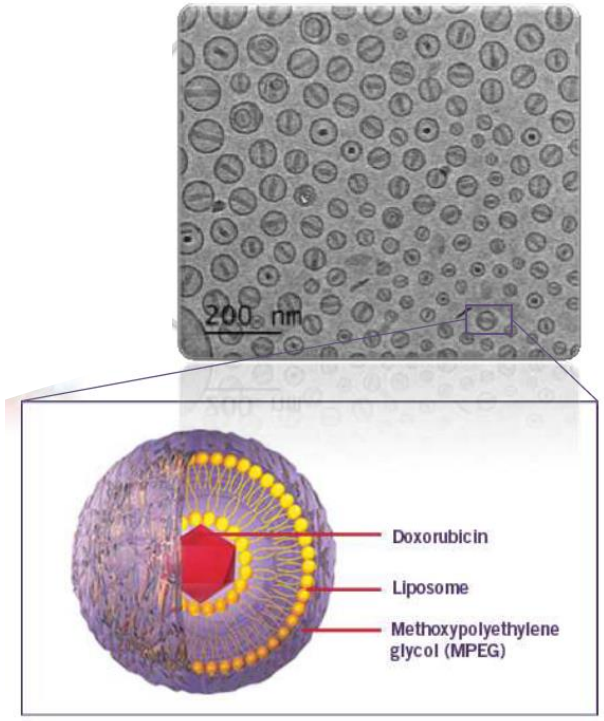
- GDUFA research priorities are set annually based on public feedback[1]
  - This year the *GDUFA Regulatory Science Initiatives Public Workshop* was held on May 9-10, 2022[2]
  - Currently 90+ on-going collaborative projects in four key areas[3]
- To date, there have been over 20 GDUFA funded research projects on the development and assessment of IVRT methods for various complex generic ophthalmic, injectable, implantable, and inserted products.

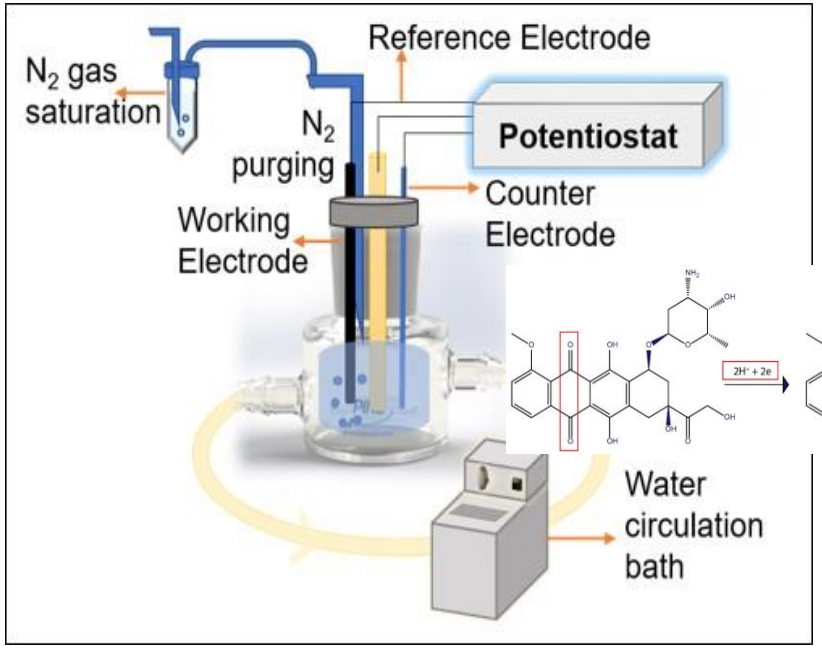


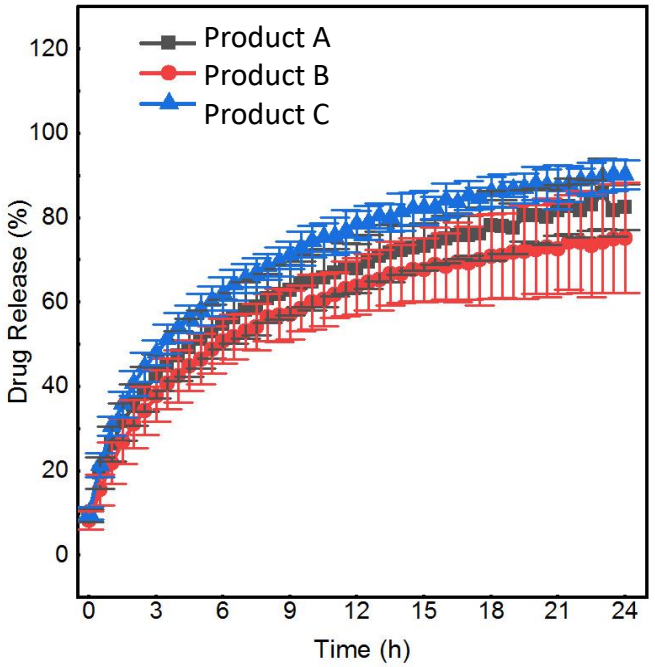
1. https://www.fda.gov/drugs/generic-drugs/science-research
2. https://www.fda.gov/drugs/news-events-human-drugs/fy-2022-generic-drug-science-and-research-initiatives-public-workshop
3. https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects

New Analytical Tools for Measuring IVRT of Complex Products

- An electroanalytical method was developed for the continuous and direct quantitation of drug released from liposomes that overcomes the limitations and inaccuracies of conventional separation analysis methods.





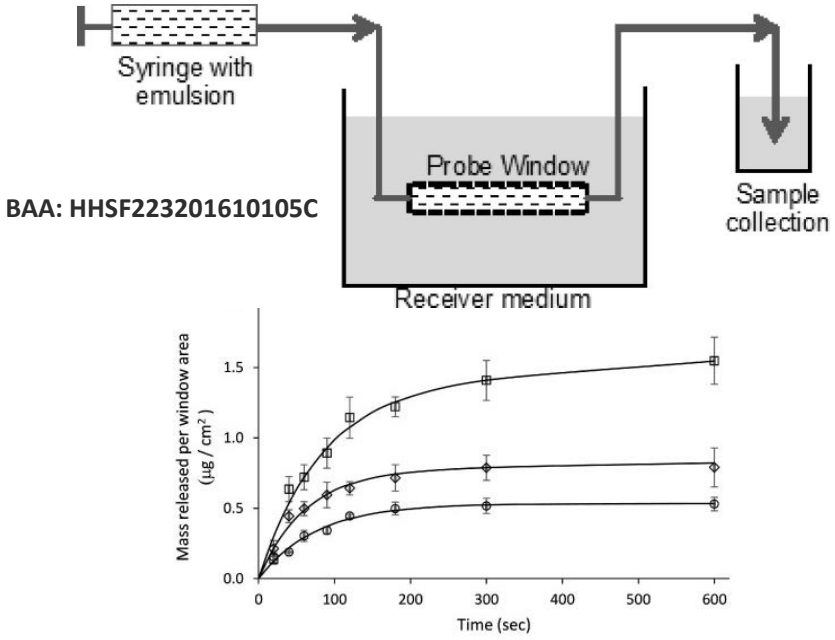


FDA GDUFA research project by F.M. Yurtsever, D.A. Siriwardane, W. Jiang, and T. Mudalige done at the Nanotechnology Core Facility (NanoCore) located on the U.S. Food and Drug Administration's Jefferson Laboratories campus (Jefferson, AR)

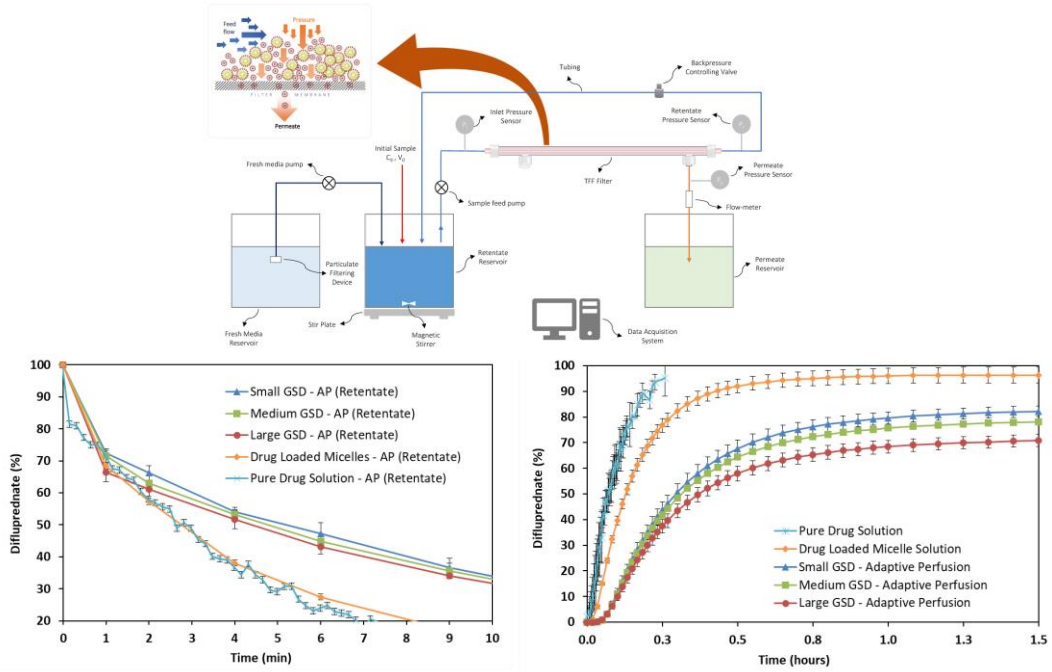
New IVRT Methods for Measuring Complex Products

- Historically, IVRT has not been broadly used for supporting ophthalmic new drug approval. Therefore, limited information and standards are in place.
- Both internal and external research has been conducted to develop understandings as well as procedures to measure drug release from low release dispersion systems, such as emulsions (two examples below).
- These systems increase the surface area-to-volume ratio of the release interface as well as interfacial fluid dynamics to increase the rate and extent of drug released.

Pulsatile Microdialysis Method



Adaptive Perfusion Method

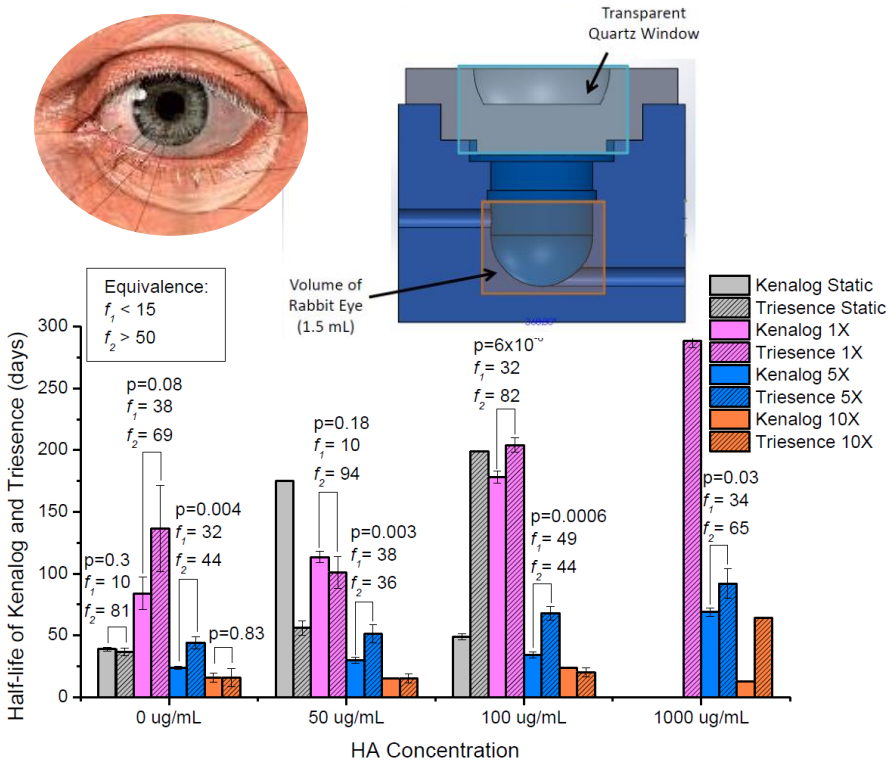


Robert Bellantone, et al. *Int J Pharm,* 2022, 121521. DOI: 10.1016/j.ijpharm.2022.121521

D. Patel et al. Journal of Controlled Release (2021), 333, pp.65-75. DOI: 10.1016/j.jconrel.2021.03.024

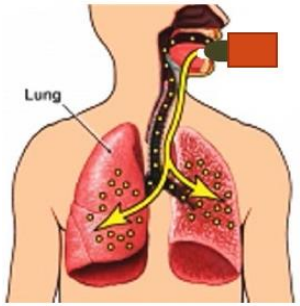
Development of New IVRT Apparatuses

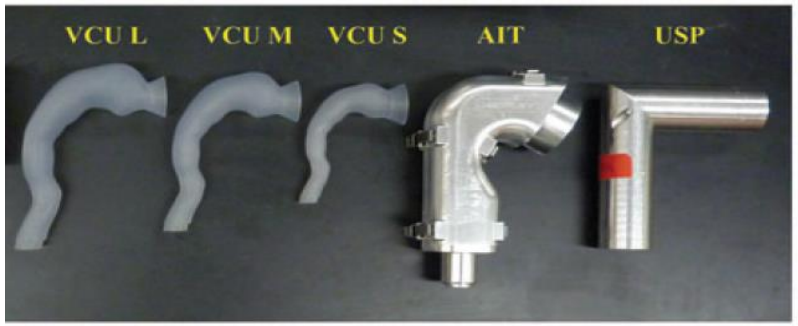
- Development and evaluation of more 'biorelevant' IVRT apparatuses that 'mimic' the in vivo conditions is expected to give rise to a more in vivo predictive platform and results.
- New simplified lithography and 3D printing technologies are enabling more realistic and complex structural apparatus designs readily available for testing and implementation.



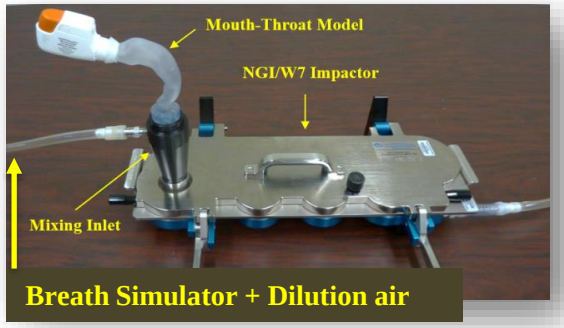
Flow cell conditions can distinguish between Kenalog and Triesence

Realistic mouth-throat (MT) models





VCU: Virginia Commonwealth University
AIT: Alberta Idealized Throat
NGI: next generation impactor



In vitro APSD method more predictive of in vivo deposition. May provide correlation to systemic pharmacokinetics when combined with dissolution data at each deposition stage

Grant: 1U01FD005173-01 UC San Diego

Wei, Xiangyin, et al. Journal of aerosol medicine and pulmonary drug delivery 31.6 (2018): 358-371.

Conclusions

- FDA is committed to supporting the latest scientific methods and tools to develop and evaluate generic products.
- IVRT is a critical performance test that reflects the physicochemical properties of a drug product.
- Although useful to support product equivalence, there are still considerable needs for more sensitive and in vivo-predictive IVRT methods for complex (e.g., suspension, emulsion, liposomal, polymeric insert) products.
- GDUFA research enables FDA to fund the development and assessment of new IVRT and analytical methods to facilitate the development and approval of high-quality generics.

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