Approaches Using Proactive Research in Support of Product-Specific Guidance (PSG) Development

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CDER | U.S. FDA

Generic Drug Forum - April 27, 2022

Outline

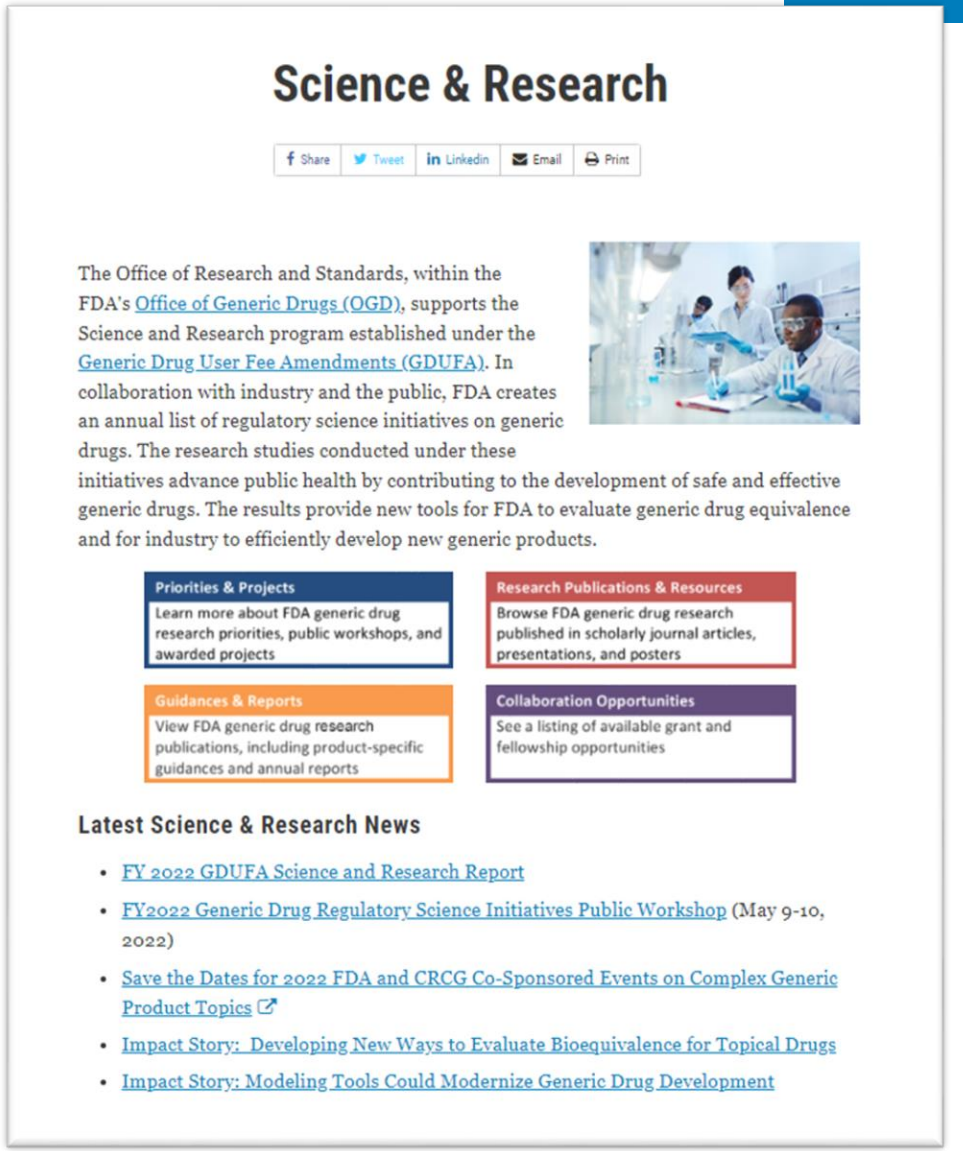
- The Generic Drug User Fee Amendments (GDUFA) Regulatory Science Program
  - Annual research priorities and research resources
- Product-Specific Guidance (PSG) Program
  - PSG priorities, complex products, and GDUFA research
- GDUFA Research Examples

GDUFA Regulatory Science and PSGs

- The Generic Drug User Fee Amendments (GDUFA), first enacted in 2012, enables FDA to assess industry user fees to bring greater predictability and timeliness to the review of generic drug applications. To advance generic drug regulatory science and decision-making, GDUFA provides resources that allow FDA to fund research.
  - Since 2013, FDA has awarded 188 research contracts and grants as well as numerous projects conducted by FDA staff.
  - This research provides new tools for FDA and industry to evaluate generic drug equivalence. This enables more efficient development and review of generic drugs, including the development of PSG recommendations.
  - Results from GDUFA research are presented at scientific and public meetings as well as published in peer-reviewed scientific journals.

GDUFA Regulatory Science and PSGs

- FDA's GDUFA Science & Research website is a valuable resource.
  - GDUFA Science and Research Reports that describe the annual research activities, progress, and outcomes
  - Links to OGD's past and upcoming Scientific Workshops & Meetings, Webinars, and Research News
  - Links to past GDUFA research contract and grant awards as well as open research funding opportunities and needs
  - List of FDA co-authored GDUFA-funded articles, presentations, and posters



Science & Research

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The Office of Research and Standards, within the FDA's Office of Generic Drugs (OGD), supports the Science and Research program established under the Generic Drug User Fee Amendments (GDUFA). In collaboration with industry and the public, FDA creates an annual list of regulatory science initiatives on generic drugs. The research studies conducted under these initiatives advance public health by contributing to the development of safe and effective generic drugs. The results provide new tools for FDA to evaluate generic drug equivalence and for industry to efficiently develop new generic products.

Priorities & Projects
Learn more about FDA generic drug research priorities, public workshops, and awarded projects

Research Publications & Resources
Browse FDA generic drug research published in scholarly journal articles, presentations, and posters

Guidances & Reports
View FDA generic drug research publications, including product-specific guidances and annual reports

Collaboration Opportunities
See a listing of available grant and fellowship opportunities

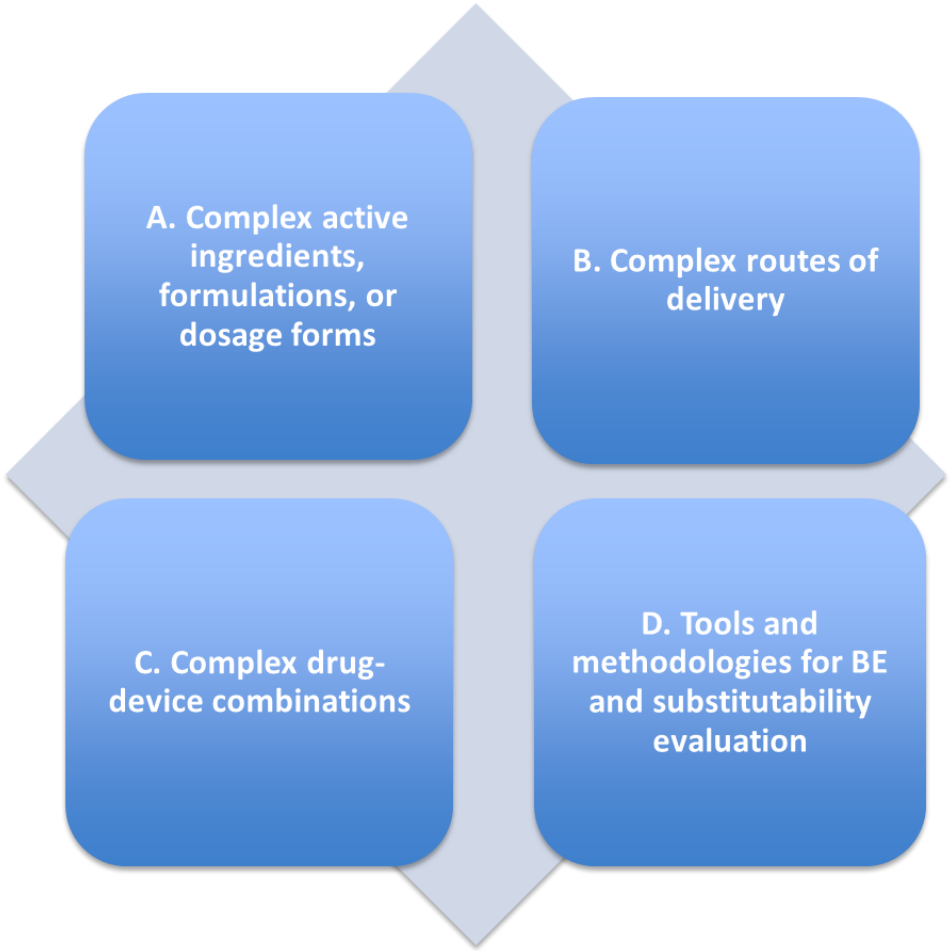
Latest Science & Research News

- FY 2022 GDUFA Science and Research Report
- FY2022 Generic Drug Regulatory Science Initiatives Public Workshop (May 9-10, 2022)
- Save the Dates for 2022 FDA and CRCG Co-Sponsored Events on Complex Generic Product Topics
- Impact Story: Developing New Ways to Evaluate Bioequivalence for Topical Drugs
- Impact Story: Modeling Tools Could Modernize Generic Drug Development

1. https://www.fda.gov/drugs/generic-drugs/science-research

GDUFA Regulatory Science and PSGs

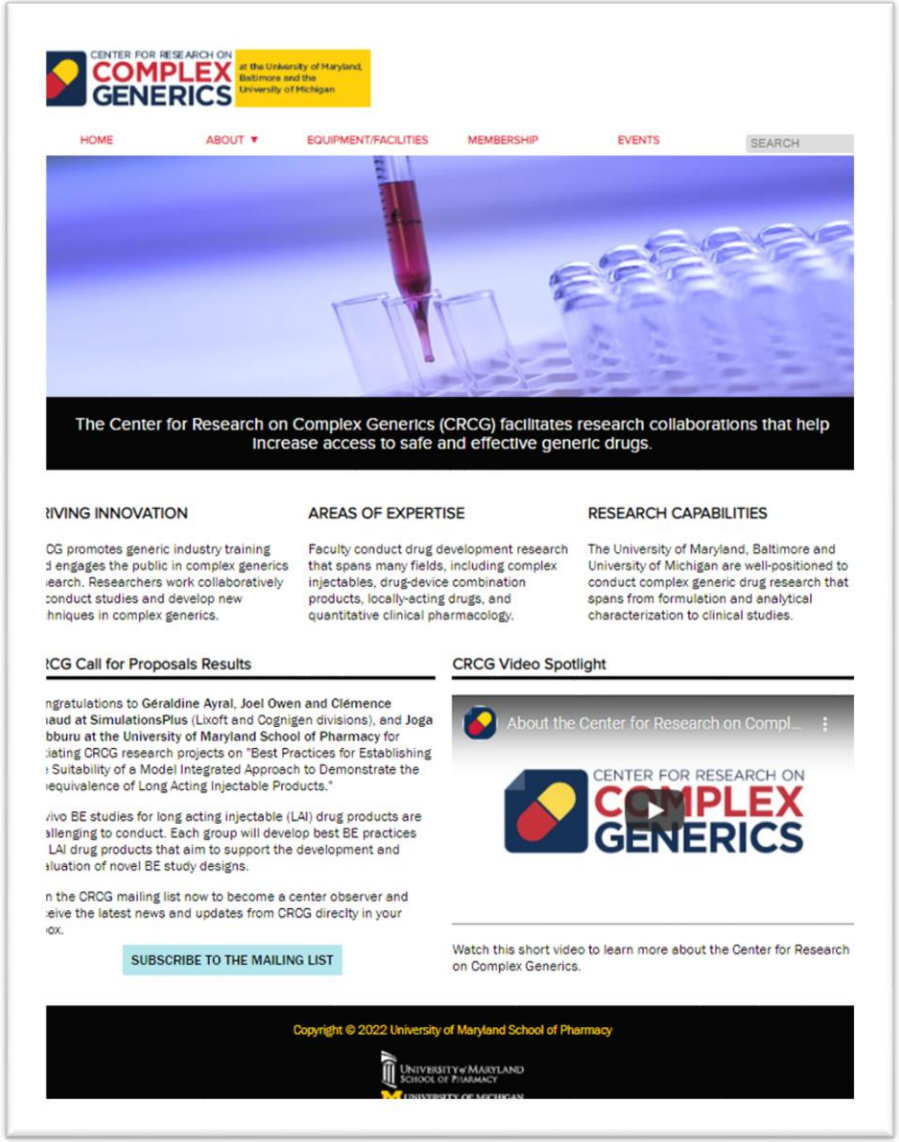
- GDUFA research priorities are set annually based on public feedback[1]
  - This year the *GDUFA Regulatory Science Initiatives Public Workshop* will be held as a virtual event on May 9-10, 2022[2]
  - Currently 90+ on-going collaborative projects in four key areas[3]
- Research projects are conducted by FDA laboratories as well as via contracts or grants with academia, industry, or other government agencies.[4]



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

GDUFA Regulatory Science and PSGs

- Started in 2020 via a GDUFA grant, the Center for Research on Complex Generics (CRCG)[1] is a partnership between FDA, the University of Maryland, and the University of Michigan to facilitate research collaborations that help increase access to safe, effective and high-quality generic drugs. The CRGC:
  - Supports FDA's efforts to enhance research collaborations with the generic industry.
  - Hosts educational events and workshops:
    - June 29, 2022; *In Vitro Release Test and In Vitro/In Vivo Correlation of Complex Generic Ophthalmic, Injectable, Implantable, and Inserted Products*
    - Oct. 27 - 28, 2022; *Model Integrated Bioequivalence Approaches in Complex Generic Product Development*
    - Nov. 3, 2022; *Evaluation of Cutaneous Pharmacokinetics to Facilitate Complex Generic Topical Product Development*
    - Dec 6, 2022: *FDA-CRCG Training on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned*
  - Promotes generic industry training and engaging the public in complex generics research.
  - Conducts collaborative research that facilitate complex generics.



1. https://complexgenerics.org/about/

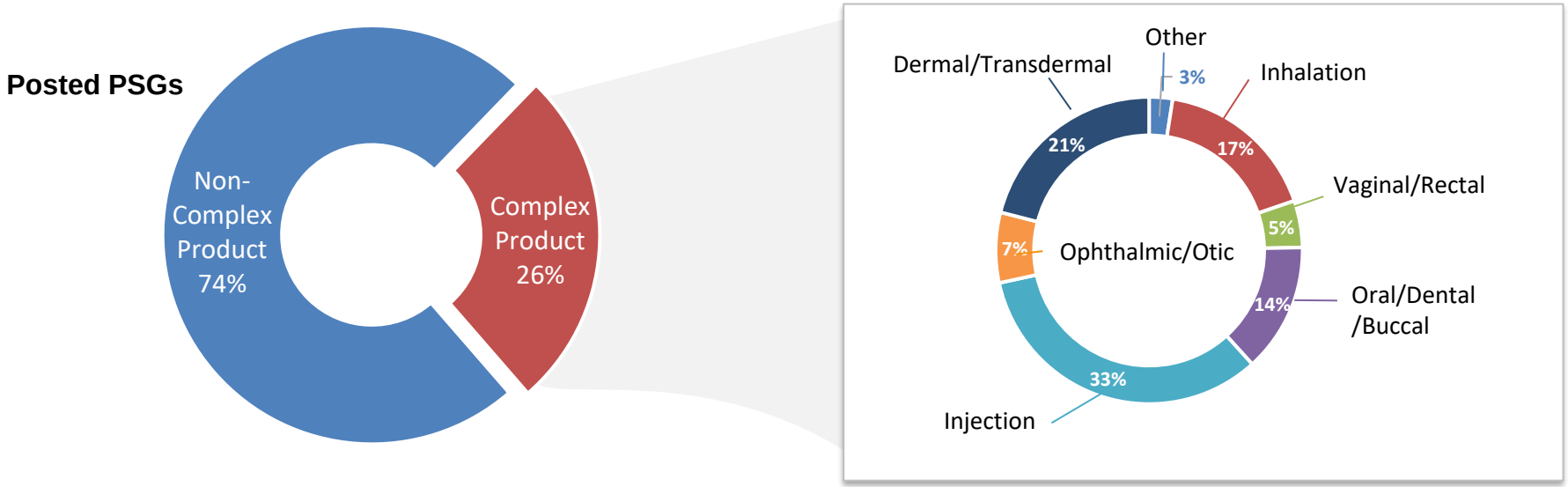
Product-Specific Guidances (PSGs)

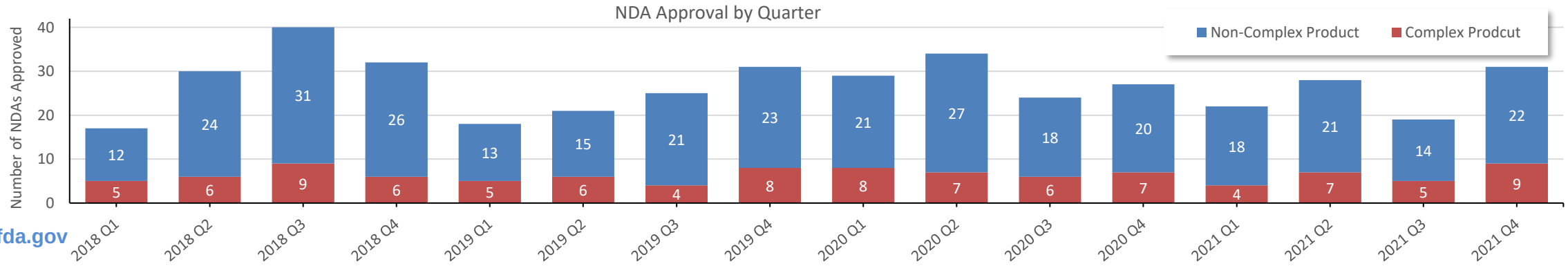
- A key outcome of GDUFA research is the development of PSGs.
- Started in 2007, PSGs outline FDA's current product-specific thinking on the type of studies and information to support the development and approval of a safe, effective, and high-quality generic drug product.
  - PSGs are posted on a quarterly basis and as of March 2022, there are 1,978 posted PSGs.
  - ANDA applicants can propose an approach that deviates from FDA posted guidance but should include justification for the alternative approach including data (Module 2.7 and Module 5) and appropriate references.[1]
- PSG priorities and goal dates.[2]
  - For New Chemical Entity non-complex products, FDA will issue a PSG for 90% at least 2 years prior to the earliest lawful ANDA filing date (e.g., not more than 3 years post New Drug Application (NDA) approval).
  - For newly approved complex products, FDA will strive to issue product-specific guidance as soon as scientific recommendations are available.
  - FDA must grant a pre-ANDA meeting to potential Abbreviated New Drug Application (ANDA) applicants proposing a complex product that does not have a posted PSG or are proposing an alternative approach to that recommended in the posted PSG.

[1] FDA's guidance for industry, *ANDA Submissions – Refuse-to-Receive Standards* (December 2016) https://www.fda.gov/media/86660/download
[2] GDUFA II Commitment Letter https://www.fda.gov/media/101052/download

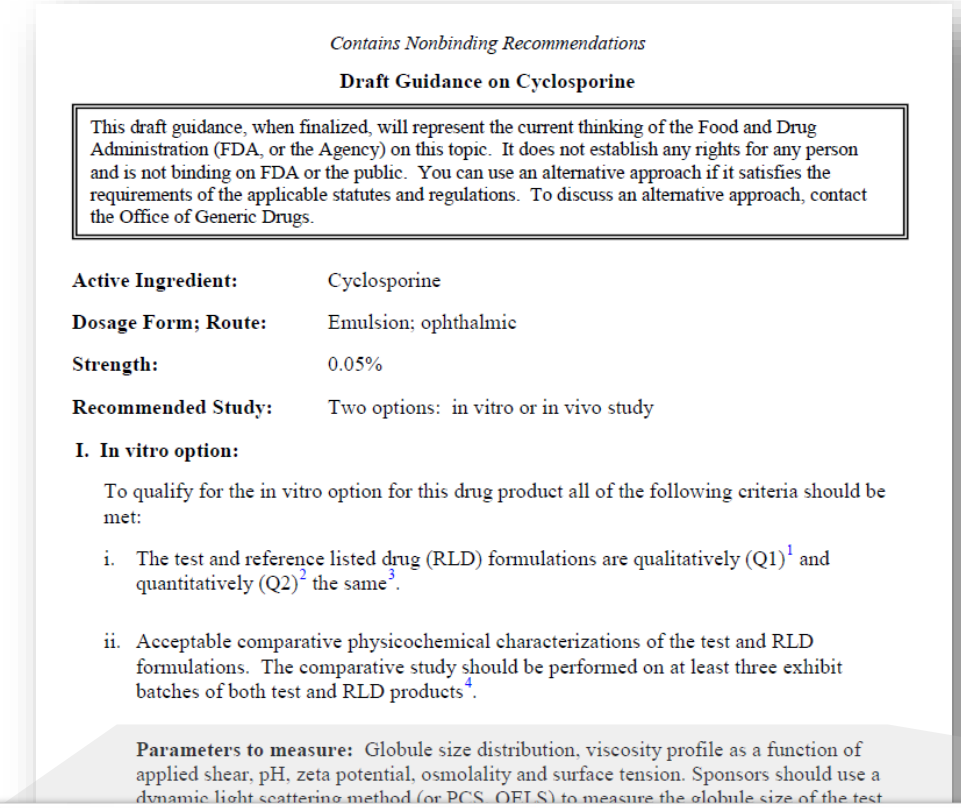
NDA Approval and PSG Development

Approximately 25% of approved NDA are complex products (on average 6 per quarter). Majority of the >500 complex products with a posted PSG have a complex dosage form. These products include different routes of administration and can meet more than one definition of complexity (e.g., complex active ingredient, complex drug-device combination, complex route of delivery, complex dosage form, etc.).





Product-Specific Guidances (PSGs)



Contains Nonbinding Recommendations

Draft Guidance on Cyclosporine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Cyclosporine

Dosage Form; Route: Emulsion; ophthalmic

Strength: 0.05%

Recommended Study: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product all of the following criteria should be met:

i. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same[3].

ii. Acceptable comparative physicochemical characterizations of the test and RLD formulations. The comparative study should be performed on at least three exhibit batches of both test and RLD products[4].

Parameters to measure: Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential, osmolality and surface tension. Sponsors should use a dynamic light scattering method (or PCS, QELS) to measure the globule size of the test

Parameters to measure: Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential, osmolality and surface tension. Sponsors should use a dynamic light scattering method (or PCS, QELS) to measure the globule size of the test and RLD formulations, and provide comparable size distribution profiles (intensity-weighted histograms) upon serial dilutions. Information on the instrument, analysis mode (if applicable), dilution medium, and level of dilution used for globule size measurement should be provided.

- To support a bioequivalence determination, PSGs commonly recommend a type of study or property of the drug product to measure. An applicant should select, develop, and justify an analytical approach including the method and evaluation criteria used.
- GDUFA research can inform FDA and industry regarding new tools, including potential development and assessment considerations for a particular analytical approach for a specific product or class of products.
  - The properties of complex products are often important, interrelated, and not straightforward to measure or compare.
    - *Research provides the insight to develop a recommended BE approach and industry a starting point for product development*

Research Example: Ophthalmic Emulsions

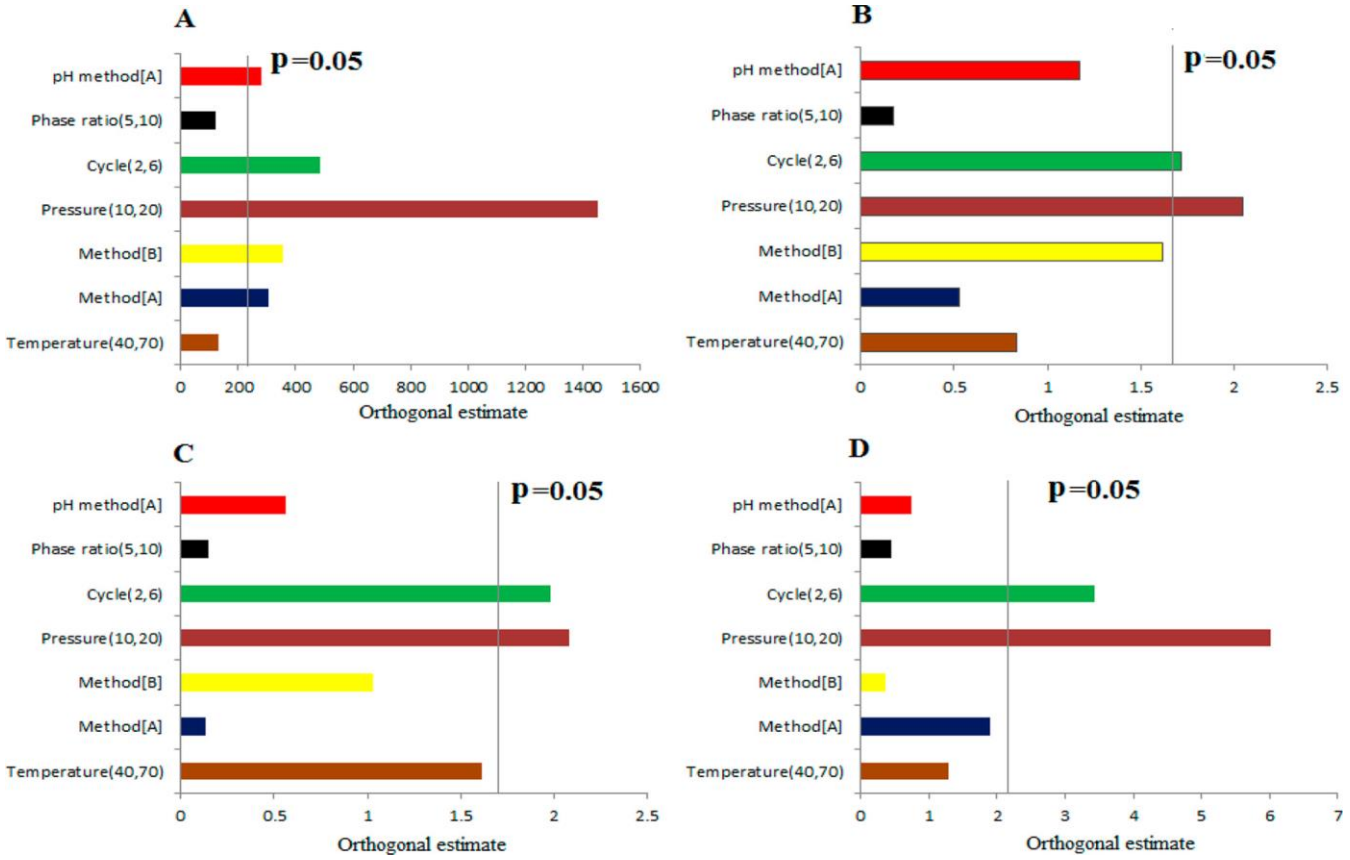
- Complex products often raise complex issues and considerations that research can help address. For example, ophthalmic emulsions are complex in terms of both formulation and route of delivery:
  - Complex formulation (emulsion):
    - Contains multi-phases (e.g., *oil globules, micelles, aqueous phase*)
    - Contains excipients to increase physical stability (e.g., *surfactants*, *viscosity modifiers*)
    - Properties are manufacturing process-dependent (e.g., *globule size distribution*)
  - Complex route of delivery (ocular):
    - Short residence time (a few seconds to a few minutes)
    - Interactions with the tear film
    - Locally acting (therefore systemic pharmacokinetics is not likely to be relevant)

- Three ophthalmic emulsions on the market:
  - Cyclosporine emulsion (Restasis®), NDA approved in 2002; **First generic approved in Feb 2022**
  - Difluprednate emulsion (Durezol®), NDA approved in 2008; **First generic approved in Aug 2021**
  - Latanoprost (Xelpros®), NDA approved in 2018

Research and supporting data allow for assessment of product-specific quality attributes, best measurement practices and assessment criteria to support equivalence.

Ophthalmic Emulsions: Process on CQAs

- Manufacturing process can have a significant effect on critical quality attributes (CQAs), which impacts the evaluation of equivalence.



Surface profilers showing the effect of microfluidizer pressure and number of pressure cycles on the microemulsion*: (A) Z-average, (B) turbidity, (C) zeta potential, and (D) viscosity.

- For emulsions that are formulated to have the qualitatively (Q1) and quantitatively (Q2) the same composition as the reference listed drug (RLD) product, process changes (e.g., number and pressure setting of the microfluidization process) can directly impact the globule size distribution, zeta-potential, and viscosity.
- To ensure adequate quality control and to support in vitro BE approach, accurate, sensitive, and reliable analytical methods are needed.

Parameters to measure: Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential, osmolality and surface tension. Sponsors should use a dynamic light scattering method (or PCS, QELS) to measure the globule size of the test and RLD formulations, and provide comparable size distribution profiles (intensity-weighted histograms) upon serial dilutions. Information on the instrument, analysis mode (if applicable), dilution medium, and level of dilution used for globule size measurement should be provided.

- Z. Rahman et al. Mol. Pharmaceutics. 2014, 11, 3. DOI: 10.1021/mp400484g

*the term "microemulsion" should be named as "nanoemulsion" in this article

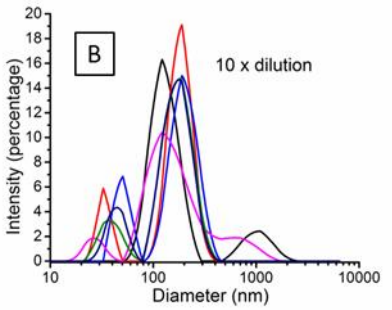
Ophthalmic Emulsions: GSD

- Globule size distribution (GSD) is a critical quality attribute for emulsions.
- Several techniques may be used to measure the GSD.
- Dynamic light scattering and laser diffraction are two most commonly used methods.
- The measurement principle varies for each sizing technique (e.g., Brownian motion, time-dependent light scattering, angle-dependent light scattering, electron density); therefore, the results differ when comparing across the techniques.
- Research found that excipient interference may occur at high particle concentration (e.g., measuring without dilution), which lead to over-estimation of GSD.
- Reliable measurement is possible after a method is appropriately developed and validated.

- H. Qu, et al. *Int J Pharm*, 2018, 538, p.215-222. DOI: 10.1016/j.ijpharm.2018.01.012
- P. Petrochenko, et al. *Int J Pharm*, 2019, 550, p229-239. DOI: 10.1016/j.ijpharm.2018.08.030
- M. Hu et al. *AAPS J*. 2018, 20(3):62. DOI: 10.1208/s12248-018-0212-y

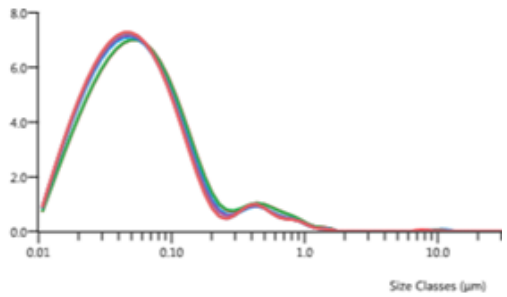
DLS

Zave=118±2 nm



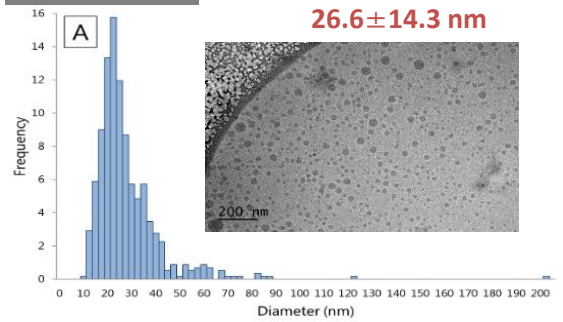
LD

D_{50}=73 ± 2 nm



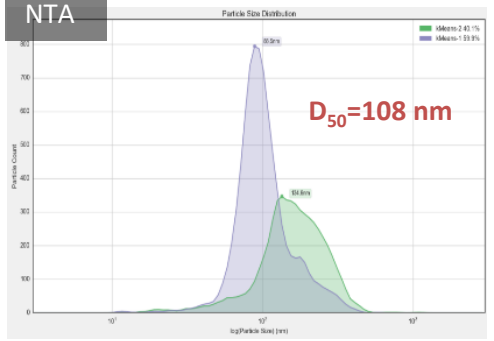
Cryo-TEM

26.6±14.3 nm



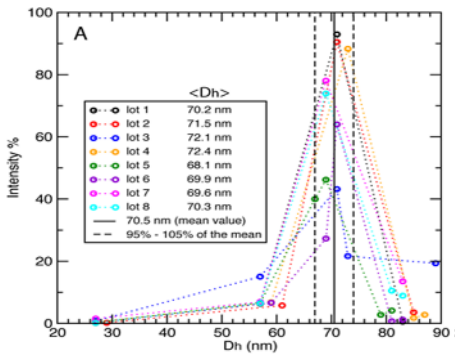
NTA

D_{50}=108 nm

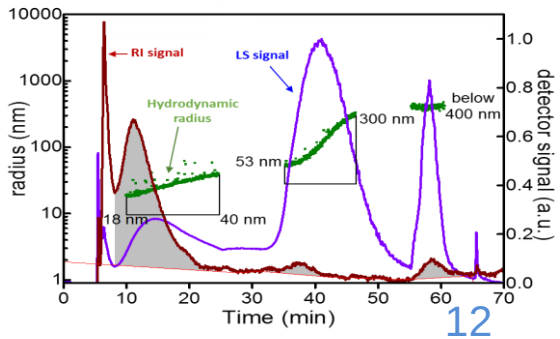


DOSY NMR

mean=70.5 nm



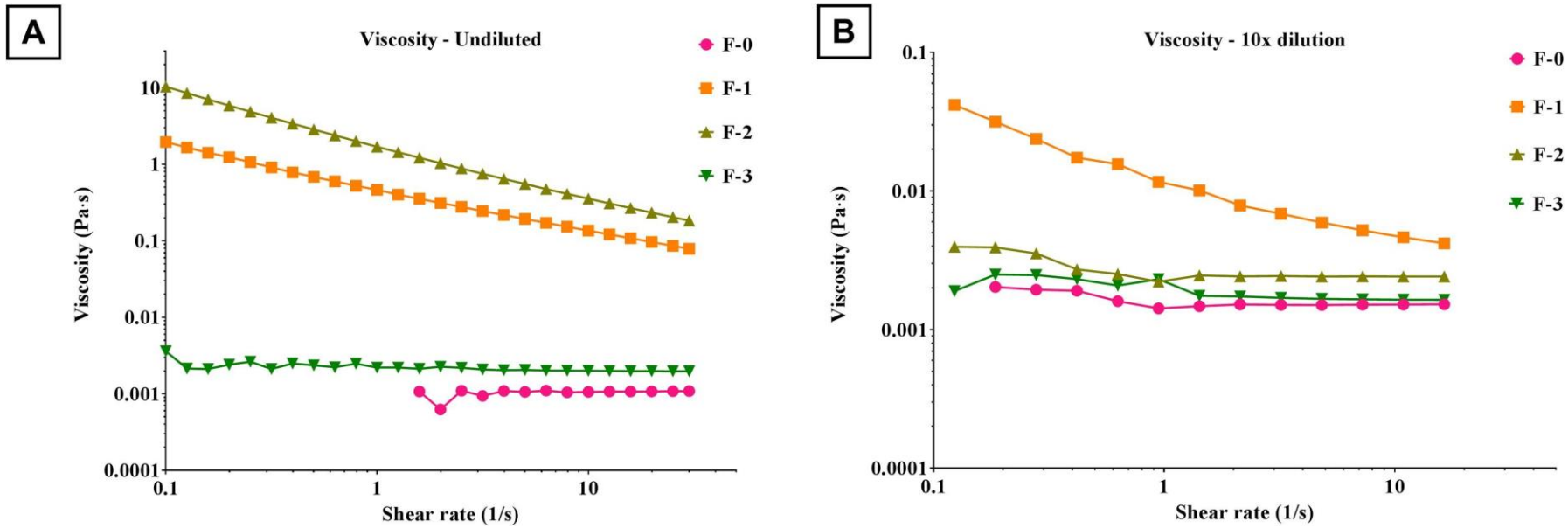
AF4+MALS+DLS+RI

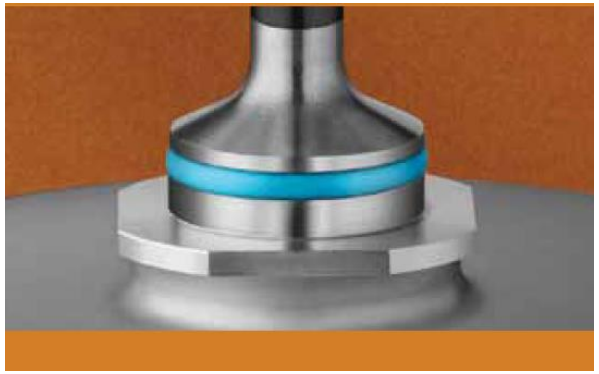


1st: 30 - 80 nm (87.8%); 2nd: 100 – 600 nm (5.3%)

Ophthalmic Emulsions: Rheology (Viscosity)

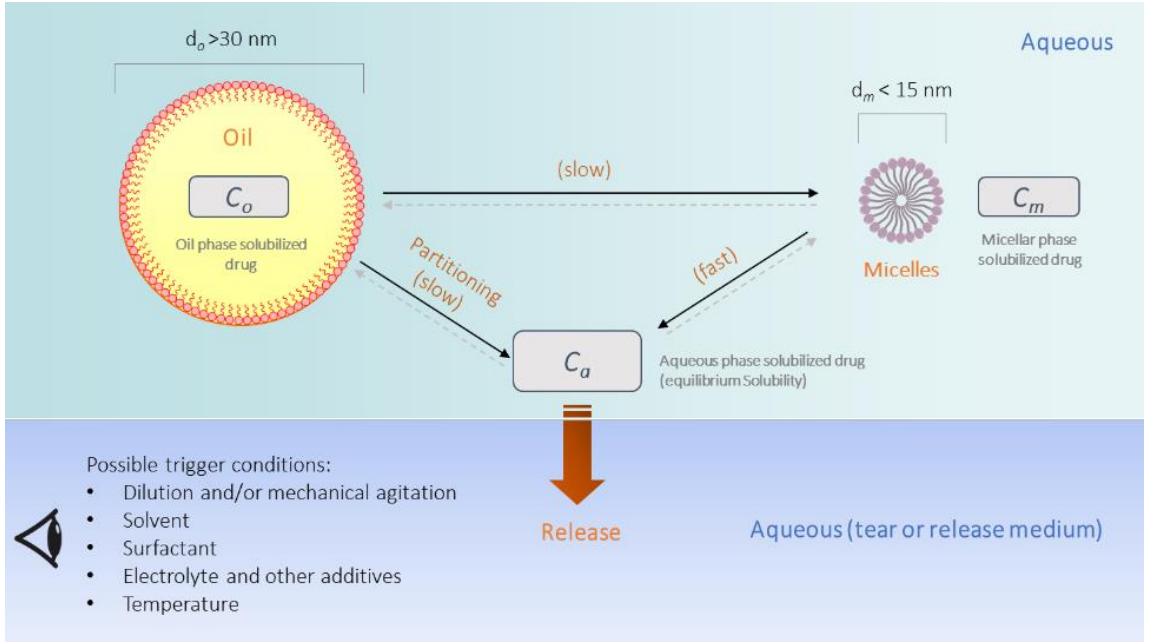
- Rheological property of emulsion (typically measured by viscosity) impacts its ocular residence time, which is related to ocular bioavailability.
- Ophthalmic emulsions may contain viscosity enhancer (e.g., carbomer) and exhibit unique shear-thinning behavior (increasing shear stress leads to lower viscosity), which is likely to occur on the eye surface (e.g., blinking).
- Measurement of viscosity of liquid is well-established and reported (example below for cyclosporine ophthalmic emulsions)

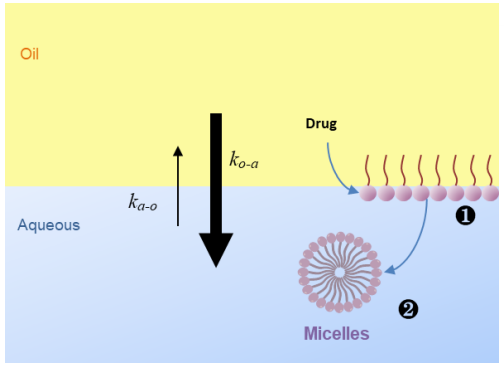


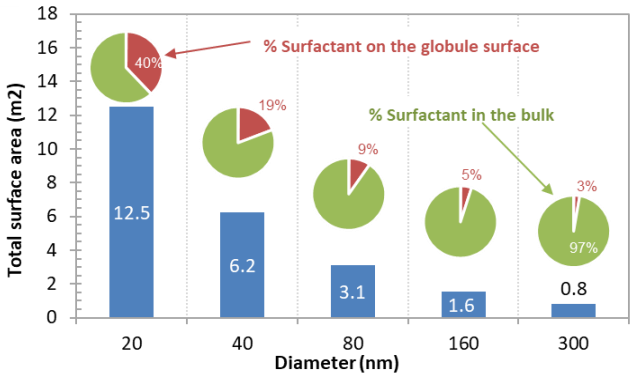


- P. Petrochenko, et al. *Int J Pharm*, 2019, 550, p229-239. DOI: 10.1016/j.ijpharm.2018.08.030

Ophthalmic Emulsions: Drug Distribution



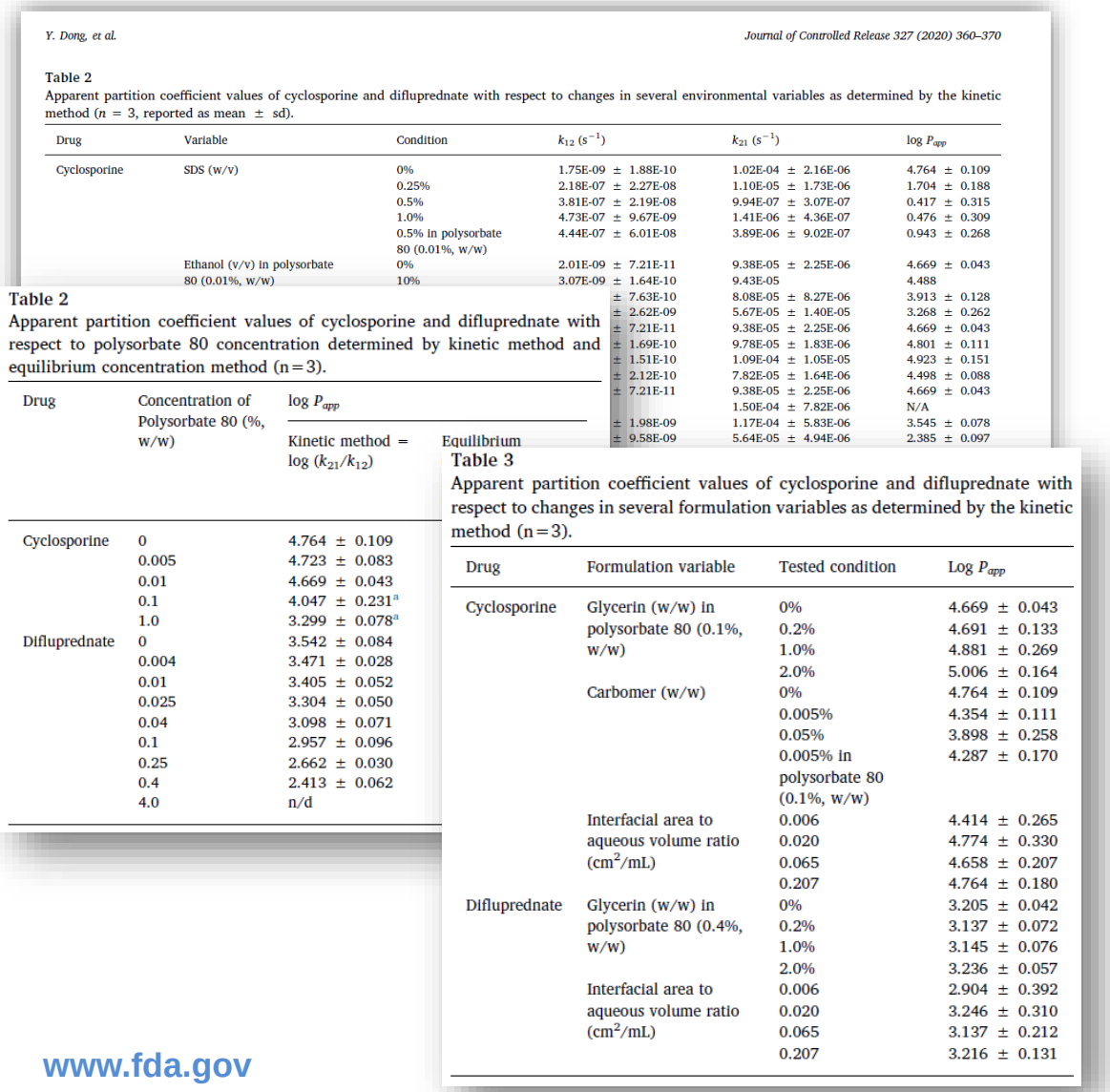




- Emulsions may contain multiple components (e.g., oil globules, micelles) with varying properties (e.g., size, drug content).
- The transfer rate of drug between these components differs, taking from seconds to a couple dozen minutes.
- Some methods may alter the formulation (e.g., phase separation after centrifugation) so may not be representative of the administered product properties (e.g., via ocular route).
- Research was done to understand the transfer kinetics of drug between various components, which allowed for a theoretical estimate of drug distribution as well as drug release.
- The globule size distribution was found to be a key parameter impacting drug distribution and release, as it can directly change the surface area of oil globules and hence the amount of surfactant available in the bulk to solubilize drug (e.g., through micelles).

- Y. Dong et al. *J Pharm Sci* (2019) 108, 2002-2011, DOI: 10.1016/j.xphs.2019.01.003
- Y. Dong et al. *J Control Release* (2019), 313, 96-105, DOI: 10.1016/j.jconrel.2019.09.010
- Y. Dong et al. *J Control Release* (2020), 327, 360-370, DOI: 10.1016/j.jconrel.2020.08.020

Ophthalmic Emulsions: Drug Distribution



Y. Dong, et al. Journal of Controlled Release 327 (2020) 360–370

Table 2
Apparent partition coefficient values of cyclosporine and difluprednate with respect to changes in several environmental variables as determined by the kinetic method (n = 3, reported as mean ± sd).

Drug	Variable	Condition	k_{12} (s^{-1})	k_{21} (s^{-1})	log P_{app}
Cyclosporine	SDS (w/v)	0%	1.75E-09 ± 1.88E-10	1.02E-04 ± 2.16E-06	4.764 ± 0.109
		0.25%	2.18E-07 ± 2.27E-08	1.10E-05 ± 1.73E-06	1.704 ± 0.188
		0.5%	3.81E-07 ± 2.19E-08	9.94E-07 ± 3.07E-07	0.417 ± 0.315
		1.0%	4.73E-07 ± 9.67E-09	1.41E-06 ± 4.36E-07	0.476 ± 0.309
		0.5% in polysorbate 80 (0.01%, w/w)	4.44E-07 ± 6.01E-08	3.89E-06 ± 9.02E-07	0.943 ± 0.268
	Ethanol (v/v) in polysorbate 80 (0.01%, w/w)	0%	2.01E-09 ± 7.21E-11	9.38E-05 ± 2.25E-06	4.669 ± 0.043
		10%	3.07E-09 ± 1.64E-10	9.43E-05	4.488
				± 7.63E-10	8.08E-05 ± 8.27E-06	3.913 ± 0.128
				± 2.62E-09	5.67E-05 ± 1.40E-05	3.268 ± 0.262
				± 7.21E-11	9.38E-05 ± 2.25E-06	4.669 ± 0.043
				± 1.69E-10	9.78E-05 ± 1.83E-06	4.801 ± 0.111
				± 1.51E-10	1.09E-04 ± 1.05E-05	4.923 ± 0.151
				± 2.12E-10	7.82E-05 ± 1.64E-06	4.498 ± 0.088
				± 7.21E-11	9.38E-05 ± 2.25E-06	4.669 ± 0.043
					1.50E-04 ± 7.82E-06	N/A
				± 1.98E-09	1.17E-04 ± 5.83E-06	3.545 ± 0.078
				± 9.58E-09	5.64E-05 ± 4.94E-06	2.385 ± 0.097

Table 2
Apparent partition coefficient values of cyclosporine and difluprednate with respect to polysorbate 80 concentration determined by kinetic method and equilibrium concentration method (n = 3).

Drug	Concentration of Polysorbate 80 (%, w/w)	log P_{app}	
		Kinetic method = log (k_{21}/k_{12})	Equilibrium
Cyclosporine	0	4.764 ± 0.109	
	0.005	4.723 ± 0.083	
	0.01	4.669 ± 0.043	
	0.1	4.047 ± 0.231[a]	
	1.0	3.299 ± 0.078[a]	
Difluprednate	0	3.542 ± 0.084	
	0.004	3.471 ± 0.028	
	0.01	3.405 ± 0.052	
	0.025	3.304 ± 0.050	
	0.04	3.098 ± 0.071	
	0.1	2.957 ± 0.096	
	0.25	2.662 ± 0.030	
	0.4	2.413 ± 0.062	
	4.0	n/d	

Table 3
Apparent partition coefficient values of cyclosporine and difluprednate with respect to changes in several formulation variables as determined by the kinetic method (n = 3).

Drug	Formulation variable	Tested condition	Log P_{app}
Cyclosporine	Glycerin (w/w) in polysorbate 80 (0.1%, w/w)	0%	4.669 ± 0.043
		0.2%	4.691 ± 0.133
		1.0%	4.881 ± 0.269
		2.0%	5.006 ± 0.164
	Carbomer (w/w)	0%	4.764 ± 0.109
		0.005%	4.354 ± 0.111
		0.05%	3.898 ± 0.258
		0.005% in polysorbate 80 (0.1%, w/w)	4.287 ± 0.170
	Interfacial area to aqueous volume ratio (cm^2/mL)	0.006	4.414 ± 0.265
		0.020	4.774 ± 0.330
		0.065	4.658 ± 0.207
		0.207	4.764 ± 0.180
Difluprednate	Glycerin (w/w) in polysorbate 80 (0.4%, w/w)	0%	3.205 ± 0.042
		0.2%	3.137 ± 0.072
		1.0%	3.145 ± 0.076
		2.0%	3.236 ± 0.057
	Interfacial area to aqueous volume ratio (cm^2/mL)	0.006	2.904 ± 0.392
		0.020	3.246 ± 0.310
		0.065	3.137 ± 0.212
		0.207	3.216 ± 0.131

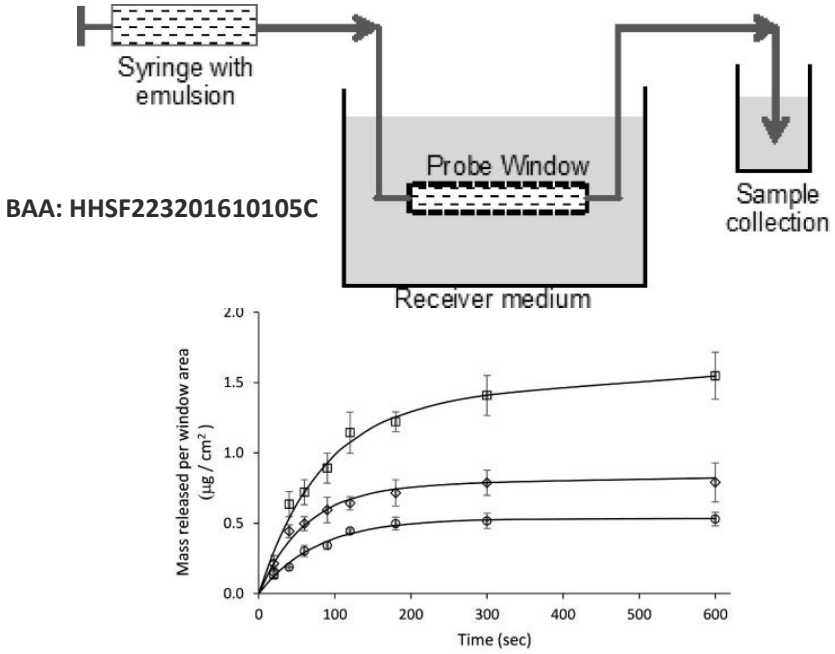
- Emulsions may contain multiple components (e.g., oil globules, micelles) with varying properties (e.g., size, drug content).
- The transfer rate of drug between these components differs, taking from seconds to a couple dozen minutes.
- Some methods may alter the formulation (e.g., phase separation after centrifugation) so may not be representative of the administered product properties (e.g., via ocular route).
- Research was done to understand the transfer kinetics of drug between various components, which allowed for a theoretical estimate of drug distribution as well as drug release.
- The globule size distribution was found to be a key parameter impacting drug distribution and release, as it can directly change the surface area of oil globules and hence the amount of surfactant available in the bulk to solubilize drug (e.g., through micelles).

- Y. Dong et al. *J Pharm Sci* (2019) 108, 2002-2011, DOI: 10.1016/j.xphs.2019.01.003
- Y. Dong et al. *J Control Release* (2019), 313, 96-105, DOI: 10.1016/j.jconrel.2019.09.010
- Y. Dong et al. *J Control Release* (2020), 327, 360-370, DOI: 10.1016/j.jconrel.2020.08.020

Ophthalmic Emulsions: In Vitro Drug Release

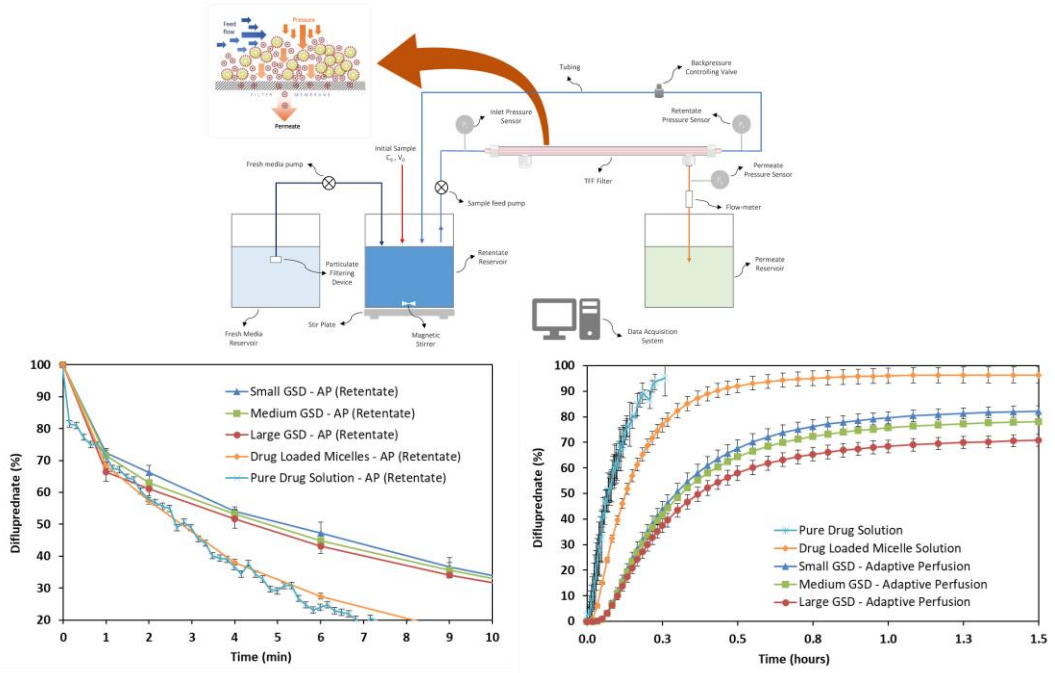
- Historically, IVRT has not been used in ophthalmic new drug development or approval. Therefore, limited information and standards are in place.
- Both internal and external research were conducted to develop understandings as well as procedures to measure drug release from emulsions (two examples below).
- Applicants are also encouraged to develop their own fit-for-purpose IVRT method, e.g., demonstrate that the method is discriminatory towards formulations with intentional changes.

Pulsatile Microdialysis Method



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

Adaptive Perfusion Method



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

GDUFA Research

- GDUFA research enables the development of PSGs for a broad range of products.

Abuse Deterrent Formulations	Complex Injectable Formulations and Nanomaterials	Long-Acting Injectables and Implants	Drug-Device Combination Products
New Guidance for Naloxone Hydrochloride; Oxycodone Hydrochloride Tablet (Nov 2020) First generic Hydrocodone Bitartrate Extended-Release Tablet (March 1, 2021)	*Revised Guidance for Ferric Oxyhydroxide Injectable (Sept 2021)* First generic Amphotericin B Liposome Injection (Dec 14, 2021)	*New Guidance for Paliperidone Palmitate Extended-Release Injectable Suspension (August 2021)* First generic Paliperidone Palmitate Extended-Release Injectable Suspension (July 6, 2021)	*New Guidance for Ethinyl Estradiol; Levonorgestrel System (Aug 2021)*
Ophthalmic Products	**Complex API Mixtures and Peptide Products**	**Topical Dermatological Products**	**Inhalation and Nasal Products**
Draft Guidance for Loteprednol Etabonate Gel (August 2021) First generic Cyclosporine Ophthalmic Emulsion (Feb 2, 2022)	*New Guidance for Semaglutide Tablet (Aug 2021)* First generic Vasopressin Injection (Dec 15, 2021)	*Draft Guidance for Estradiol Transdermal Gel, Metered (August 2021)* First generic Brimonidine Topical Gel (Sept 23, 2021)	*Guidance for Albuterol Sulfate; Ipratropium Bromide Spray, Metered (August 2021)* Albuterol Sulfate Inhalation Aerosol (April 8, 2020)

GDUFA research also facilitates industry's generic product development and FDA's pre-ANDA and ANDA assessment, and can be found on FDA's GDUFA Science & Research website.

Summary

- GDUFA provides resources to allow FDA to perform and fund research that increases access to safe, effective and high-quality generic drugs by creating and testing new tools that enable more efficient development and review of generic drugs.
- Started in 2007, FDA's product-specific guidance program provide FDA's current thinking on the type of studies and information to support the development and approval of a safe and effective generic drug product.
- GDUFA research aids the development of PSG recommendations as well as provides generic industry potential starting points and considerations in the development of their drug product and associated analytical methods to support equivalence.

Challenge Question #1

- Which of the following is NOT true about a PSG?

A. It includes recommendations about demonstration of BE

B. PSGs are posted on a quarterly basis on FDA website

C. PSG is legally binding

D. Research may be needed to support the development of PSG

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Challenge Question #2

- GDUFA research can facilitate:

A. PSG development

B. ANDA review

C. Generic product development

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