Role of IVRT in Generic Drug Development

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About the presenter

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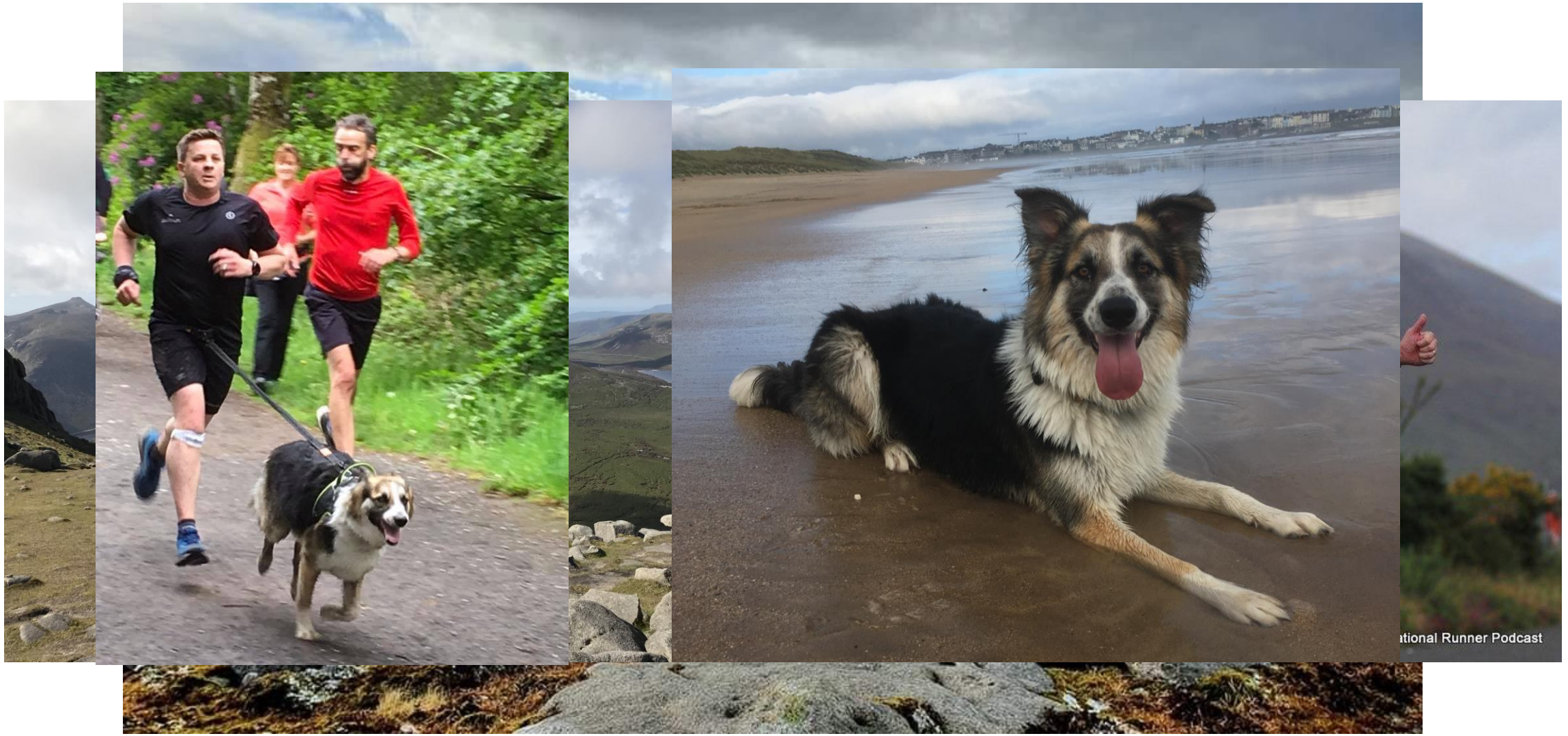
Dr Halus is an Associate Director working within Analytical Development in TEVA's Combination Products and Semi-Solids Group.

BSc in Chemistry from the University of Strathclyde in Glasgow and a PhD from the School of Pharmacy at Queens University of Belfast.

The focus of the team he leads at TEVA is on development and validation of the full range of analytical test methods for complex combination products

He has been involved in research and development of drug release test methods for many solid oral dosage forms and more novel methods for topicals, vaginal inserts, IUDs, subcutaneous implants and ophthalmic products, all in support of regulatory filings.

About the Presenter



Role of IVRT in Generic Drug Development

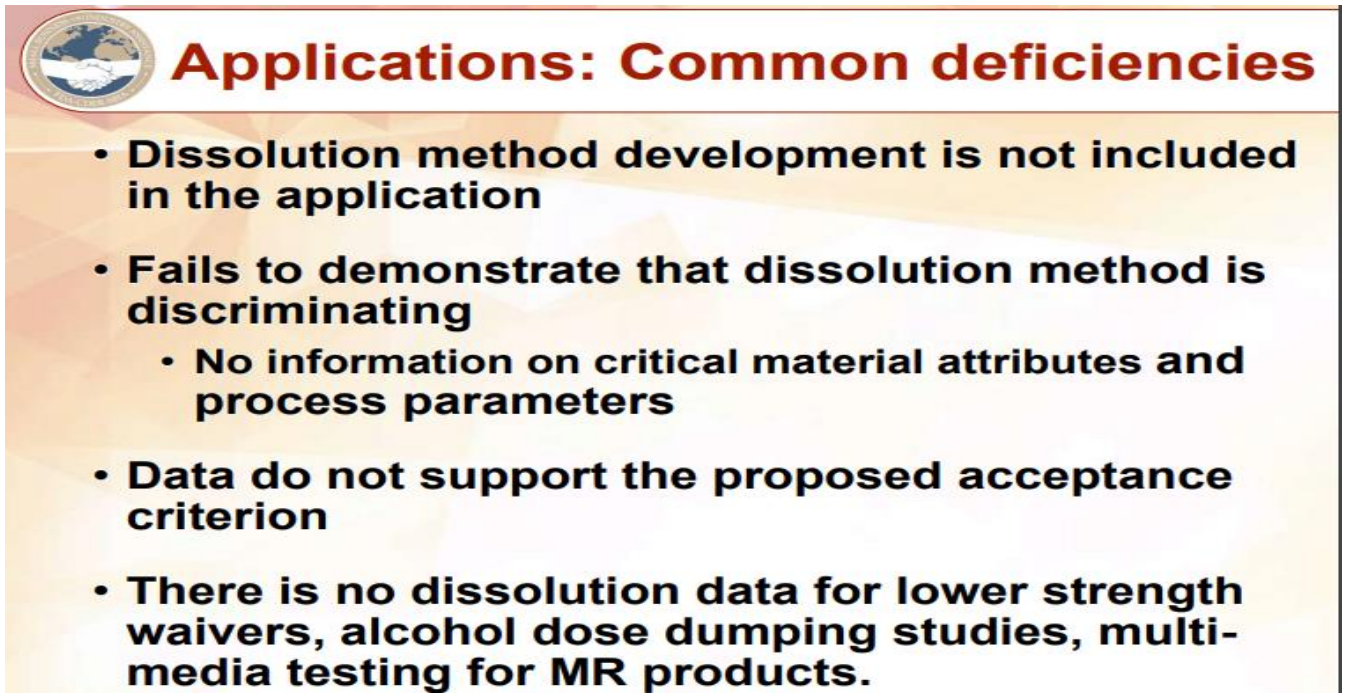
- Why do we need an IVRT?
- The IVRT is critical in supporting the regulatory filing
  - Starts with helping define the formulation and the processing parameters
  - Comparing release profiles to reference products in advance of clinical studies
  - QC release and stability testing supporting product quality in the long term

- A review of regulatory guidance and other publications tell us what the regulatory expectations are for the IVRT
  - Dissolution test parameters must be justified
  - As part of justification, dissolution test must be discriminatory

FDA: Common Deficiencies

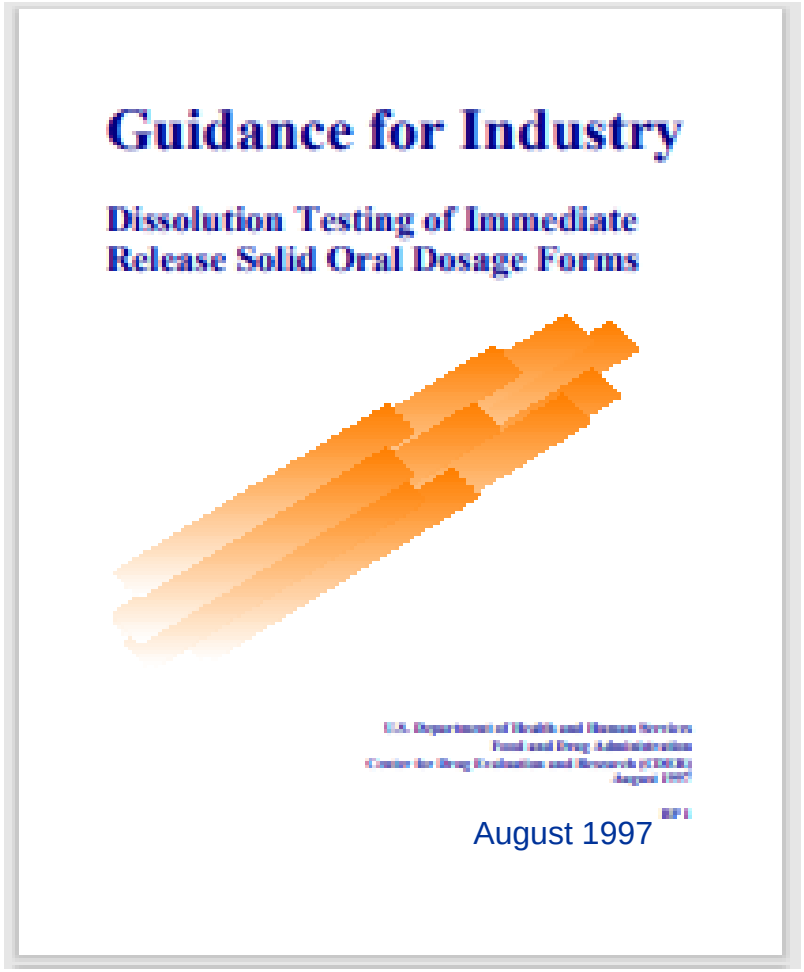
It is expected that the regulatory filing includes an IVRT that has a justifiable acceptance criteria and that is suitably discriminating

Without this filing may not be received



https://www.fda.gov/files/drugs/published/Dissolution-Method-Development-for-Generic-Drug-Products.pdf

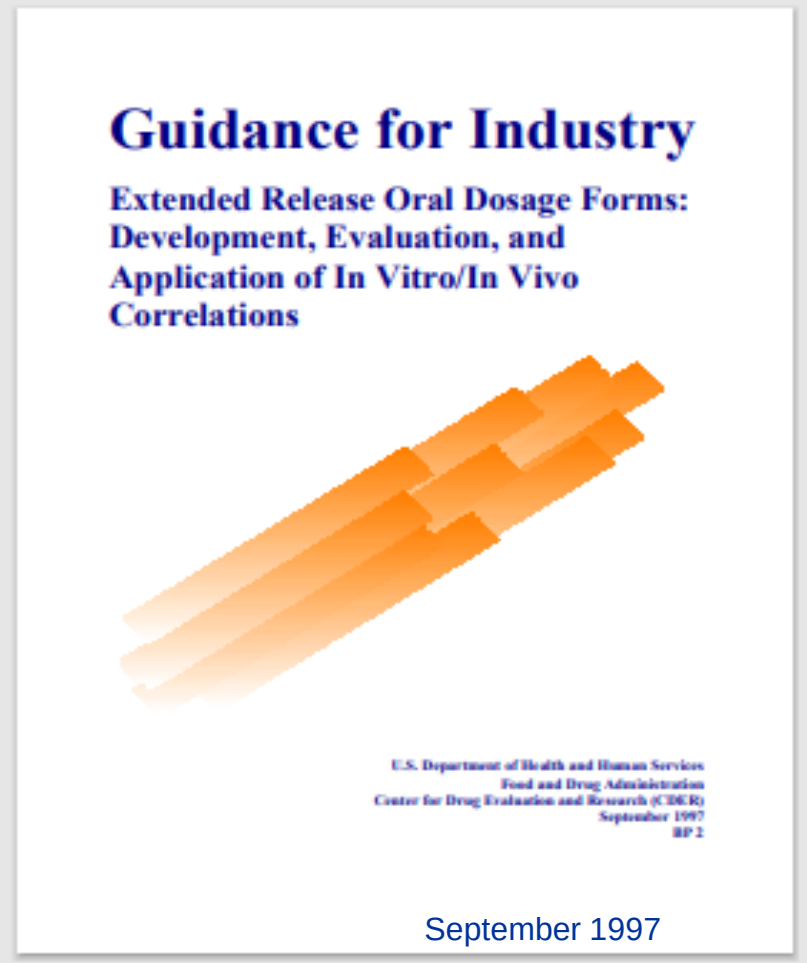
Discriminative Dissolution Method Requirement - FDA Guidance



"From a quality assurance point of view, a more discriminative dissolution method is preferred, because the test will indicate possible changes in the quality of the product before in vivo performance is affected."

https://www.fda.gov/media/70936/download

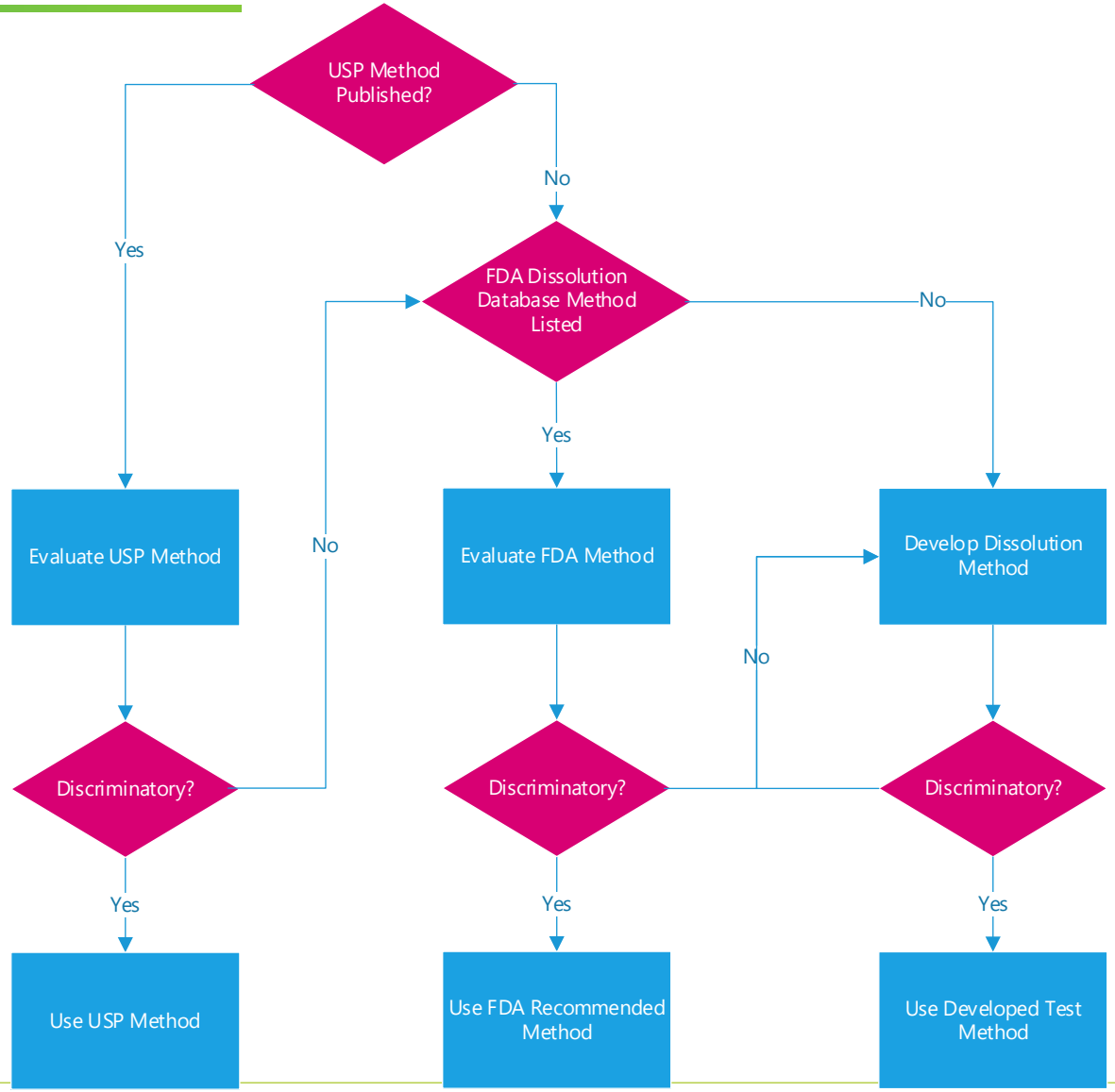
Discriminative Dissolution Method Requirement - FDA Guidance



The in vitro dissolution methodology should adequately discriminate among formulations. ….. Once a discriminating system is developed, dissolution conditions should be the same for all formulations tested in the biostudy for development of the …..

https://www.fda.gov/media/121311/download

Selecting an IVRT



Release and Stability Testing

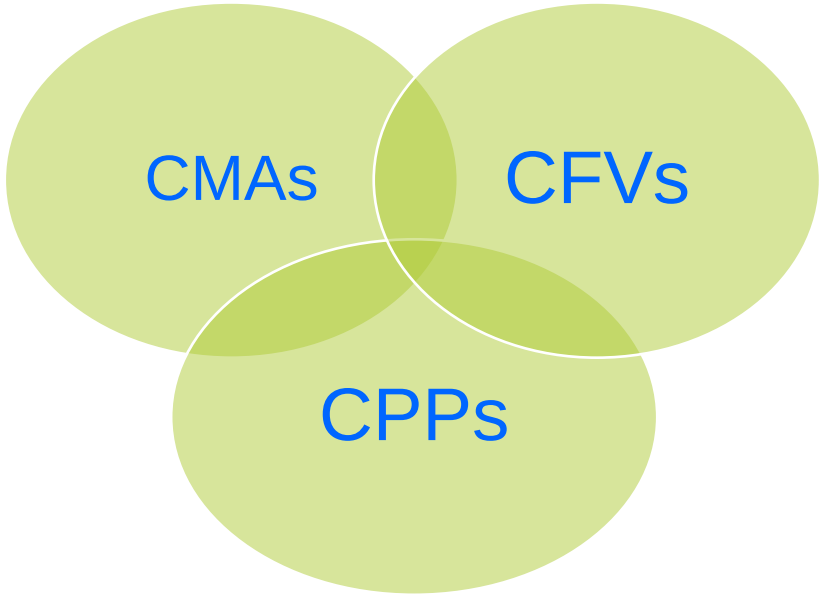
- Proposed drug release test must be supported by a development report justifying selection of;

Apparatus	Dissolution Media	Agitation Rate
Filter/Membrane Selection	Sampling Regime	Specification

- The aim of any IVRT is to be discriminatory with respect to meaningful changes in critical process parameters or excipients

What is Discriminatory Power?

- The discriminatory power of the dissolution method is **the ability of the method to detect changes in drug product performance**, generally demonstrated by determining the effect of deliberate meaningful changes in the formulation or process on dissolution characteristics



CMAs: Material Attributes
CFVs: Formulation Variables
CPPs: Process Parameters

What is Discriminatory Power?

- ICH Q8/9/10 lay out the tools to help develop robust products using a quality by design approach
  - Risk assessment of the proposed product is used to identify Critical Quality Attributes (CQAs)
  - In turn each material characteristic, formulation variable and manufacturing process parameter are risk assessed against the CQA to identify where risks exist

What is Discriminatory Power?

		Drug Product Critical Quality Attributes (* Stability Indicating CQAs)									
Step	Component / Process	Description*	Assay*	BHA Content	Content Uniformity	Related Substances*	Dissolution*	Fill Moisture	Particle Size*	Residual Solvents	Microbial Limits*
Raw Materials / Components	API	high	high	high	high	high	high	low	low	med	high
	PEG 400	high	high	high	low	high	high	low	low	low	low
	Polysorbate 20	high	low	low	low	low	high	low	high	low	high
	Povidone K-90	high	high	high	high	high	high	low	high	med	low
	BHA	high	low	low	low	low	low	low	low	low	low
	Gelatin	high	low	low	low	low	low	high	low	low	low
	Plasticizer (Glycerin and Sorbitol)	high	low	low	low	low	low	high	low	low	low
	Titanium dioxide	high	low	low	low	low	low	low	low	low	low
	Isopropyl alcohol (processing aid)	high	low	low	low	low	low	low	low	med	low
	MCT/Lecithin (processing aid)	high	low	low	low	low	low	low	low	low	low
Gelatin Mix Manufacture	Gelatin Melting	low	low	low	low	low	high	low	high	low	low
	Tranfer to Receiver Tanks	low	low	low	low	low	low	low	low	low	high
	Gelatin Conversion	high	low	low	low	low	high	low	high	low	low
	Gelatin Holding	low	low	low	low	high	high	low	high	low	high
Fill Mix Manufacture	Pre-mixing of API	high	high	high	high	high	high	low	high	low	low
	Pre-mix transfer and rinsing steps	high	high	high	high	high	high	low	high	low	low
	Main mixing	high	high	high	high	high	high	low	high	low	low
	Homogenization of suspension mixture	high	high	high	high	high	high	low	high	low	low
	Deaerate & Vent with nitrogen	low	low	low	low	low	low	low	low	low	low
	Transfer to Receiver Tanks	low	low	low	low	low	low	low	low	low	low
	Fill Holding	low	high	high	low	high	low	low	low	low	low

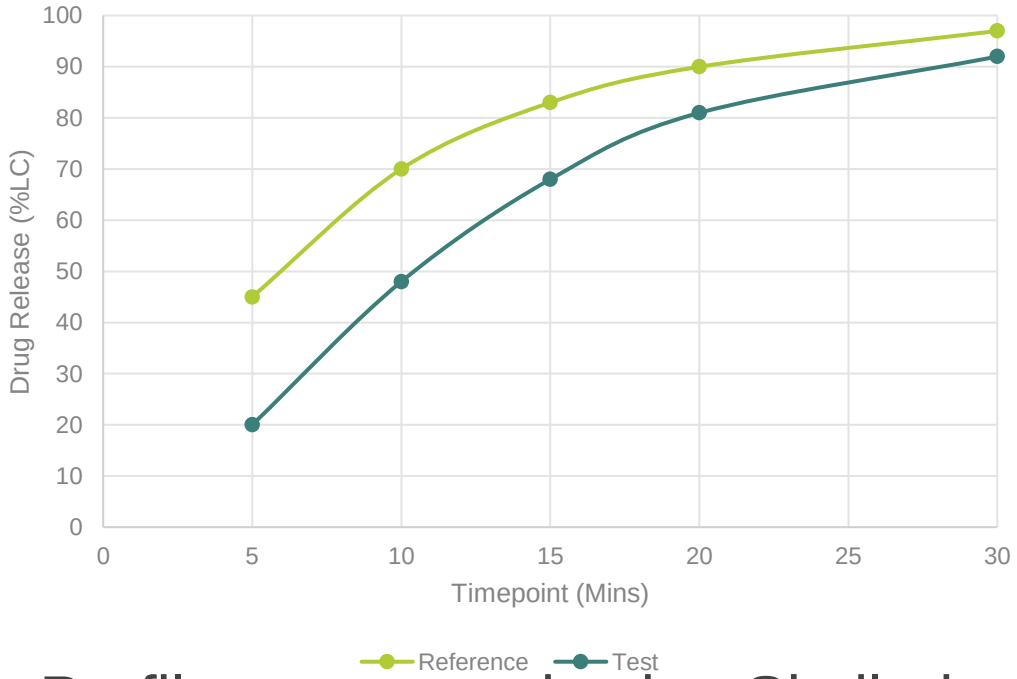
What is Discriminatory Power?

- This resulting matrix is used to determine which product variables should be varied to assess method discriminating power

- In order to establish discriminatory power batches of product with meaningful changes have to be manufactured
  - For composition ‘meaningful’ can be +/- 10% of target
  - For processing parameters range to be justified on case by case

What is Discriminatory Power?

- Discriminatory batches are tested and the drug release profile is compared to the target product.



	Drug Release (%LC)	
Time (Mins)	REFERENCE (R_t)	TEST (T_t)
	Reference	Test
5	45	20
10	70	48
15	83	68
20	90	81
30	97	92

$$f2 = 50 \times \log\{ [(1 + (1/n) \times \sum(R_t - T_t)^2]^{-0.5} \} \times 100$$

f2 = 38.5

- Profiles compared using Similarity Factor (f2)*

*FDA Guidance for Industry SUPAC IR Dosage Forms (https://www.fda.gov/media/70949/download)

Role of IVRT in Generic Drug Development

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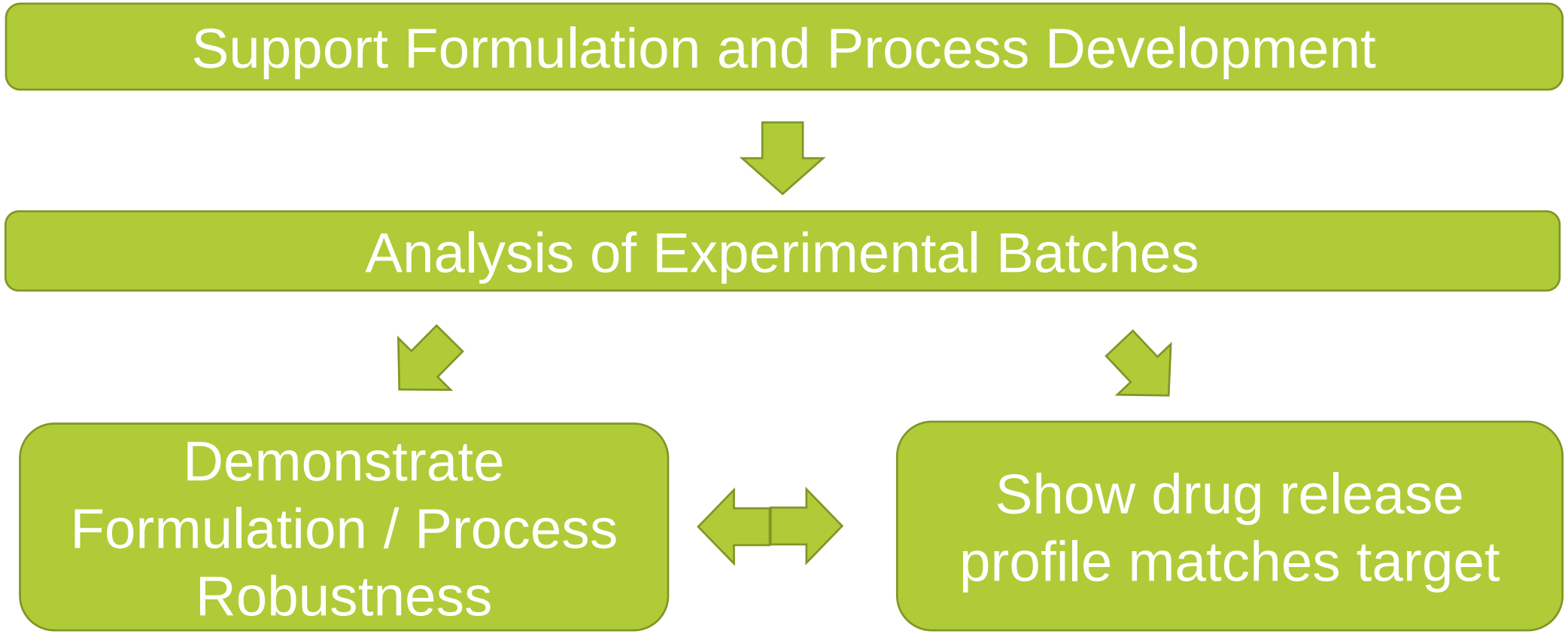

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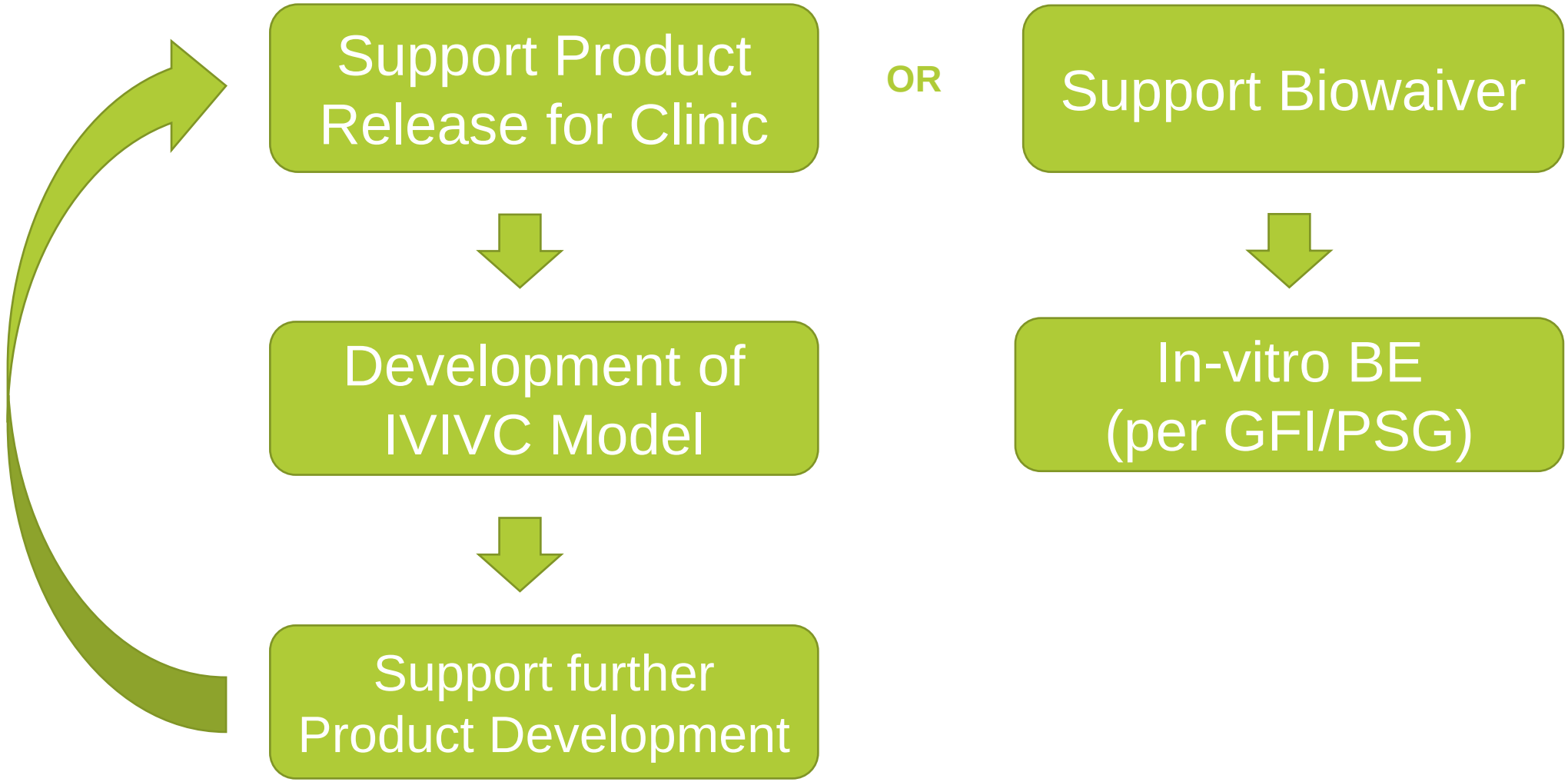

Role of IVRT in Generic Drug Development

Release and Stability Testing of Registration Batches

Ensure Batch to Batch Consistency in Commercial Production

Assessment of SUPAC

Role of IVRT in Generic Drug Development

- IVRT has a critical role in generic drug development
  - From the first experimental batches through pilot and pivotal clinical studies to the commercial process and beyond

- IVRT can be used to aid design of robust formulation and process
  - Thorough Risk Assessments of CMAs, CFVs, CPPs are essential to understanding impact to product CQAs

- IVRT will support release of product to clinic
  - As well as mitigating patient risk, can provide some degree of confidence that reference and test will match

- Following submission and approval the IVRT will support product Quality throughout rest of the product lifecycle

Role of IVRT in Generic Drug Development

- Starting point must be a discriminatory IVRT to ensure the correct decisions are being made
  - Very risky to take USP/FDA/SBOA method without challenging the discriminatory power for your product
  - Risk of failing clinic if method not discriminatory
  - Bigger risk of Major CRL or Refusal to Receive

Thank you.