Regulated Bioanalysis for Small Molecules

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Disclaimer

*This presentation reflects the views of the author. It should not be construed to represent FDA's views or policies.

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

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A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


FDA
Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence
in their *next* dose of medicine.

Learning Objectives

- Understand the regulatory scope of the BMV guidance.
- Understand the link between the BMV and data quality.
- Understand the FDA laboratory implementation of BMV guidance.

Presentation Outline

- Introduction
- BMV & data quality
- Implementation of BMV
  - Case Study I: In vivo evaluation of pediatric products of Oseltamivir (Tamiflu) and Brompheniramine in a pre-clinical pig model
  - Case Study II: Bioavailability evaluation and pharmacokinetic assessment of novel galantamine formulations
  - Case Study III: Determination of systemic exposure level of dexamethasone in rabbit following implantation of the sustained release intravitreal implant drug product.
- Summary

2018 BMV Guidance: Purposely

- This guidance applies to bioanalytical procedures such as **chromatographic assays** and **ligand binding assays** that quantitatively determine the levels of drugs, their metabolites, therapeutic proteins, and biomarkers in biological matrices.
- This recommendations can be modified with justification, depending on the specific type of bioanalytical method.
- The fit-for-purpose (FFP) concept states that the level of validation should be appropriate for the intended purpose of the study.

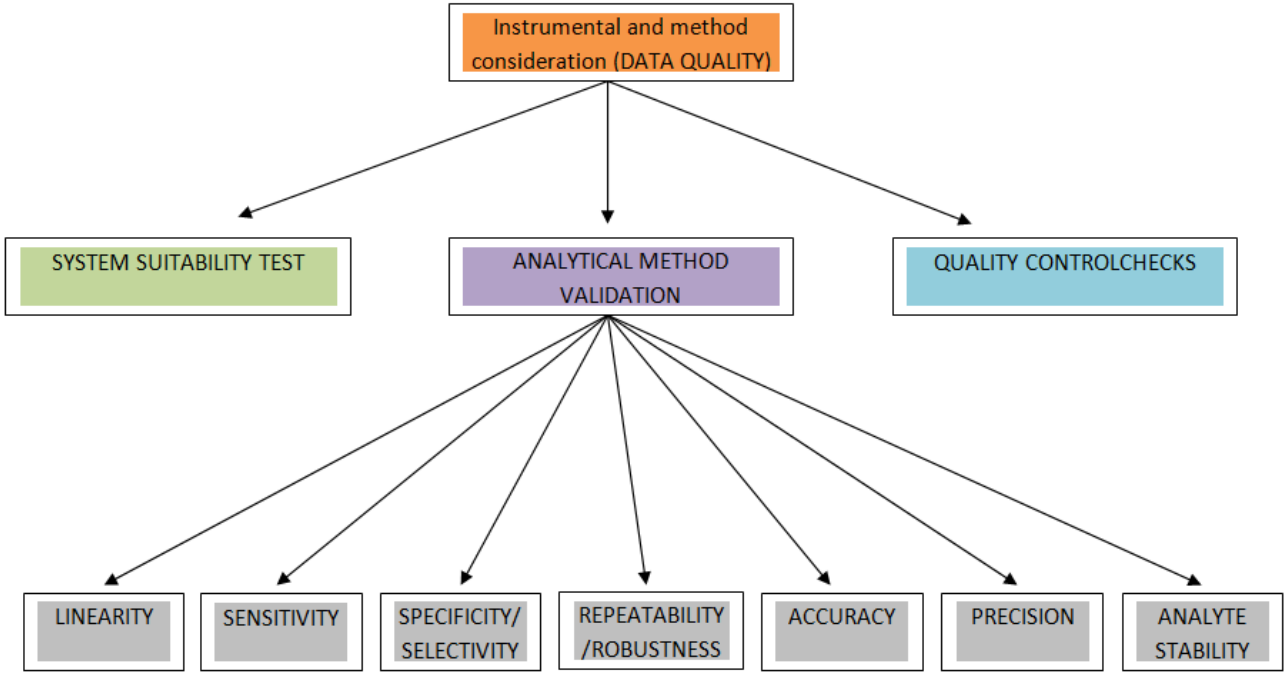
Method Validation

- Procedures that demonstrate that a method is reliable and reproducible for the intended use.
- Types of Validation:
  - **Full validation**: first time, new drug, or addition of metabolites.
  - **Partial validation**: modification of a validated method.
    - Change in sample volume.
    - Change in anticoagulant, matrix, species within matrix.
    - Change in sample processing procedures.
  - **Cross-validation**: comparison of validation parameters when two or more bioanalytical methods are used to generate data within the same study or across different studies.

Validation Batch Design

Calibration Standards		Quality Control Samples		Other Validation Samples	
Name	**Replicate**	**Name**	**Replicate**	**Name**	**Replicate**
Level 1	1	Level 1	6	Pooled blank plasma	1
Level 2	1	Level 2	6	Zero standard	1
Level 3	1	Level 3	6	System verification sample	3
Level 4	1	Level 4	6	LLOQ	6
Level 5	1			ULOQ	6
Level 6	1				
Level 7	1				
Level 8	1				
Level 9	1				
Level 10	1				

BMV & Data Quality



Case Studies

Case Study I: In vivo evaluation of pediatric products

Study Objective:

to investigate and evaluate the relative bioavailability with pharmacokinetic measurements of:

A. **two taste-masked pediatric products** brompheniramine maleate (BPM) and brompheniramine tannate (BPT), and

B. **Tamiflu** enhanced taste-masked formulation in porcine models

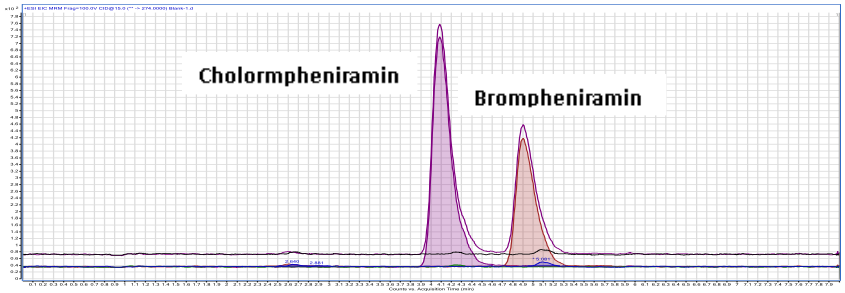
Study Design:

- Formulation drug complexes were prepared in-house.
- Overnight fasted eight male juvenile pigs were dose orally with 6mg/kg of the drug complexes.
- Plasma PK samples were collected at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours post-dose.
- Validated LC/MS method was used for the quantitative bioanalysis.

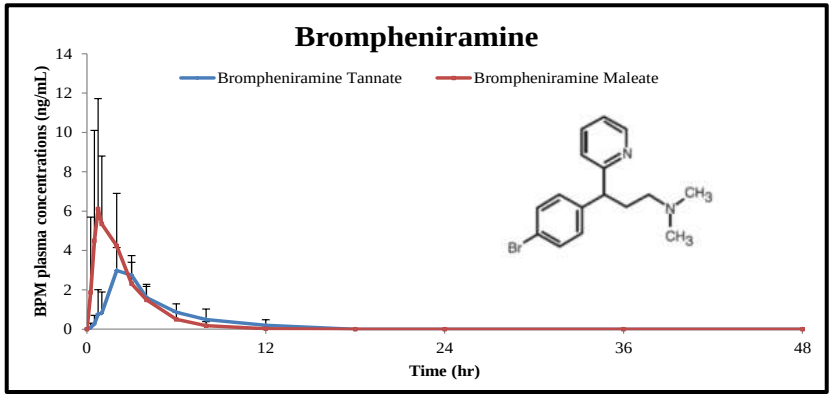
Case Study I: Brompheniramine

Study Outcome:

- The validation parameters were all found to be in accordance with BMV guidance.
- Although pigs dosed with maleate complex showed slight smaller t_{max} and higher C_{max} than those doses with tannate complex, no significant differences were observed.

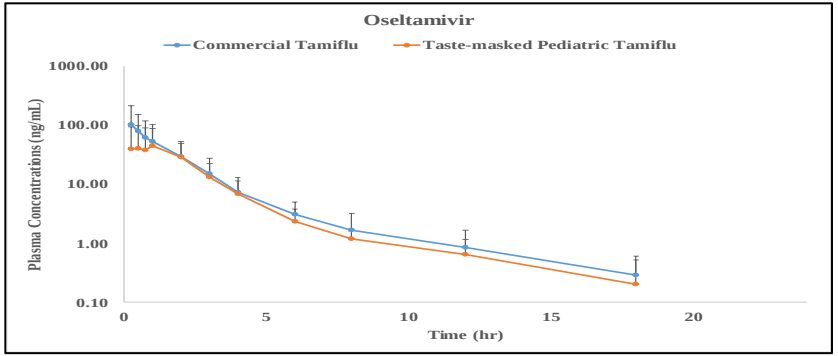


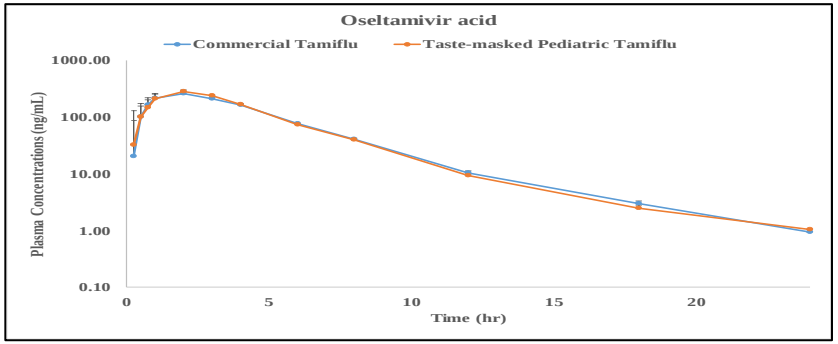
	Mean ± SD	
	Bromph. tanate	Bromph. maleate
AUC_{inf} (ng*hr/mL)	26.35± 4.26	28.48 ± 16.79
AUC_{0-t} (ng*hr/mL)	25.06 ± 3.90	27.27 ± 17.04
C_{max} (ng/mL)	6.40 ± 2.28	10.68 ± 7.71
T_{max} (hr)	2.29 ± 0.76	1.51 ± 1.19



Case Study I: Tamiflu (Oseltamivir)

Analyte	Formulation	Commercial Tamiflu		Taste-masked Pediatric Tamiflu	
	Parameters	AVE	SD	AVE	SD
Oseltamivir	AUC_{0-t} (ng*hr/mL)	164.0	137.4	119.72	103
	AUC_{inf} (ng*hr/mL)	166.7	138.6	123.61	105
	C_{max} (ng/mL)	108.0	102.9	57.87	47
	T_{max} (hr)	0.63	0.68	0.88	0.63
	$T_{1/2}$ (hr)	3.1	2.1	3.8	2.4
Oseltamivir acid	AUC_{0-t} (ng*hr/mL)	1256.0	320.1	1289.2	461
	AUC_{inf} (ng*hr/mL)	1261.1	321.1	1295.1	462
	C_{max} (ng/mL)	265.7	76.1	280.7	105
	T_{max} (hr)	2.00	0.63	2.17	0.41
	$T_{1/2}$ (hr)	3.13	1.01	3.19	1.86





Case Study II: Galantamine

Study Objective:

To evaluation of the bioavailability of novel galantamine formulations for approved indications and as a prospective medical counter-measure for use in the event of a nerve agent attack.

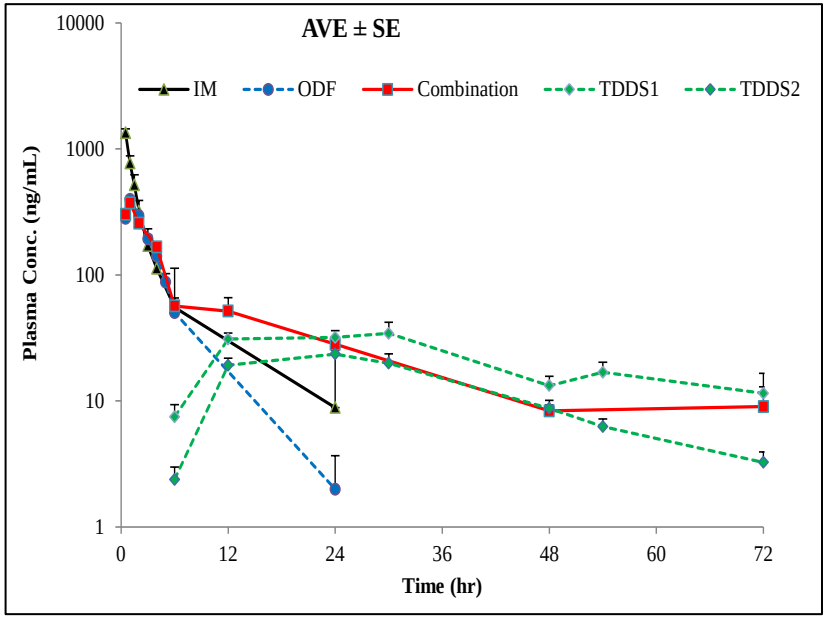
Study Design:

- Formulation drug complexes were prepared in-house.
- Overnight fasted guinea pigs were dose with galantamine through intramuscular injection (IM), transdermal drug delivery systems (TDDS), oral dissolving film (ODF) and the combination of TDDS and ODF.
- Plasma PK samples were collected at different time interval.
- Validated LC/MS method was used for the quantitative bioanalysis.

Case Study II: Galantamine

Routes	Parameters (Mean ± SD)			
	AUC_{inf} (ng*hr/mL)	AUC_{0-t} (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (hr)
IM	2347.27± 487.45	2132.84 ± 345.56	1266.65 ± 251.34	0.55 ± 0.16
ODF	1323.15 ± 289.15	1199.28 ± 200.88	399.25 ± 70.13	0.94 ± 0.18
TDDS1	1441.87 ± 725.53	1357.24 ± 670.60	48.79 ± 22.66	20.40 ± 9.03
TDDS2	988.17 ± 337.78	870.03 ± 326.09	28.67 ± 10.45	22.67 ± 6.56
Combination	2717.95 ± 781.40	2460.25 ± 524.47	365.24 ± 102.51	1.00 ± 0.43

The pharmacokinetic results have demonstrated that the galantamine oral dissolving film and two transdermal drug delivery systems were all bioavailable.



Jiang W., Naresh P., Xu X, Krishnaiah & Patrick Faustino., BioMed Chrom 2018

Case Study III: Dexamethasone Intravitreal Implant

Study Objective:

Determination of systemic exposure level of dexamethasone in rabbit following implantation of the sustained release intravitreal implant drug product.

Study Design:

- Overnight fasted New Zealand Rabbit was dose with dexamethasone intravitreal implant (0.7 mg).
- ***Plasma PK samples*** were collected at pre-dose, 8 hrs, 1, 2, 3, 4, 7, 11, 14, 18, 22, and 25 days post-dose. ***Aqueous humor***, ***Vitreous humor*** and ***retina tissue*** samples were collected at different time intervals.
- The LC-MS/MS bioanalytical method was designed according the BMV guidance requirements as **fit for purpose** and applied to a pilot PK study.

Case Study III: Dexamethasone Intravitreal Implant

Matrix	Sampling Time	Concentration (ng/mL or ng/g)	
		Dexamethasone	6ß-hydroxydexamethasone
Plasma	0 h – Day 7	BLQ	BLQ
	Day 11	0.10	BLQ
	Day 14	0.10	BLQ
	Day 18	0.17	BLQ
	Day 22	0.21	BLQ
	Day 25	0.24	BLQ
Aqueous humor	0 h	BLQ	BLQ
	Day 2	21.6	0.25
	Day 9	25.9	0.27
	Day 16	103	0.56
	Day 23	177	0.61
	Day 25-Con	BLQ	BLQ
	Day 25	93.2	0.31
Vitreous humor	Day 25-Con	BLQ	BLQ
	Day 25	318	0.51
Retina	Day 25-Con	BLQ	BLQ
	Day 25	2120	2.16

Summary

- Regulatory bioanalytical method validation is essential for the bioanalysis of pre-clinical studies.
- Bioanalysis of complex biological matrixes by new technologies will reduce sample processing time and improve data interpretation.
- The current bioanalytical method validation guidance supported by emerging bioanalytical tools can advance the regulatory science and delivery high quality data to support product quality over the product lifecycle.

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