ADA Validation Testing and Reporting Global Harmonization

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EBF

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ADA Validation Testing and Reporting Global Harmonization (ADAH) Objectives

- **Objective:**
  - Provide recommendations for the harmonization of validation data reporting to reduce health authority queries received during filing
    - Comprehensive validation data summary tables w/ change history and data links
    - Publish recommendations in a manuscript, submission Dec-2019

- **Collaboration:**
  - Twenty-nine BioPharma and CRO organizations
  - FDA included throughout process as core contributors and advisors
  - Partner with EBF representatives for EU alignment

Sub-Teams and Leaders

1. Population-specific (in-study) cut point, Carol Gleason, BMS
2. System suitability criteria for in-study plate acceptance, Viswanath Devanaryan, GSK
3. Assay sensitivity and LPC selection, Kelli Phillips, PPD
4. Drug interference, Marta Manning, Amgen
5. Target tolerance, Honglue Shen, Teva
6. Sample stability, Susan Richards, Sanofi
7. Selectivity, Joanne Goodman, MedImmune
8. Multi-domain specificity, Shobha Purushothama
9. MRD and sample processing for titer reporting, Jad Zoghbi, Sanofi

Disclaimer

- The proposed model acknowledges that the scope of information to be presented will depend on the therapeutic modality and the immunogenicity risk profile.

- While it is not feasible to define criteria that reflect the full diversity of appropriate fit-for-purpose practices, we provide examples of approaches that are consistent with current regulatory standards and would suffice for most ADA assay platforms.

- It is important to emphasize that many avoidable questions arise during the regulatory review process because pertinent information is either missing or not clearly presented in the method validation report.

Table 1. Method Summary *(examples of data collected in italics)*

Project(s)			
Method Id(s)			
Validation Id(s)			
Dates method in use			
Bioanalytical site			
Analyte	*Anti-drug antibodies*		
Critical Reagents	**Analyte/Reagent**	**Source/Lot(s)**	**Expiry or retest date**
Capture reagent	*Biotin-Drug*		
Detection reagent	*Ruthenylated-Drug*		
Positive control/s	*Rabbit anti-drug pAb*		
Negative control/s	*Healthy human serum*		
Assay Information	**Platform**	*Electrochemiluminescent*	
	Format	*Bridging, Direct, Indirect*	
	Sample Pre-treatment	*x-fold MRD, Acid Dissociation, SPEAD, BEAD, ACE, PandA dilution factor*	
	Drug conc. in confirm tier	*x ug/mL*	
	Sample volume collected	*500 uL-1mL*	
	Sample volume required for 3 tier analysis	*x uL-x uL*	
Sample Storage	*-20°C or colder (no frost-free freezers) for up to 3 months*		
	-60°C or colder for up to 36 months		

Control Criteria	Tier	Control (conc.)	Run Acceptance Criteria
	Screen	*NC*	*≤ 20% CV between duplicates*
			Median or mean NC signal ≤ upper bound (99%): xx
		LPC (x ng/mL) *HPC (x (ng/mL)*	*≤ 20% CV between duplicates*
			HPC >LPC ≥ SCP
			LPC/NC ratio ≥ lower bound (99%): xx
			HPC/NC ratio ≥ lower bound (99%): xx
	Confirm	*NC-I*	*NC-I < CCP*
		LPC-I *HPC-I*	*LPC-I ≥ CCP*
			HPC-I ≥ CCP
			Upper and lower bounds may also be established
	Titer	*Titer controls*	*≤ 20% CV for dilutions involved in titer calculation*
			Titer is within XXX - XXX

Sample Criteria	Tier	%CV	Result Reporting
	Screen	*≤ 20% CV between duplicates*	*Samples with mean replicate response ≥ the SCP are considered "potential positive" and progress to confirmatory analysis.*
			Samples with mean replicate response < the SCP are reported as "negative."
	Confirm	*≤ 20% CV between duplicates*	*Samples with % inhibition ≥ CCP are considered "positive" and progress to titer analysis.*
			Samples with % inhibition < CCP are reported as "negative."
	Titer	*≤ 20% CV for dilutions involved in titer calculation*	*≥1 dilution must be <SCP.*
			The last dilution above the cut point will be used to report sample titer.
Links to reports and amendments			

Table 1. Method Summary Top Line

- Used to capture salient method details over the life cycle of use.

- The validation report should clearly detail any changes to the methods (outlined in Table 1).

- Special attention to overall control trending is important to avoid continuous updates to control criteria and possibly uncontrolled assay drift.
    - Trending data may be requested by health authorities and there has been discussion about adding it to the bioanalytical reports.
    - Changes to control criteria over the lifecycle of the method should be documented.

- Critical reagent changes should be outlined in table 1 and described in the validation addendum.
    - Critical reagent details beyond those in table 1 should be described in the validation report, including purpose of use, i.e. method development, validation, domain specificity and/or sample analysis.
    - Pertinent reagent characterization information should be described in the validation report such as concentration, purification and labeling procedures and results.

Table 2. Validation Summary

Validation Report Title	
Validation ID(s)	

Screening Cut Point (*Floating, Multiplicative, 95% upper limit*)	**Source Data**	**Population (n)**	**SCP Factor**
	Val report#; Table#	NHS (n)	x.x
		Pop 1 (n)	x.x
	In-Study (Amend#)	Pop 1 (n)	x.x

Cumulative cut point data: For all populations should be recorded in Table 1 (i.e. a single location) for traceability

Confirmatory Cut Point *(%inhibition, Fixed, Floating, 99% upper limit*)	**Source Data**	**Population (n)**	**CCP**
Whole Drug	Val report#; Table#	NHS (n)	xx%
		Pop 1 (n)	xx%
	In-Study (Amend#)	Pop 1 (n)	xx%

Domain Specificity CP	Source Data	Population (n)	CCP
Domain x	Val report#; Table#	NHS (n)	xx%
		Pop 1 (n)	xx%
	In-Study (Amend#)	Pop 1 (n)	xx%

Titer Cut Point (*99.9% upper limit, other*)	Source Data	Population (n)	TCP Factor
	Val report#; Table#	NHS (n)	x.x
		Pop 1 (n)	x.x
	In-Study (Amend#)	Pop 1 (n)	x.x

Domain testing

- Should be according to an immunogenicity risk assessment and should be described in the validation report.
- All domain testing should be included in Table 2 w/ pertinent PC described in Table 1.

Sensitivity (*pAb in neat matrix*)	Source Data	Tier	CP (Population)	Conc. (ng/mL)
	Val report#; Table#	Screen	x.x (NHS)	
		Confirm	xx% (NHS)	
	Amend#	Screen	x.x (Pop 1)	
		Confirm	xx% (Pop 1)	

Population specific sensitivity:

- Can frequently be calculated by applying population-specific CPs to the sensitivity curve in NHS
- In some cases, it may be needed to determine sensitivity by spiking the PC into the diseased matrix

Drug Tolerance (pAb/drug in neat matrix)	Source Data	Tier	CP (Population)	PC Conc. (ng/mL)	Tolerated Drug Conc. (µg/mL)
	Val report#; Table#	Screen	x.x (NHS)	LPC conc.	Conc. 1
				100 ng/mL	Conc. 2
				250 ng/mL	Conc. 3
		Confirm	xx% (NHS)	LPC conc.	Conc. 1
				100 ng/mL	Conc. 2
				250 ng/mL	Conc. 3
	Amend#	Screen	x.x (Pop 1)	LPC conc.	Conc. 1
				100 ng/mL	Conc. 2
				250 ng/mL	Conc. 3
		Confirm	xx% (Pop 1)	LPC conc.	Conc. 1
				100 ng/mL	Conc. 2
				250 ng/mL	Conc. 3

Drug tolerance:

- Can frequently be calculated by applying population-specific CPs to the DT samples in NHS
- In some cases, it may be needed to determine DT by spiking the PC/drug into the diseased matrix
- It is helpful to describe what levels of drug are expected in the ADA samples to put the drug tolerance data into context.

(If you do not do this, expect a HA query during filing)

Target tolerance can be reported similar to drug tolerance.

Selectivity	Source Data	Tier	Population	CP (Pop)	PC Conc. (ng/mL)	Met Criteria
	Val report #; Table#	Screen	NHS	x.x (NHS)	**Blank**	x/10
					LPC	x/10
		Confirm	NHS	xx% (NHS)	**Blank**	x/10
					LPC	x/10
	Amend#	Screen	Pop 1	x.x (Pop 1)	**Blank**	x/10
					LPC	x/10
		Confirm	Pop 1	xx% (Pop 1)	**Blank**	x/10
					LPC	x/10

Pre-existing antibody prevalence	Source Data	Population	Prevalence
	Val Report #; Table#	NHS	x% (x/x)
	Amend#	Pop 1	x% (x/x)

Selectivity

- Should be tested in each disease indication.
- 8/10 individuals spiked w/ PC should meet criteria.
- Data from screen cut point individuals can be used for blank sample selectivity reporting.
- If selectivity cannot pass at the LPC, a higher level PC may be tested.
- If the sensitivity in diseased matrix is vastly different than that in NHS, you may consider establishing sensitivity, DT and TT in the diseased matrix.

Control Precision (Val report #; Table #)	Level	Conc. (ng/mL)	Screen %CV Signal or Ratio		Confirm %CV %Inhibition	
			Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
	HPC					
	MPC					
	LPC					
	NC					
	TC1-X					

Hook Effect	(Val report#; Table#)	No apparent hook effect observed at concentrations up to x ng/mL
Hemolysis	(Val report#; Table#)	No effect up to x
Lipemia	(Val report#; Table#)	No effect up to x
Thawed matrix stability (hours)	(Val report#; Table#)	x hours at 2-8 °C, x hours at RT
Processed sample stability (MRD, etc.)	(Val report#; Table#)	x hours at 2-8 °C, x hours at RT
Freeze-thaw stability (cycles)	(Val report#; Table#)	x cycles thawed for x hrs cumulatively at RT

Table 2. Validation Data Summary Top Line

- Used to capture salient validation data details over the life cycle of use.

- Fields have been included for the first clinical population with the expectation, that this table will be updated with details pertinent to further populations and filings.

- Precision is tested and reported across all control levels during validation, including typically 5 titer controls spanning the assay cut point, but only the NC, LPC and HPC are carried into in sample analysis.

- Any updates to the control levels as part of assay life cycle management or amended testing (such as additional selectivity testing) should be clearly noted in Tables 1 and 2.

- Impact assessment should be described for drug tolerance and target tolerance in the validation report specific to the levels of drug or target expected in study samples. (If this is not done, expect a HA query during filing).

If a reviewer cannot find the data required to FULLY understand the suitability of the assay to support a specific filing, expect HA queries during filing. THANK YOU!

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