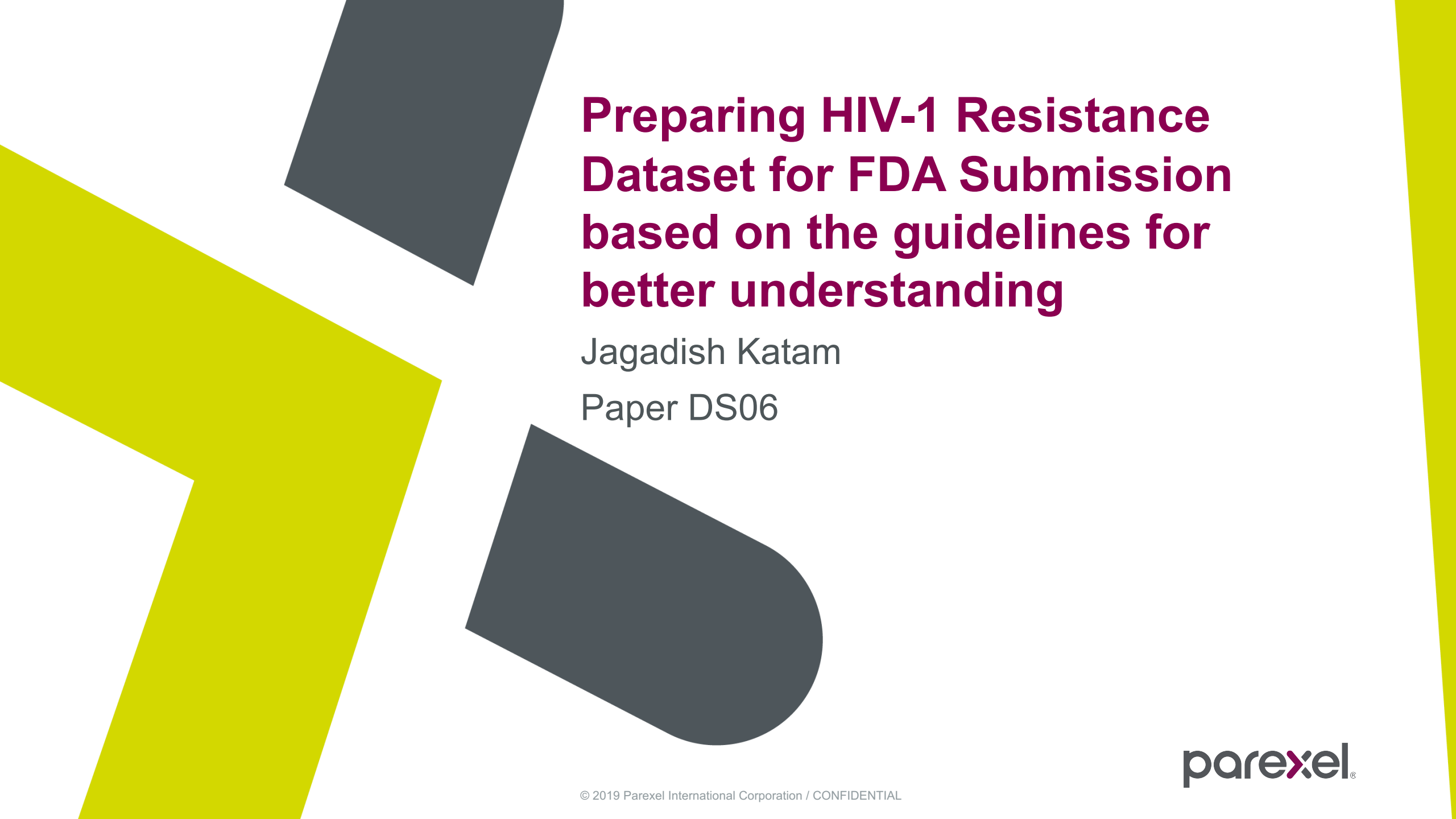




Preparing HIV-1 Resistance Dataset for FDA Submission based on the guidelines for better understanding

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Agenda

- Guidance for Submitting HIV-1 Resistance Data
- Resistance Data Includes
 - Patient Data
 - Endpoint Data
 - Genotypic Data
 - Phenotypic Data

Guidance for Submitting HIV-1 Resistance Data

- › Sponsors are encouraged to use the following sample format for submitting HIV-1 resistance data.
- › The ADRES (Resistance) dataset combines patient data, endpoint data, genotypic data, and phenotypic data. There are several ways datasets can be subdivided (i.e., by clinical study, baseline isolates, or virologic failure isolates) and this should be discussed with the Division of Antiviral Products (DAVP) before submission.

Cont'd.

- To identify any potential formatting problems as early as possible, all sponsors are encouraged to submit preliminary (or mock) resistance datasets to the DAVP before assembling formal clinical trial resistance datasets.
- The specific criteria for defining virologic failures should be discussed with the DAVP and may include multiple primary and secondary protocol endpoints.
- The endpoints for virologic and resistance outcome analyses should be consistent.
- Sponsors should consult with the DAVP in advance if considering alternative approaches to any of the recommended column headings, variables, or definitions.

Patient Data

- **USUBJID:** Unique subject identification number (ID number should be unique for all studies).
- **ARM:** Treatment group.
- **VISIT:** (e.g., SCREENING, BASELINE, DAY#, WEEK#, FOLLOWUP WK#). Visit windows should be as defined in the protocol or statistical analysis plan.
- **VISITDY:** Study day (planned), protocol-defined, relative to initiation of protocol treatment.

ISOLID

- **ISOLDY:** Study day (actual) of isolate, relative to initiation of protocol treatment.
- **ISOLID:** Unique identifier for isolate analyzed. To derive, we considered the last 2 digits from STUDYID and last 4 digits from SUBJID and concatenated with '00000' and then add with 100+ISOLDY. So it makes it unique per every visit per subject.

STUDYID	SUBJID	VISIT	VISITDY	ISOLDY	ISOLID
200121	101200	Screening	-28	-15	21120000085
200121	101200	Day 1	1	1	21120000101
200121	101200	Week 4	29	29	21120000129
200121	101200	Week 8	57	57	21120000157
200121	101200	Week 12	85	85	21120000185
200121	101200	Week 16	113	113	21120000213
200121	101200	Week 24	169	169	21120000269
200121	101200	Week 36	253	251	21120000351
200121	101200	Week 48	337	335	21120000435
200121	101200	Week 60	421	412	21120000512

HIV-1 ARV Variables

- **HIVHIST:** Previous therapeutic products (listing of all previous antiretrovirals (ARVs)).
- **EXTRTHIV:** Concomitant HIV-1 treatment drugs.
- **PRVARV1:** Previous HIV-1 ARV product (e.g., AMPRENAVIR, ATAZANAVIR). Additional columns should be added as needed to provide information on multiple ARV exposures (e.g., PRVARV2, PRVARV3). NULL if no previous ARV products.

HIVHIST & PRVARV1

STUDYID	SUBJID	VISIT	HIVHIST	PRVARV1	PRVARV2
200121	101200	Screening	EFAVIRENZ, EMTRICITABINE	EFAVIRENZ	EMTRICITABINE
200121	101200	Day 1	EFAVIRENZ, EMTRICITABINE	EFAVIRENZ	EMTRICITABINE
200121	101200	Week 4	EFAVIRENZ, EMTRICITABINE	EFAVIRENZ	EMTRICITABINE
200121	101200	Week 8	EFAVIRENZ, EMTRICITABINE	EFAVIRENZ	EMTRICITABINE
200121	101200	Week 12	EFAVIRENZ, EMTRICITABINE	EFAVIRENZ	EMTRICITABINE
200121	101200	Week 16	EFAVIRENZ, EMTRICITABINE	EFAVIRENZ	EMTRICITABINE
200121	101200	Week 24	EFAVIRENZ, EMTRICITABINE	EFAVIRENZ	EMTRICITABINE
200121	101200	Week 36	EFAVIRENZ, EMTRICITABINE	EFAVIRENZ	EMTRICITABINE
200121	101200	Week 48	EFAVIRENZ, EMTRICITABINE	EFAVIRENZ	EMTRICITABINE

Endpoint Data

- **HIVVLBL:** HIV-1 ribonucleic acid (RNA) (copies/mL) at baseline (identify assay in column heading description).
- **LOGVLBL:** HIV-1 RNA (log10 copies/mL) at baseline.
- **HIVVL:** HIV-1 RNA (copies/mL) at time points in protocol (e.g., Week 24 and Week 48); one row for each time point. HIV-1 RNA (copies/mL) from additional time points not specified in protocol can also be included.
- **LOGHIVVL:** HIV-1 RNA (log10 copies/mL) at all time points from protocol, one row for each time point. HIV-1 RNA (log10 copies/ml) from additional time points not specified in protocol can also be included.

Protocol-defined Virologic Failure

- › **NONRECAT**: Failure or Nonresponder category for currently tested therapy as defined by the protocol (e.g., REBOUND).
- › Rebound is defined as Confirmed rebound in plasma HIV-1 RNA levels to ≥ 200 c/mL at any time (not necessarily immediately) after prior confirmed suppression to < 200 c/mL.
- › **VFFL**: A flag (Y or NULL) used to indicate the specific study visit in which the subject met the criteria for protocol-defined virologic failure (e.g., rebound, end of treatment).

STUDYID	SUBJID	VISIT	HIVVL	NONRECAT	VFFL
200121	101200	Screening	353198		
200121	101200	Day 1	341817		
200121	101200	Week 4	72		
200121	101200	Week 8	39		
200121	101200	Week 12	52		
200121	101200	Week 16	71		
200121	101200	Week 24	39		
200121	101200	Week 36	48		
200121	101200	Week 48	39		
200121	101200	Week 60	350	Rebound	Y
200121	101200	Week 72	280		

Discontinuation Variables

- **DISCTXFL:** A flag used to indicate subject discontinued from protocol treatment (Y or N).
- **DISCTXVL:** HIV-1 viral RNA load when subject discontinued protocol treatment.
- **DISCREAS:** Reason for early protocol treatment discontinuation (e.g., ADVERSE EVENT, DEATH, OTHER); or NULL if no information available or not applicable. Reasons are defined according to protocol or statistical analysis plan.

STUDYID	SUBJID	VISIT	HIVVL	DISCTXFL	DISCTXVL	DISCREAS
200121	101200	Screening	353198	Y	280	Lack of efficacy
200121	101200	Day 1	341817	Y	280	Lack of efficacy
200121	101200	Week 4	72	Y	280	Lack of efficacy
200121	101200	Week 8	39	Y	280	Lack of efficacy
200121	101200	Week 12	52	Y	280	Lack of efficacy
200121	101200	Week 16	71	Y	280	Lack of efficacy
200121	101200	Week 24	39	Y	280	Lack of efficacy
200121	101200	Week 36	48	Y	280	Lack of efficacy
200121	101200	Week 48	39	Y	280	Lack of efficacy
200121	101200	Week 60	350	Y	280	Lack of efficacy
200121	101200	Week 72	280	Y	280	Lack of efficacy

Genotypic Data

- Genotypic data should be provided for the HIV-1 target, one amino acid per column, with the wild-type (WT) amino acid in the column heading. Changes from WT standard sequence should be indicated in the row (i.e., blanks indicate no change).
- For reverse transcriptase (RT), RTAXXX where A = amino acid code and XXX is amino acid position (e.g., RTK162, RTK288); for protease (PR), PRAXXX (e.g., PR I084, PRL090); for integrase (IN), INAXXX.

Derive Mutation Variables

› The mutation dataset (ADPF)

STUDYID	SUBJID	VISIT	PARAM	PARAMCD	CODON	AVALC	DNAREG
200121	101200	DAY 1	Amino Acid	AA	11	E11D	INTEGRASE
200121	101200	DAY 1	Amino Acid	AA	17	S17T	INTEGRASE
200121	101200	DAY 1	Amino Acid	AA	71	A71V	PROTEASE
200121	101200	DAY 1	Amino Acid	AA	208	P79P/S	PROTEASE
200121	101200	DAY 1	Amino Acid	AA	218	A288T	REVERSE TRANSCRIPTASE
200121	101200	DAY 1	Amino Acid	AA	219	C162S	REVERSE TRANSCRIPTASE

› In Resistance Dataset

STUDYID	SUBJID	VISIT	INE011	INS017	PRA071	PRP079	RTA162	RTC288
200121	101200	DAY 1	D	T	V	P/S	S	T

Derive Insertion Mutations

› Handling Insertion mutations

STUDYID	SUBJID	VISIT	PARAM	PARAMCD	CODON	AVALC	DNAREG
200121	101200	DAY 1	Amino Acid	AA	254	254 1G	INTEGRASE

- › In resistance dataset the naming convention for the insertion mutation variable names should follow the below approach:
 - › region (2 chars) + wild type (1 char, for insertion case: if wildtype is unknown, using '-' as replacement) + position (3 chars)+A or B or C (for insertion case only: ._1X means the first insertion using A, 2nd using B, 3rd using C, etc.,).

STUDYID	SUBJID	VISIT	IN_254A
200121	101200	DAY 1	G

Assay

- › **GENOMET**: Genotypic assay name. When we get the mutation data from central lab, the type of assay performed is collected, that assay name is displayed in this variable.

STUDYID	SUBJID	VISIT	GENOMET
200121	101200	DAY 1	GSIN, PSGT
200121	101200	Week 48	GSIN, PSGT

- › **GENOFAIL**: This flag is used to identify samples with sufficient HIV-1 RNA to be analyzed but results not reported because of poor sequence quality or other technical reasons (e.g., RT-PCR amplification not successful) (Y or NULL).
- › We might receive resistance data that comes from mixed datasets: PSGT, PSIN, GSIN (primary assays) vs PSGT+IN (secondary assay). Sometimes the primary assay could be secondary assay and vice versa depending on the assay results.

Assay

- If one of the primary assay does not work for a specific timepoint, we might report the secondary assay if data is available. If all primary assays for a specific timepoint work then we report primary.
- For example, for baseline if the same assay section (PSGT, PSIN, GSIN) works then it is reported. If at least one of PSGT or PSIN or GSIN doesn't work then we report secondary PSGT+IN.
 - PSGT - provides both geno and pheno data for PR/RT (NRTI and NNRTI) only.
 - PSIN - Provides pheno data on Integrase only.
 - GSIN - Provides geno data on Integrase only.
 - PSGT+IN - Secondary assay used if PSGT or GSIN assay fails; it provides both geno and pheno data on PR, RT and Integrase.

Resistance Analysis

- **RESISTFL:** A resistance analysis flag is used to identify any isolate/time point (including baseline, on-treatment, and during follow-up) with resistance analysis data reported. This flag should allow reviewers to pull out all reported resistance data (Y or NULL). It should be specific for all the 3 DNA regions as below

STUDYID	SUBJID	VISIT	GENOMET	RESISTR	RESISTPR	RESISTIN	RESBLRT	RESBLPR	RESBLIN
200121	101200	DAY 1	GSIN, PSGT	Y	Y	Y	Y	Y	Y
200121	101200	Week 48	GSIN, PSGT	Y	Y	Y			

- Similarly we need to derive the same variables for baseline records.

Count of Substitutions

- **TOTINSTI**: Column with total number of INSTI substitutions in subject isolate (for baseline and endpoint isolates). These are Resistance Associated Mutations. We need to derive same for other DNA regions as well.

STUDYID	SUBJID	VISIT	PARAM	PARAMCD	CODON	AVALC	DNAREG
200121	101200	DAY 1	Amino Acid	AA	74	L74I	INTEGRASE
200121	101200	DAY 1	Amino Acid	AA	30	D30N	PROTEASE
200121	101200	DAY 1	Amino Acid	AA	41	M41L	REVERSE TRANSCRIPTASE

- We count the number of mutations at that timepoint and put that count in the Variables below in resistance dataset

STUDYID	SUBJID	VISIT	TOTINSTI	TOTNRTI	TOTNNRTI	TOTPI
200121	101200	DAY 1	1			
200121	101200	DAY 1		1		
200121	101200	DAY 1				1

Count of Substitutions - DTG

➤ **TOTDRG**: Column with total number of target substitutions (or mutations for genome targeting products) in subject isolate (for baseline and endpoint isolates) for a drug with a novel target. DRG is a placeholder for the three-character abbreviation of drug.

Major Integrase Inhibitor (INSTI) Resistance Mutations										
Consensus	66 T	92 E	118 G	138 E	140 G	143 Y	147 S	148 Q	155 N	263 R
Bictegravir (BIC)	K	Q	R	KAT	SAC			HRK	H	K
Dolutegravir (DTG)	K	Q	R	KAT	SAC			HRK	H	K
Elvitegravir (EVG)	AIK	Q	R	KAT	SAC		G	HRK	H	K
Raltegravir (RAL)	AIK	Q	R	KAT	SAC	RCH		HRK	H	K

STUDYID	SUBJID	VISIT	TOTDTG
200121	101200	DAY 1	1
200121	101200	Week 48	1

Phenotypic Data

- For the candidate drug, approved/investigational drug(s) in the same class, and approved/investigational drug(s) outside the candidate drug class with the same target protein (e.g., NNRTIs and NRTIs) or protein complex (e.g., gp120/gp41), sponsors should provide the following data:
- **DRGIC50** (i.e., DRUG ABBREVIATION IC50 value): IC50 values (nmol/L) at baseline and post-baseline time points for candidate drug. DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay.

STUDYID	SUBJID	VISIT	DTGIC50	ABCIC50
200121	101200	DAY 1	3260	2370
200121	101200	Week 48	2980	2000

Fold Change

- **DRGICRF** (i.e., DRUG ABBREVIATION RF): Fold change values in IC50 value at time of assessment (BASELINE or ENDPOINT) compared to reference strain for drug. DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay.
- **DRGICBL** (i.e., DRUG ABBREVIATION BL): Fold change in IC50 value at time of endpoint assessment or failure compared to baseline for drug. DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay.

STUDYID	SUBJID	VISIT	DTGICRF	ABCICRF	DTGICBL	ABCICBL
200121	101200	DAY 1	0.5	0.79	0.5	0.79
200121	101200	Week 48	1.5	1	0.5	0.79

Assay

- **PHENOMET:** Phenotypic method or assay name.
- **PHENFAIL:** Phenotype analysis conducted but failed because of poor replication in phenotype assay (Y or NULL).
- We need to derive PHENFRT, PHENFPR and PHENFIN for each DNA region.
- The value here are blank since the phenotypic assay data is available.

STUDYID	SUBJID	VISIT	PHENOMET	PHENFRT	PHENFPR	PHENFIN
200121	101200	DAY 1	PSIN, PSGT			
200121	101200	Week 48	PSIN, PSGT			

References

- Stanford University, HIV Drug Resistance Database. Retrieved from <https://hivdb.stanford.edu/>
- Guidance for Submitting HIV-1 Resistance Data. Retrieved from <https://www.fda.gov/media/88255/download>
- Guidance for Industry Role of HIV Resistance Testing in Antiretroviral Drug Development. Retrieved from <https://www.fda.gov/media/71044/download>



Thank you

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