Attachment to

Guidance on Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency

Guidance for Submitting HCV Resistance Data

DRAFT GUIDANCE

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For questions regarding this draft document contact Lisa K. Naeger at 301-796-0771.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Revision 1

Guidance for Submitting HCV Resistance Data[1]

STANDARDIZATION OF COLUMN HEADINGS AND VARIABLES FOR HCV RESISTANCE DATASETS[2]

Points to Consider

- The column headings, variables, and definitions provided in this attachment can be used as a guide by sponsors of hepatitis C virus (HCV) direct-acting antiviral (DAA) clinical trials when assembling electronic datasets of HCV virology and drug resistance data. We recommend submitting final datasets as SAS transport files (.xpt).

- The recommendations in this attachment are not intended to be applicable to all situations. Sponsors should consult with the Division of Antiviral Products (DAVP) in advance when more detailed guidance is needed, or if considering alternative approaches to any of the recommended column headings, variables, or definitions. Given the rapid pace of HCV DAA drug development, we expect continued evolution in trial designs and technologies used for collection of genotypic and phenotypic resistance data, and we intend to update this attachment frequently as new information accumulates.

- Sponsors should use this attachment for submission of data from phase 3 and larger phase 2b efficacy trials. Sponsors can use this attachment for the submission of HCV virology and resistance data from other clinical trials, although in most cases data from early-stage clinical trials can be submitted in the form of study reports.

- There are a number of ways datasets can be subdivided (i.e., by clinical trial, genotype, subtype) and this should be discussed with the DAVP before submission of datasets.

- As detailed in section III., Genotypic Data, separate resistance datasets should be constructed to report amino acid sequence data from patient populations according to their HCV genotype or subtype.

- To identify any potential formatting problems as early as possible, all sponsors are encouraged to submit preliminary (or mock) resistance datasets to DAVP before assembling formal clinical trial resistance datasets.

[1] This attachment is being revised to provide the current format, recommended definitions, standardization of column headings and variables, and recommended data for submission of HCV resistance datasets.

[2] See the Glossary of Abbreviations and Acronyms at the end of this attachment.

RECOMMENDED COLUMN HEADINGS, VARIABLES, AND DEFINITIONS

NULL = blank cell

I. Patient Data:

- **USUBJID**: Unique subject identification number (ID number should be unique for all studies)

- **STUDYID**: Study identification number

- **IL28MET**: IL28B single nucleotide polymorphism (SNP) genotype assay name or other method identifier

- **IL28POL**: IL28B SNP analyzed (rs12979860, rs8099917, or other as appropriate; genotypes' relationship to response to Peg-IFN/RBV should be identified in column notes (e.g., for rs12979860 CC>CT>TT)). The rs number, if available, should always be used to identify the SNP analyzed. If multiple IL28B SNPs are analyzed and reported, additional columns can be added to identify the different SNPs (e.g., IL28POL1, IL28POL2).

- **IL28GEN**: IL28B SNP genotype result (CC, CT, TT, GG, GT, or other polymorphism genotype result). If multiple IL28B SNPs are analyzed and reported, additional columns can be added to report the results of the different SNPs analyzed (e.g., IL28GEN1, IL28GEN2 corresponding to IL28POL1, IL28POL2).

- **ARM**: Treatment group

- **LEADINFL**: Subject received a protocol regimen that includes an initial lead-in period of one or multiple drugs before receiving full regimen (e.g., 4-week Peg-IFN/RBV lead-in (Y or N))

- **RGTFL**: Subject received an abbreviated duration of therapy according to the protocol, based on achieving a protocol-defined early response (Y or N; OTHER should be used if subject did not follow protocol guidelines (e.g., discontinued before response-guided therapy (RGT) decision point); NULL if no RGT in arm or trial)

- **VISIT**: (SCREENING, BASELINE, DAY#, WEEK#, FOLLOWUP WK#). Visit windows should be as defined in protocol or statistical analysis plan.

- **VISITDY**: Study day, protocol-defined, relative to initiation of protocol treatment. Counting should be continued upwards into Peg-IFN/RBV tail, rollover, or follow-up phases. Baseline = Day 1 or Day 0 should be indicated in column notes.

- **ISOLDTC**: Date of isolate. Time of isolate can be included as appropriate (e.g., if multiple samples collected at different times in same day).

- **ISOLID**: Unique identifier for isolate analyzed (e.g., barcode or other means to identify specific isolate)

- **FUDY**: Day of isolate from end-of-treatment. Last day of treatment considered FUDY = 0 (NULL if pre-treatment or on-treatment time point).

- **RFSTDTC**: Start date of protocol treatment

- **RFENDTC**: End date of protocol treatment (actual end date, not planned end date)

- **HCVHIST**: Anti-HCV treatment exposure history. See recommended terms and definitions in Table 1.

Table 1. Recommended Controlled Terms and Definitions for Documenting Previous HCV Treatment Exposure History for the HCVHIST Column[*]

NAÏVE-ALL	Naïve to all anti-HCV treatment
P/R EXPERIENCED	Previously treated with Peg-IFN/RBV, but naïve to HCV DAAs
P/R PLUS DAA EXPERIENCED	Previously treated with Peg-IFN/RBV in combination with 1 or more HCV DAAs
DAA EXPERIENCED	Previously exposed to 1 or more HCV DAAs (including short courses of DAA monotherapy), but never treated with Peg-IFN/RBV
DAA AND P/R EXPERIENCED	Previously treated with Peg-IFN/RBV and HCV DAAs, but never in the form of a Peg-IFN/RBV/DAA combination regimen
OTHER[**]	Treatment history not captured by any of the above definitions.

[*] **Note:** Peg-IFN can refer to any pegylated interferon (e.g., α-2a, α-2b, λ); specific Peg-IFN exposure is defined elsewhere (e.g., CMTRTIFN).

[**] Sponsors should consult with the DAVP before using this variable, because it may be appropriate to create an additional treatment history definition.

- **CMTRTIFN**: Previous HCV interferon (IFN) therapeutic products (e.g., PEGASYS, PEGINTRON). NULL if no previous IFN products.

- **CMTRTRBV**: Previous HCV ribavirin (RBV) therapeutic products (e.g., COPEGUS, REBETOL). NULL if no previous RBV products.

- **PRVDAA1**: Previous HCV DAA therapeutic products (e.g., BOCEPREVIR, TELAPREVIR). Additional columns should be added as needed to provide information on multiple DAA exposures (e.g., PRVDAA2, PRVDAA3). NULL if no previous DAA products.

- **PRVDAA1D**: Approximate duration of PRVDAA1 exposure (actual, not planned), using the following categories: ≤1 WEEK, >1-4 WEEKS, >4-12 WEEKS, >12-24 WEEKS, >24 WEEKS. Additional columns should be added as needed for additional DAA exposures. UNKNOWN can be used if necessary, although efforts should be made to capture this information. NULL if no previous DAA exposure.

- **PRVDAA1T**: Approximate time since previous exposure to DAA1, using the following categories: ≤1 MONTH, >1-3 MONTHS, >3-6 MONTHS, >6-12 MONTHS, >1-2 YEARS, >2-4 YEARS, >4 YEARS. Additional columns should be added as needed for additional DAA exposures. UNKNOWN can be used if necessary, although efforts should be made to capture this information. NULL if no previous DAA exposure.

- **EXPERCAT**: Previous response category; see recommended terms and definitions in Table 2. Note: If multiple prior treatments, response category during most recent DAA-containing treatment regimen takes precedence. Alternatively, prior responses used for determining trial eligibility can take precedence. Additional descriptive information should be provided to the DAVP as appropriate.

Table 2. Recommended Controlled Terms and Definitions for Documenting Previous Treatment Responses for the EXPERCAT Column*

NAÏVE-ALL	Naïve to all anti-HCV treatment
P/R NULL RESPONDER	<2 $\log_{10}$ IU/mL reduction in HCV RNA at Week 12 of a Peg-IFN/RBV regimen
P/R WEEK 4 FUTILITY	<1 $\log_{10}$ IU/mL decline from baseline at Week 4 futility rule and discontinued therapy before Week 12 of a Peg-IFN/RBV regimen
P/R PARTIAL RESPONDER	≥2 $\log_{10}$ IU/mL reduction in HCV RNA at Week 12, but not achieving HCV RNA target not detected at end-of-treatment with a Peg-IFN/RBV regimen. Can include subjects who met 24-week virologic futility rule.
P/R BREAKTHROUGH	Confirmed ≥1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, or confirmed increase in HCV RNA ≥LLOQ if HCV RNA previously declined to <LLOQ (detected or not detected). Occurred during treatment with a Peg-IFN/RBV regimen.
P/R RELAPSER	HCV RNA target not detected at end-of-treatment with a Peg-IFN/RBV regimen, but HCV RNA quantifiable (≥LLOQ) during follow-up
P/R+DAA NONRESPONDER	HCV RNA detected at end-of-treatment with a regimen that included one or more HCV DAAs dosed in combination with Peg-IFN/RBV. Can include subjects who met protocol-defined virologic futility rule (except for breakthrough which is captured elsewhere).
P/R+DAA BREAKTHROUGH	Confirmed ≥1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, or confirmed increase in HCV RNA ≥LLOQ if HCV RNA previously declined to <LLOQ (detected or not detected). Occurred during the DAA dosing period with a regimen that included one or more HCV DAAs dosed in combination with Peg-IFN/RBV.
P/R TAIL BREAKTHROUGH	Confirmed ≥1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, or confirmed increase in HCV RNA ≥LLOQ if HCV RNA previously declined to <LLOQ (detected or not detected). Occurred during Peg-IFN/RBV tail dosing period that followed a Peg-IFN/RBV/DAA(s) dosing period.
P/R+DAA RELAPSER	HCV RNA target not detected at end-of-treatment with a regimen that included one or more HCV DAAs dosed in combination with Peg-IFN/RBV, but HCV RNA quantifiable (≥LLOQ) during follow-up

continued

Table 2, continued

DAA NONRESPONDER	HCV RNA detected at end-of-treatment with a regimen that included only HCV DAAs (can also include RBV, but not IFNs). Can include subjects who met protocol-defined virologic futility rule (except for breakthrough, which is captured elsewhere).
DAA BREAKTHROUGH	Confirmed ≥1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, or confirmed increase in HCV RNA ≥LLOQ if HCV RNA previously declined to <LLOQ (detected or not detected). Occurred during treatment with a regimen that included only HCV DAAs (can also include RBV, but not IFNs).
DAA RELAPSER	HCV RNA target not detected at end-of-treatment with a regimen that included only HCV DAAs (can also include RBV, but not IFNs), but HCV RNA quantifiable (≥LLOQ) during follow-up

[*] **Notes:**

- The recommended terms and definitions for EXPERCAT are identical to those for NONRECAT.
- Other protocol-defined or retrospectively defined responses can be used as appropriate, and should be discussed in advance with the DAVP.
- Peg-IFN can refer to any pegylated interferon (e.g., α-2a, α-2b, λ).
- For DAA-containing treatment regimens, breakthrough should take precedence. Exceptions to this guideline should be discussed in advance with the DAVP.
- UNKNOWN can be used if necessary, although efforts should be made to capture this information.

- **EXTRTIFN**: Concomitant HCV IFN treatment drugs (e.g., PEGASYS, PEGINTRON). NULL if no concomitant IFN.

- **EXTRTRBV**: Concomitant RBV HCV treatment drugs (e.g., COPEGUS, REBETOL). NULL if no concomitant RBV.

- **HCVGTSC**: HCV subtype at screening (e.g., 1a, 1b, 2a, 2b, 2c, 3a, 3b, 4a, 4b, 4c, 4d, 4e, 5a, 6a). Mixed infections should be reported as Gt/Gt (e.g., 1a/1b).

- **HCVGTAN**: HCV subtype for analysis (e.g., 1a, 1b, 2a, 2b, 2c, 3a, 3b, 4a, 4b, 4c, 4d, 4e, 5a, 6a; NA (not assigned); or NULL (if not done (i.e., screening method used for analysis))). Mixed infections should be reported as Gt/Gt (e.g., 1a/1b).

- **HCVGTSCM**: Assay used for determining HCV genotype/subtype at screening (e.g., TRUGENE, VERSANTLIPA2.0, VERSANTLIPA1.0, NS3 SEQUENCE, NS3_4A SEQUENCE, NS5A SEQUENCE, NS5B SEQUENCE)

- **HCVGTANM**: Assay used for determining HCV genotype/subtype for analysis (e.g., TRUGENE, VERSANTLIPA2.0, VERSANTLIPA1.0, NS3 SEQUENCE, NS3_4A SEQUENCE, NS5A SEQUENCE, NS5B SEQUENCE) or NULL

- **HBVCOINF**: HBV co-infected (Y or N)

- **HIVCOINF**: HIV co-infected (Y or N)

- **CIRRFL**: Subject has cirrhosis as defined in protocol (Y or N)

II. Endpoint Data:

Note regarding reporting of HCV RNA viral load data: For the purposes of populating the viral load data described below, HCV RNA viral load results of target not detected should be reported using the term NOT DETECTED. HCV RNA viral load results of detectable/<LLOQ should be reported using the term DETECTED <LLOQ.

- **VLMET**: HCV RNA viral load assay name and version

- **VLVEND**: Name of vendor, contract laboratory, or other central laboratory conducting HCV RNA viral load assessments

- **VLLOQ**: lower limit of quantitation for HCV RNA viral load assay

- **VLOD**: limit of detection for HCV RNA viral load assay

- **VLBL**: HCV RNA (IU/mL) at baseline

- **LOGVLBL**: HCV RNA (log_{10} IU/mL) at baseline

- **HCVVL**: HCV RNA (IU/mL) at all time points from protocol, one row for each time point. HCV RNA (IU/ml) from additional time points not specified in protocol can also be included (e.g., virologic breakthrough confirmatory sample, retest sample). Imputed data should not be reported; only observed data should be reported.

- **LOGHCVVL**: HCV RNA (log_{10} IU/mL) at all time points from protocol, one row for each time point. HCV RNA (log_{10} IU/ml) from additional time points not specified in protocol can also be included (e.g., virologic breakthrough confirmatory sample, retest sample). Imputed data should not be reported; only observed data should be reported.

- **HCVVL(TIME)**: Individual column headings for HCV RNA measurements (IU/mL) at selected visit times of interest. Each column represents a single time point of interest. In the example shown in Table 3, the selected time points of interest are: Treatment Weeks (W) 4, 8, 12, 24, and 48, and Follow-Up Weeks (F) 12 and 24. These time points can be adjusted or reduced as appropriate depending on the trial design. Time points/results for RGT decision making should be included as time points of interest. Visit windows defined in protocol or statistical analysis plan should be used. If there are multiple discordant results in a visit window of interest, the results should be reported according to statistical analysis plan. Cells should be NULL for any time points that are not applicable for individual subjects, or where data are not available.

- **VLEOT**: HCV RNA (IU/mL) at end-of-treatment; this usually is duplicate data for subjects who complete protocol-specified treatment (i.e., duplicate with Week 48, if a 48-week

treatment duration). Based on actual end-of-treatment, not planned end-of-treatment, for subjects who discontinued early.

- **LOGVLEOT**: HCV RNA (log_{10} IU/mL) at end-of-treatment (Note: Not shown in Table 3 example). Based on actual end-of-treatment, not planned end-of-treatment, for subjects who discontinued early.

- **VLEOTFL**: HCV RNA target not detected at end-of-treatment (Y or N, NULL if not available)

Table 3. Example Illustrating Formatting of HCV RNA Viral Load Data*

USUBJID	VISIT	VISITDY	HCVVL	LOGHCVVL	VLBL	LOGVLBL	HCVVLW4	HCVVLW8	HCVVLW12	HCVVLW24	HCVVLW48	VLEOT	HCVVLF12	HCVVLF24
101	SCREENING													
101	BASELINE													
101	DAY 2													
101	DAY 4													
101	WEEK 1													
101	WEEK 2													
101	WEEK 4													
101	WEEK 8													
101	WEEK 12													
101	WEEK 16													
101	WEEK 20													
101	WEEK 24													
101	WEEK 28													
101	WEEK 36													
101	WEEK 48													
101	EOT													
101	FOLLOWUP WK4													
101	FOLLOWUP WK8													
101	FOLLOWUP WK12													
101	FOLLOWUP WK24													

*__Note:__ In this example, HCV RNA viral load assessments were conducted at SCREENING, BASELINE, DAY 2, DAY 4, WEEKS 1, 2, 4, 8, 12, 16, 20, 24, 28, 36, and 48, EOT (e.g., can be a duplicate of Week 48 if a 48-week treatment course is completed), and FOLLOW-UP Weeks 4, 8, 12, and 24. HCVVL and LOGHCVVL data are provided for each of these time points, with each time point representing a unique row. The RESISTFL and related columns (described in section III., Genotypic Data) will be used to flag time point(s) where resistance assessments were performed. HCV RNA viral load data for select time points of interest are also provided in column format.

- **SVR2FL**: Sustained virologic response (SVR) at Week 2 after end-of-treatment (Y or N, or NULL). Use visit window defined in protocol or statistical analysis plan. NULL used if visit not specified in protocol or data missing. Do not impute Y or N. Currently, we define SVR based on HCV RNA <LLOQ.

- **SVR4FL**: Sustained virologic response at Week 4 after end-of-treatment (Y or N, or NULL). Visit window defined in protocol or statistical analysis plan should be used. NULL should be used if visit not specified in protocol or data missing. Y or N should not be imputed. Currently, we define SVR based on HCV RNA <LLOQ.

- **SVR12FL**: Sustained virologic response at Week 12 after end-of-treatment (Y or N, or NULL). Visit window defined in protocol or statistical analysis plan should be used. NULL should be used if visit not specified in protocol or data missing. Y or N should not be imputed. Currently, we define SVR based on HCV RNA <LLOQ.

- **SVR24FL**: Sustained virologic response at Week 24 after end-of-treatment (Y or N, or NULL). Visit window defined in protocol or statistical analysis plan should be used. NULL

should be used if visit not specified in protocol or data missing. Y or N should not be imputed. Currently, we define SVR based on HCV RNA <LLOQ.

- **EFFICFL**: Achieved primary efficacy endpoint as defined in protocol and statistical analysis plan, including sponsor-imputed results (Y or N).

- **VR1FL**: Protocol-defined virologic response, intended for RGT decisions or key protocol-defined endpoints; additional column headings can be added if other protocol-defined responses are used (e.g., VR2FL, VR3FL); the definition of the protocol-defined response(s) should be included as notes to the column heading(s). Additional descriptive information should be provided to the DAVP as needed to define the virologic responses (Y or N).

- **NDSTDY**: Study day of first documented result of HCV RNA NOT DETECTED. NULL should be used if never achieved HCV RNA not detected.

- **NONRECAT**: Nonresponder category for currently tested therapy as defined by the protocol. See recommended terms and definitions in Table 4.

- **DISCTXFL**: A flag used to indicate subject discontinued from protocol treatment (Y or N)

- **DISCTXVL**: HCV viral RNA load when subject discontinued protocol treatment (e.g., NOT DETECTED, DETECTED <LLOQ, specific IU/mL, or NULL for those who did not discontinue treatment early)

- **DISCREAS**: Reason for early protocol treatment discontinuation (ADVERSE EVENT, DEATH, STOPPING RULE, LACK OF EFFICACY, LOST TO FOLLOW-UP, NONCOMPLIANCE WITH STUDY DRUG; OTHER; PHYSICIAN DECISION; PREGNANCY; PROGRESSIVE DISEASE; PROTOCOL VIOLATION; SCREEN FAILURE; TECHNICAL PROBLEMS; WITHDRAWAL BY SUBJECT); or NULL if no information available or not applicable. Reasons should be defined according to protocol or statistical analysis plan.

- **DISCFUFL**: A flag used to indicate subject discontinued from follow-up (Y or N)

- **DISCFUVL**: HCV viral RNA load when subject discontinued follow-up (e.g., NOT DETECTED, DETECTED <LLOQ, specific IU/mL, or NULL for those who did not discontinue follow-up early)

- **DISCREA2**: Reason for early follow-up discontinuation (ADVERSE EVENT, DEATH, STOPPING RULE, LACK OF EFFICACY, LOST TO FOLLOW-UP, NONCOMPLIANCE WITH STUDY DRUG; OTHER; PHYSICIAN DECISION; PREGNANCY; PROGRESSIVE DISEASE; PROTOCOL VIOLATION; SCREEN FAILURE; TECHNICAL PROBLEMS; WITHDRAWAL BY SUBJECT); or NULL if no information available. Reasons should be defined according to protocol or statistical analysis plan.

- **BTFL**: A flag (Y or NULL) used to indicate the specific study visit with a viral load value that met the definition for protocol-defined virologic breakthrough

- **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., when the subject met a protocol-defined treatment futility rule, experienced virologic relapse). Will duplicate BTFL for subjects who experienced breakthrough as the specific reason for virologic failure.

- **SVRRELFL**: A flag (Y or NULL) used to indicate the specific study visit that met the criteria for a late virologic relapse.

Table 4. Recommended Controlled Terms and Definitions for Documenting Protocol Treatment Responses for the NONRECAT Column*

NAÏVE-ALL	Naïve to all anti-HCV treatment
P/R NULL RESPONDER	<2 $\log_{10}$ IU/mL reduction in HCV RNA at Week 12 of a Peg-IFN/RBV regimen
P/R WEEK 4 FUTILITY	<1 $\log_{10}$ IU/mL decline from baseline at Week 4 futility rule and discontinued therapy before Week 12 of a Peg-IFN/RBV regimen
P/R PARTIAL RESPONDER	≥2 $\log_{10}$ IU/mL reduction in HCV RNA at Week 12, but not achieving HCV RNA target not detected at end-of-treatment with a Peg-IFN/RBV regimen. Can include subjects who met 24-week virologic futility rule.
P/R BREAKTHROUGH	Confirmed ≥1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, or confirmed increase in HCV RNA ≥LLOQ if HCV RNA previously declined to <LLOQ (detected or not detected). Occurred during treatment with a Peg-IFN/RBV regimen.
P/R RELAPSER	HCV RNA target not detected at end-of-treatment with a Peg-IFN/RBV regimen, but HCV RNA quantifiable (≥LLOQ) during follow-up
P/R+DAA NONRESPONDER	HCV RNA detected at end-of-treatment with a regimen that included one or more HCV DAAs dosed in combination with Peg-IFN/RBV. Can include subjects who met protocol-defined virologic futility rule (except for breakthrough, which is captured elsewhere).
P/R+DAA BREAKTHROUGH	Confirmed ≥1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, or confirmed increase in HCV RNA ≥LLOQ if HCV RNA previously declined to <LLOQ (detected or not detected). Occurred during the DAA dosing period with a regimen that included one or more HCV DAAs dosed in combination with Peg-IFN/RBV.
P/R TAIL BREAKTHROUGH	Confirmed ≥1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, or confirmed increase in HCV RNA ≥LLOQ if HCV RNA previously declined to <LLOQ (detected or not detected). Occurred during Peg-IFN/RBV tail dosing period that followed a Peg-IFN/RBV/DAA(s) dosing period.
P/R+DAA RELAPSER	HCV RNA target not detected at end-of-treatment with a regimen that included one or more HCV DAAs dosed in combination with Peg-IFN/RBV, but HCV RNA quantifiable (≥LLOQ) during follow-up

continued

Table 4, continued

DAA NONRESPONDER	HCV RNA detected at end-of-treatment with a regimen that included only HCV DAAs (can also include RBV, but not IFNs). Can include subjects who met protocol-defined virologic futility rule (except for breakthrough, which is captured elsewhere).
DAA BREAKTHROUGH	Confirmed ≥1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, or confirmed increase in HCV RNA ≥LLOQ if HCV RNA previously declined to <LLOQ (detected or not detected). Occurred during treatment with a regimen that included only HCV DAAs (can also include RBV, but not IFNs).
DAA RELAPSER	HCV RNA target not detected at end-of-treatment with a regimen that included only HCV DAAs (can also include RBV, but not IFNs), but HCV RNA quantifiable (≥LLOQ) during follow-up

[*]**Notes:**

- The recommended terms and definitions for NONRECAT are identical to those for EXPERCAT.
- Other protocol-defined or retrospectively defined responses can be used as appropriate, and should be discussed in advance with the DAVP.
- Peg-IFN can refer to any pegylated interferon (e.g., α-2a, α-2b, λ).
- For DAA-containing treatment regimens, breakthrough should take precedence. Exceptions to this guideline should be discussed in advance with the DAVP.

III. Genotypic Data:

General Information:

- There are a number of ways datasets can be subdivided (e.g., clinical trial, genotype, subtype). This should be discussed with the DAVP before submission of datasets.

- Separate resistance datasets can be constructed to report amino acid sequence data from patient populations according to their HCV genotype. Data from HCV genotype 1 populations can be assembled in separate datasets for HCV genotype 1a- and 1b-infected patient populations or submitted in a single dataset, even if using different subtype-specific reference strains for reporting amino acid sequences. Non-genotype 1 HCV data can be reported according to HCV genotype in separate resistance datasets using genotype-specific reference strains. Again, this should be discussed with the DAVP before submission of datasets.

- Subject sequence data should be reported using subtype-specific reference strains (see Table 5).

Table 5. Reference Strains for Reporting of Amino Acid Sequence Data

HCV Genotype	Reference Strain	GenBank Accession ID
Genotype 1a	H77	NC_004102
Genotype 1b	Con1	AJ238799
Other genotype 1 subtypes, mixed subtypes, or subtype unknown	H77	NC_004102
Genotype 2	JFH-1	AB047639
Genotype 3	S52	GU814263
Genotype 4	ED43	GU814265
Genotype 5	SA13	AF064490
Genotype 6	EUHK2	Y12083

Reporting Amino Acid Substitutions:

- Genotype information for all relevant coding regions sequenced should be reported using one amino acid position per column:

  COLUMN HEADING FORMAT EXAMPLE: N30XXX (e.g., N30155, N4A0030, N5A0002, N5B0200)

- Changes from the prototypic reference sequence (Table 5) should be indicated for each reported sequence. Blank cells indicate no change from prototypic reference strain sequence. Mixed populations of WT/Variant or Variant/Variant should be reported as such (e.g., R155R/K reported as R/K; R155K/T reported as K/T).

- To report insertions in subject sequence data relative to the prototypic reference strain used to generate the dataset, additional columns should be added where appropriate. For example, a 5-amino acid stretch that includes a 3-amino acid insertion between NS3 position 131 and 132 should be reported under the column headings N30131, N30131A, N30131B, N30131C, and N30132.

- To report deletions in subject sequence data relative to the prototypic reference strain used to generate the dataset, X should be reported for appropriate positions.

- Missing sequence data caused by poor sequence quality or other technical problems should be reported as a question mark (?) for appropriate positions. Efforts should be made not to have stretches of missing sequence information caused by poor sequence quality or other technical problems.

- A composite of all substitutions emerging on treatment should be reported (i.e., POST-BL ALL). For datasets that include genotypic data for multiple post-baseline time points for individual subjects, a single row (one row per subject) should be added that reports the composite of all substitutions detected post-baseline relative to standard reference. This row should be indicated by a VISIT term of POST-BL ALL, as shown in Table 6.

Table 6. Recommendation for Reporting POST-BL ALL Composite Substitution Data

USUBJID	VISIT	N30001	N30002	N30003
H77 1A REFERENCE		A	P	I
A001	BASELINE			Y
A001	WEEK 8	F		Y
A001	WEEK 12		S	Y
A001	WEEK 24	R/H		Y
A001	FOLLOWUP WK 36	R		Y
A001	POST-BL ALL	F/R/H	S	Y

Reporting Reference Strain Information:

- The amino acid sequences of the specific reference strains used for reporting of the data should be reported in the top rows of the dataset (see example in Table 7). Below each reference strain sequence, sponsors should include two additional rows to indicate the following:

  - Percent conservation at each amino acid position (from large HCV sequence databases) for the genotype/subtype included in the dataset

  - Summary of the most common variants (comprising ~5 percent or more of variants available in sequence databases) at the amino acid position in decreasing frequency

- The following is additional information regarding the reporting of reference strain, percent conservation, and variant information:

  - The USUBJID column can be used to designate rows for reference strains (REFERENCE NAME), percent conservation (GT CONSERVATION), and common variants (GT VARIANTS) (see Table 7).

  - Both public databases and internal data (e.g., baseline sequences from trial) can be used to report percent conservation and common variants. Internal data may be valuable in the event that inadequate sequence data are available in the public domain for certain HCV genotypes.

  - Database sequences used should be from subjects with no known previous exposure to therapies that target the region of interest. No more than one sequence per subject.

  - It is not necessary to continually update database sequence information for percent conservation and most common variants each time a new resistance dataset is assembled and submitted to the DAVP unless a large volume of sequence data has recently become available for certain HCV genotypes that previously had only limited available sequence data.

  - When reporting genotype 1a and 1b sequences all in the same dataset, there will be a total of six rows that provide the necessary background information for the reference strains,

percent conservation, and common variants. Percent conservation and common variants should be calculated separately for subtype 1a and subtype 1b.

- For non-genotype 1 populations, database sequences used to report percent conservation and common variants within a given HCV genotype should be comprised of HCV subtypes that are reasonably representative of the HCV subtypes included in the clinical trial.

- Descriptive information should be provided to the DAVP in the study report summarizing the source and number of sequences used for reporting this information.

Table 7. Recommendation for Reporting Reference Strain, Percent Conservation, and Common Variant Information in Resistance Datasets

USUBJID	N30078	N30079	N30080	N30081
H77 1A REFERENCE	V	D	Q	D
1A CONSERVATION	99.0	99.5	60.2	100.0
1A VARIANTS	V	D	Q/K/L/R	D

Reporting Clonal Nucleotide Sequence Analysis:

- For data generated by clonal nucleotide sequence analysis (or other sensitive method), we recommend consulting with the DAVP in advance of assembling these data because a number of different formats may be appropriate for submission.

- A separate dataset or study report should be submitted that includes more specific details of clonal analysis results (e.g., all variants detected at a specific position of interest and their percent prevalence in the population).

Additional column headings and terms related to genotypic data that should be included in the dataset:

- **GENORF**: HCV reference strain for genotypic sequence (CON1, H77, or other as appropriate). See reference strain recommendations in Table 5.

- **GENOMET**: Genotypic method (CLONAL, POPULATION)

- **GENOFAIL**: A flag used to identify samples with sufficient HCV 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)

- **RESISTFL**: A resistance analysis flag 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).

- **RESBLFL**: A flag used to identify baseline sample with resistance analysis data reported. Can indicate multiple rows per subject if multiple baseline or screening samples analyzed (Y or NULL).

- **RESEOTFL**: A flag used to identify the last on-treatment isolate/time point with resistance analysis data reported. Should indicate no more than one time point per subject (Y or NULL).

- **RESFU1FL**: A flag used to identify the first treatment-free follow-up isolate/time point with resistance analysis data reported. Should indicate no more than one time point per subject (Y or NULL).

- **RESFU2FL**: Flag to identify the last treatment-free follow-up isolate/time point with resistance analysis data reported. Should indicate no more than one time point per subject (Y or NULL).

IV. Phenotypic Data (if available):

We recommend the following guidelines for submission of phenotypic resistance data generated using subject sample-derived amplicons evaluated in cell-based or biochemical phenotyping assays. Data on the effect of specific substitutions (e.g., in site-directed mutant replicons) should not be included in these datasets and can be reported in summary format in study reports. We recommend consulting with the DAVP before finalizing phenotypic resistance data formats for submission, because additional columns/variables may be needed.

- DRUG ABBREVIATION EC_{50} value (e.g., **DRGEC50**): EC_{50} values at baseline and post-baseline time points; with cell culture assay. DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay.

- DRUG ABBREVIATION RF (e.g., **DRGECRF**): Fold change values in EC_{50} value at time of assessment (BASELINE or ENDPOINT) compared to reference strain for DRUG, with cell culture assay. DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay.

- DRUG ABBREVIATION BL (e.g., **DRGECBL**): Fold change in EC_{50} value at time of endpoint assessment or failure compared to baseline for DRUG, with cell culture assay. DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay.

- DRUG ABBREVIATION IC_{50} (e.g., **DRGIC50**): IC_{50} values at baseline and post-baseline time points, with biochemical assay. DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay.

- DRUG ABBREVIATION RF (e.g., **DRGICRF**): Fold change values in IC_{50} value at time of assessment (BASELINE or ENDPOINT) compared to reference strain for DRUG, with biochemical assay. DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay.

- DRUG ABBREVIATION BL (e.g., **DRGICBL**): Fold change in IC_{50} value at time of endpoint assessment or failure compared to baseline for DRUG, with biochemical assay. DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay.

- **PHENOMET**: Phenotypic method (REPLICON, BIOCHEMICAL, CELL-BASED, VIRUS, SDM). An example of a CELL-BASED method is a secreted alkaline phosphatase protease assay.

- **PHENORF**: Reference strain (e.g., H77; CON1)

- **PHENFAIL**: Phenotype analysis conducted but failed because of poor replication in phenotype assay (Y or NULL).

- DRUG ABBREVIATION IQ (e.g., **DRGIQ**): Inhibitory quotient (C_{min} value/serum(or plasma)-adjusted EC_{50} value) (when available). DRG is a placeholder for the three-character abbreviation of drug used in phenotype assay. Method for serum or plasma protein-binding adjustment should be based on the effect of 40 percent human serum on the drug EC_{50} value in a cell culture assay, or discussed in advance with DAVP if other means of adjustment are necessary.

GLOSSARY OF ABBREVIATIONS AND ACRONYMS

DAA	direct-acting antiviral
EC_{50} value	50 percent effective concentration (cell-based assay)
EOT	end-of-treatment
FU	follow-up
GT	genotype
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IC_{50} value	50 percent inhibition concentration (biochemical assay)
ID	identification
IU/mL	international unit/milliliter
LLOQ	lower limit of quantitation
LOD	limit of detection
Peg-IFN	pegylated interferon (α-2a, α-2b or λ)
P/R	pegylated interferon (α-2a, α-2b or λ) plus ribavirin
RBV	ribavirin
RGT	response-guided therapy
RNA	ribonucleic acid
SNP	single nucleotide polymorphism
SVR	sustained virologic response
WT	wild-type