BARDS
Biostatistics and
Research Decision Sciences

MSD

FDA Specific Data Standard Requirements for HCV Studies

Weibin Cai

MSD R&D (China) Co., Ltd.

4Nov2016

Outlines

BARDS
Biostatistics and Research Decision Sciences

- What's Hepatitis C and Hepatitis C Virus (HCV)

- FDA Specific Data Standard Requirements for HCV Studies
  - Well-designed HCV viral load dataset
  - HCV resistance dataset
  - Efficacy outcomes and related covariates dataset (ADEFFOUT)

- Summary

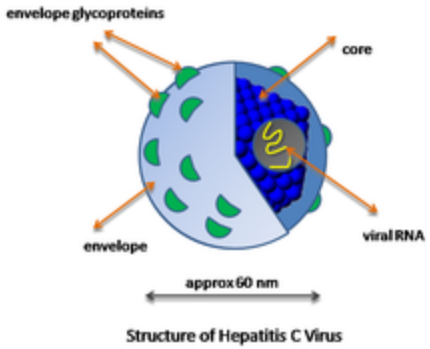
What's Hepatitis C

- Hepatitis C is a liver disease caused by the hepatitis C virus: the virus can cause both acute and chronic hepatitis infection, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness.
- Globally, between 130–150 million people globally have chronic hepatitis C infection.
- A significant number of those who are chronically infected will develop liver cirrhosis or liver cancer.
- Approximately 700 000 people die each year from hepatitis C-related liver diseases .
- The hepatitis C virus is a blood borne virus and the most common modes of infection are through unsafe injection practices, inadequate sterilization of medical equipment, and the transfusion of unscreened blood and blood products.
- There is currently no vaccine for hepatitis C; however research in this area is ongoing.

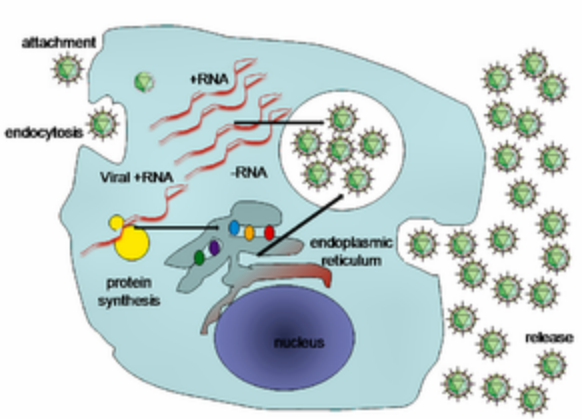
http://www.who.int/mediacentre/factsheets/fs164/en/

Hepatitis C Virus (HCV)

- **Hepatitis C virus** (**HCV**) is a small (55–65 nm in size), enveloped, positive-sense single-stranded RNA virus of the family *Flaviviridae*.



Structure of Hepatitis C Virus



- Molecular
  - The proteins of this virus are arranged along the genome in the following order: N terminal-core-envelope (E1)–E2–p7-nonstructural protein 2 (NS2)–NS3–NS4A–NS4B–NS5A–NS5B–C terminal.

https://en.wikipedia.org/wiki/Hepatitis_C_virus

Hepatitis C Virus (HCV)

HCV:

单股正链RNA病毒，显著异源性和高度可变性(6 GT)

HCV-RNA

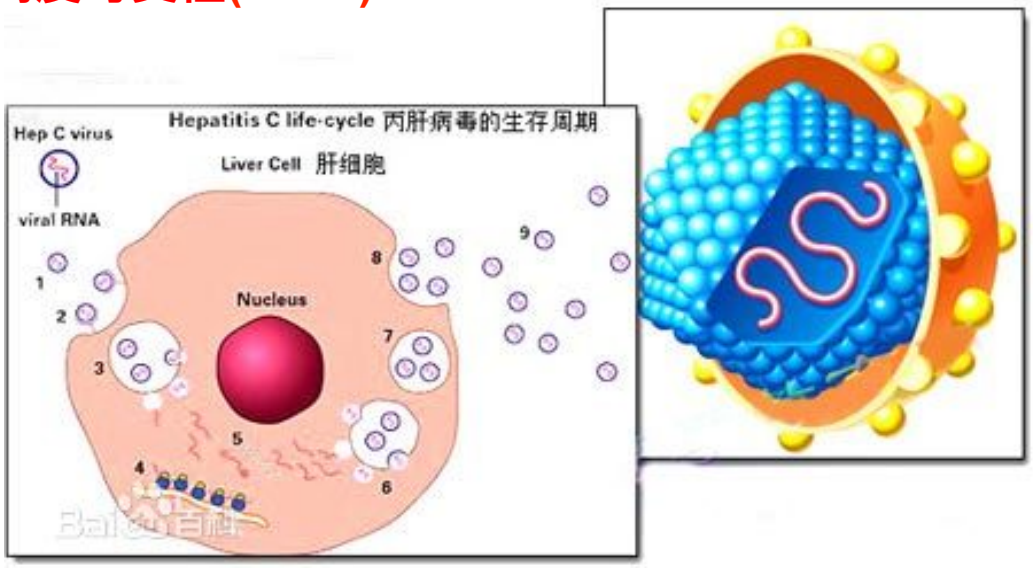
编码 ↓

多聚蛋白前体

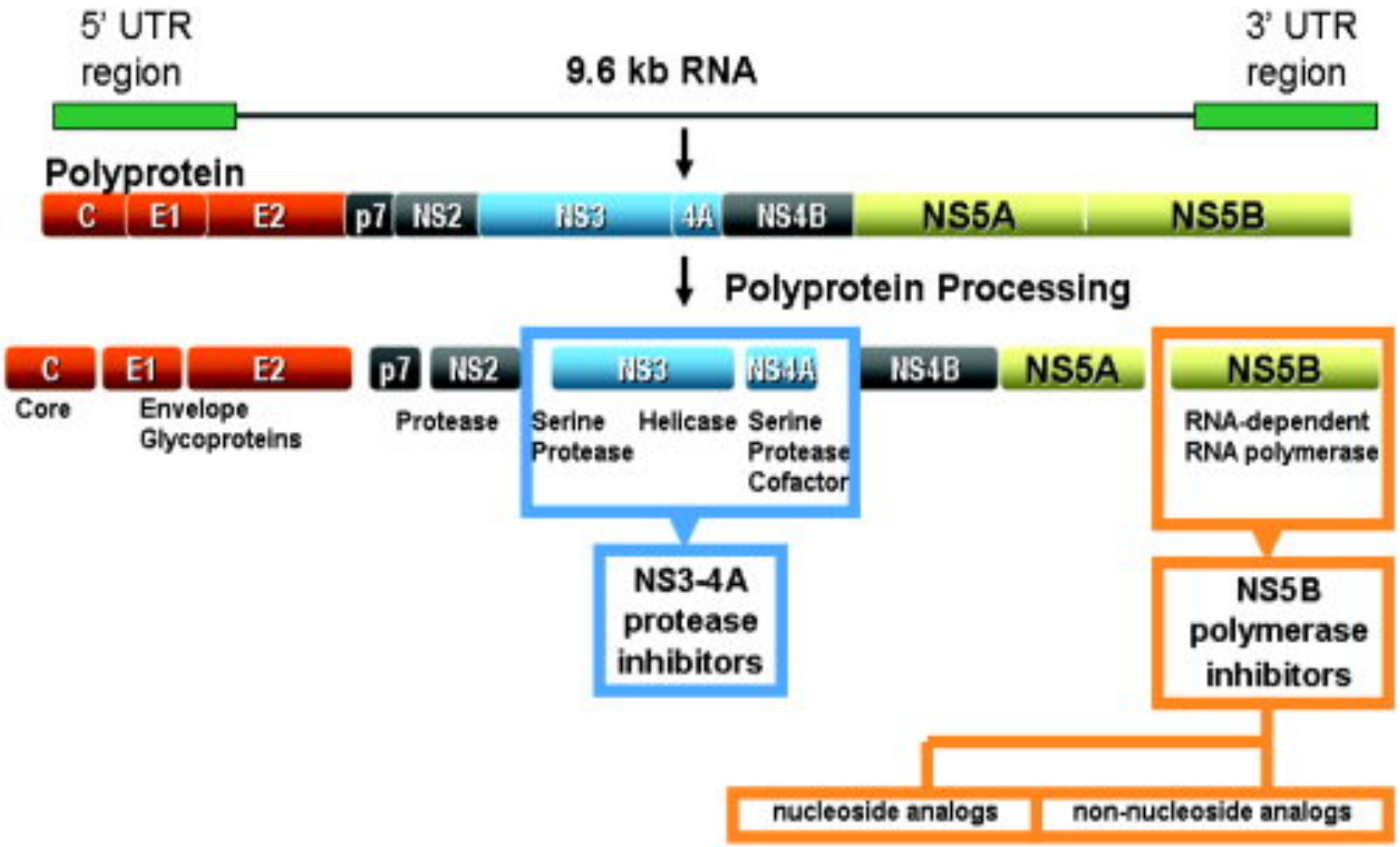
宿主细胞 → 自身蛋白酶 ↓

病毒蛋白（10）

- 结构蛋白（3）
- 膜内在蛋白（1）
  - **NS2**：具有蛋白酶活性，参与病毒多聚蛋白前体切割
- 非结构蛋白（6）
  - **NS3**：具有蛋白酶和螺旋酶活性，参与病毒多聚蛋白前体切割和解旋HCV-RNA分子，协助复制
  - **NS4A/NS4B**：尚不清楚
  - **NS5A**：磷酸蛋白，可与多种宿主细胞蛋白相互作用
  - **NS5B**：具有RNA依赖的RNA聚合酶活性，参与HCV基因组复制



Hepatitis C Virus (HCV)



Modified from McGovern B, et al. Hepatology. 2008; 48:1700-12

Approved Treatments for Hepatitis C

BARDS Biostatistics and Research Decision Sciences

Brand Name	Generic Names	Indication
EPCLUSA Gilead	sofosbuvir (nucleotide analog **NS5B** polymerase inhibitor) velpatasvir (**NS5A** inhibitor) -- 28Jun2016	HCV genotype 1, 2, 3, 4, 5, or 6 infection
Zepatier MSD	elbasvir (**NS5A** inhibitor) and grazoprevir (**NS3/4A** protease inhibitor) – 28Jan2016	HCV genotypes 1 or 4 infection
Daklinza BMS	Daclatasvir (**NS5A** replication complex inhibitor) – 24Jul2015	HCV genotype 3 infection
VIEKIRA PAK VIEKIRA XR AbbVie	ombitasvir (**NS5A** inhibitor), paritaprevir (**NS3/4A** protease inhibitor), ritonavir (**CYP3A** inhibitor), and dasabuvir (non-nucleoside **NS5B** palm polymerase inhibitor) –25Jul2016	HCV genotype 1 infection
Harvoni Gilead	ledipasvir (**NS5A** inhibitor) sofosbuvir (nucleotide analog **NS5B** polymerase inhibitor) –10Oct2014	chronic hepatitis C virus HCV genotype 1, 4, 5 or 6 infection
Sovaldi Gilead	sofosbuvir (nucleotide analog **NS5B** polymerase inhibitor) – 06Dec2013	HCV genotypes 1 and 4, TN adults in combination with PEG-IFN and ribavirin and the first approved interferon-free treatment regimen for people with HCV genotypes 2 and 3.

http://hepatitisnewdrugresearch.com/approved-treatments-for-hepatitis-c.html

FDA Specific Data Standard Requirements for HCV Studies

- FDA Specific Data Standard Requirements for HCV Studies
  - Well-designed HCV viral load dataset
  - HCV resistance dataset
  - Efficacy outcomes and related covariates dataset (ADEFFOUT)

FDA Guidance for HCV Studies

BARDS
Biostatistics and Research Decision Sciences

Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Jeffrey Murray at 301-796-1500.

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

May 2016
Clinical/Antimicrobial

Revision 2

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

Guidance for Submitting HCV Resistance Data

DRAFT GUIDANCE

This guidance attachment is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft document. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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

February 2013
Clinical Antimicrobial

Well-designed HCV Viral Load Dataset

- Outcome of DAA Drugs Treatment for HCV

Outcome	Outcome Subcategory	Definition
Success	*SVR12 Achieved*	Has RNA < LLOQ at follow-up week 12
Virologic Failure	*Non-response*	Has RNA detected at end of treatment without HCV RNA < LLOQ* on treatment
	Rebound	>1 log10 IU/mL increase in HCV RNA from nadir while on treatment.
	Virologic Breakthrough	Has a confirmed HCV RNA ≥ LLOQ after being < LLOQ previously while on treatment
	Relapse	Has a confirmed HCV RNA ≥ LLOQ following end of all study therapy, after becoming undetectable (TND*) at end of treatment
Reinfection		A new HCV infection confirmed by sequencing analysis in patients who initially clear the original or primary HCV infection

*LLOQ: Lower limit of quantification, TND: Target not Detected.

Well-designed HCV Viral Load Dataset

BARDS
Biostatistics and Research Decision Sciences

- It requests the data designer to create the efficacy analysis dataset satisfying the requirements.
  - Include all HCV RNA measures during the course of the trial for all subjects;
  - Includes the derived window variables;
  - Identify the missing measurement in each time point, especially, follow-up 12 weeks;
  - The missing data type, intermittent missing or monotone missing and the discontinuation reasons for monotone missing;
  - Can perform appropriate sensitivity analyses to demonstrate that the primary analysis is robust to discontinuation and missing data

An Example from HCV Study

	USUBJID	MFASRFL	PPROTRFL	VISITNUM	VISIT	AVISIT	AVISITN	ADY	ADT	FUADY	AWRANGE	AWTARGET	AWTDIFF
2	1111_00001			10100	Screening	Screen	-1	-26	16-Apr-2014	-110	ADY < 0 day	-1	25
3	1111_00001			40001	Day 1	Day1	0	1	12-May-2014	-83	ADY = 1 day	1	0
4	1111_00001			40007	Day 7	TW1	1	8	19-May-2014	-76	2 days <= ADY <= 11 days	7	1
5	1111_00001			41020	Week 2	TW2	2	15	26-May-2014	-69	12 days <= ADY <= 18 days	14	1
6	1111_00001					TW3	3				19 days <= ADY <= 25 days	21	
7	1111_00001			41040	Week 4	TW4	4	28	8-Jun-2014	-56	26 days <= ADY <= 35 days (5WK)	28	0
8	1111_00001			41060	Week 6	TW6	6	42	22-Jun-2014	-42	36 days <= ADY <= 49 days (7WK)	42	0
9	1111_00001			41080	Week 8	TW8	8	56	6-Jul-2014	-28	50 days <= ADY <= 63 days (9WK)	56	0
10	1111_00001			41100	Week 10	TW10	10	70	20-Jul-2014	-14	64 days <= ADY <= 77 days (11WK)	70	0
11	1111_00001			41120	Week 12	TW12	12	84	3-Aug-2014	0	78 days <= ADY <= 98 days (14WK)	84	0
12	1111_00001			54004	Follow-up Week 4	FW4	104	119	7-Sep-2014	35	21 days (3WK) <= FUADY <= 69 days	28	0
13	1111_00001					FW12	112				70 days (10WK) <= FUADY <= 146 days	84	
14	1111_00001					FW24	124				147 days (21WK) <= FUADY	168	
15	1111_00001			10100	Screening	Screen	-1	-26	16-Apr-2014	-110	ADY < 0 day	-1	25
16	1111_00001			40001	Day 1	Day1	0	1	12-May-2014	-83	ADY = 1 day	1	0
17	1111_00001			40007	Day 7	TW1	1	8	19-May-2014	-76	2 days <= ADY <= 11 days	7	1
18	1111_00001			41020	Week 2	TW2	2	15	26-May-2014	-69	12 days <= ADY <= 18 days	14	1
19	1111_00001			41040	Week 4	TW4	4	28	8-Jun-2014	-56	26 days <= ADY <= 35 days (5WK)	28	0
20	1111_00001			41060	Week 6	TW6	6	42	22-Jun-2014	-42	36 days <= ADY <= 49 days (7WK)	42	0
21	1111_00001			41080	Week 8	TW8	8	56	6-Jul-2014	-28	50 days <= ADY <= 63 days (9WK)	56	0
22	1111_00001			41100	Week 10	TW10	10	70	20-Jul-2014	-14	64 days <= ADY <= 77 days (11WK)	70	0
23	1111_00001			41120	Week 12	TW12	12	84	3-Aug-2014	0	78 days <= ADY <= 98 days (14WK)	84	0
24	1111_00001			54004	Follow-up Week 4	FW4	104	119	7-Sep-2014	35	21 days (3WK) <= FUADY <= 69 days	28	7
25	1111_00001	Y	Y	41020	Week 2	TW2	2	15	26-May-2014	-69	12 days <= ADY <= 18 days	14	1
26	1111_00001	Y	Y	41020	Week 2	TW2	2	15	26-May-2014	-69	12 days <= ADY <= 18 days	14	1
27	1111_00001	Y	Y	41040	Week 4	TW4	4	28	8-Jun-2014	-56	26 days <= ADY <= 35 days (5WK)	28	0
28	1111_00001	Y	Y	41040	Week 4	TW4	4	28	8-Jun-2014	-56	26 days <= ADY <= 35 days (5WK)	28	0
29	1111_00001	Y	Y	41120	Week 12	TW12	12	84	3-Aug-2014	0	78 days <= ADY <= 98 days (14WK)	84	0
30	1111_00001	Y	Y	41120	Week 12	TW12	12	84	3-Aug-2014	0	78 days <= ADY <= 98 days (14WK)	84	0
31	1111_00001	Y	Y	54004	Follow-up Week 4	FW4	104	119	7-Sep-2014	35	21 days (3WK) <= FUADY <= 69 days	28	7
32	1111_00001	Y	Y	54004	Follow-up Week 4	FW4	104	119	7-Sep-2014	35	21 days (3WK) <= FUADY <= 69 days	28	7
33	1111_00001	N	N			FW12	112				70 days (10WK) <= FUADY <= 146 days	84	
34	1111_00001	N	N			FW12	112				70 days (10WK) <= FUADY <= 146 days	84	
35	1111_00001	N	N			FW12	112				70 days (10WK) <= FUADY <= 146 days	84	
36	1111_00001	N	N			FW24	124				147 days (21WK) <= FUADY	168	
37	1111_00001	N	N			FW24	124				147 days (21WK) <= FUADY	168	
38	1111_00001	N	N			FW24	124				147 days (21WK) <= FUADY	168	

This is from a randomized, double blinded, placebo control study. Subject would receive the treatment for 12 weeks with 24 weeks of follow-up after dosing completed.

An Example from HCV Study

BARDS
Biostatistics and Research Decision Sciences

	USUBJID	PARAM	PARAMCD	PARAMN	PARAMTY	CRIT1	CRIT1FL	CRIT2	CRIT2FL	CRIT3	CRIT3FL	DTYPE
2	1111_00001	Hepatitis C Viral RNA (IU/mL)	HCRNA	1								
3	1111_00001	Hepatitis C Viral RNA (IU/mL)	HCRNA	1								
4	1111_00001	Hepatitis C Viral RNA (IU/mL)	HCRNA	1								
5	1111_00001	Hepatitis C Viral RNA (IU/mL)	HCRNA	1								
6	1111_00001	Hepatitis C Viral RNA (IU/mL)	HCRNA	1		Intermittent missing	Y					PHANTOM
7	1111_00001	Hepatitis C Viral RNA (IU/mL)	HCRNA	1								
8	1111_00001	Hepatitis C Viral RNA (IU/mL)	HCRNA	1								
9	1111_00001	Hepatitis C Viral RNA (IU/mL)	HCRNA	1								
10	1111_00001	Hepatitis C Viral RNA (IU/mL)	HCRNA	1								
11	1111_00001	Hepatitis C Viral RNA (IU/mL)	HCRNA	1								
12	1111_00001	Hepatitis C Viral RNA (IU/mL)	HCRNA	1								
13	1111_00001	Hepatitis C Viral RNA (IU/mL)	HCRNA	1						Monotone missing	Y	PHANTOM
14	1111_00001	Hepatitis C Viral RNA (IU/mL)	HCRNA	1						Monotone missing	Y	PHANTOM
15	1111_00001	Hepatitis C Viral RNA (log10 IU/mL)	HCRNAL	2	DERIVED							
16	1111_00001	Hepatitis C Viral RNA (log10 IU/mL)	HCRNAL	2	DERIVED							
17	1111_00001	Hepatitis C Viral RNA (log10 IU/mL)	HCRNAL	2	DERIVED							
18	1111_00001	Hepatitis C Viral RNA (log10 IU/mL)	HCRNAL	2	DERIVED							
19	1111_00001	Hepatitis C Viral RNA (log10 IU/mL)	HCRNAL	2	DERIVED							
20	1111_00001	Hepatitis C Viral RNA (log10 IU/mL)	HCRNAL	2	DERIVED							
21	1111_00001	Hepatitis C Viral RNA (log10 IU/mL)	HCRNAL	2	DERIVED							
22	1111_00001	Hepatitis C Viral RNA (log10 IU/mL)	HCRNAL	2	DERIVED							
23	1111_00001	Hepatitis C Viral RNA (log10 IU/mL)	HCRNAL	2	DERIVED							
24	1111_00001	Hepatitis C Viral RNA (log10 IU/mL)	HCRNAL	2	DERIVED							
25	1111_00001	HCV RNA Undetectable (TND) at Treatment Week 2	WK2TND	3	DERIVED							
26	1111_00001	HCV RNA < 15 IU/mL (either TD(u) or TND) at Treatment Week 2	WK2TDU	4	DERIVED							
27	1111_00001	HCV RNA Undetectable (TND) at Treatment Week 4	WK4TND	5	DERIVED							
28	1111_00001	HCV RNA < 15 IU/mL (either TD(u) or TND) at Treatment Week 4	WK4TDU	6	DERIVED							
29	1111_00001	HCV RNA Undetectable (TND) at Treatment Week 12	WK12TND	7	DERIVED							
30	1111_00001	HCV RNA < 15 IU/mL (either TD(u) or TND) at Treatment Week 12	WK12TDU	8	DERIVED							
31	1111_00001	HCV RNA Undetectable (TND) at 4 Weeks After End of Treatment	SVR4TND	9	DERIVED							
32	1111_00001	Sustained Viral Response 4 Weeks After End of Treatment (SVR4)	SVR4	10	DERIVED							
33	1111_00001	Sustained Viral Response 12 Weeks After End of Treatment (SVR12)	SVR12	11	DERIVED					Monotone missing	Y	PHANTOM
34	1111_00001	Sustained Viral Response 12 Weeks After End of Treatment (SVR12)	SVR12	11	DERIVED					Monotone missing	Y	TRD=F
35	1111_00001	Sustained Viral Response 12 Weeks After End of Treatment (SVR12)	SVR12	11	DERIVED					Monotone missing	Y	M=F
36	1111_00001	Sustained Viral Response 24 Weeks After End of Treatment (SVR24)	SVR24	12	DERIVED					Monotone missing	Y	PHANTOM
37	1111_00001	Sustained Viral Response 24 Weeks After End of Treatment (SVR24)	SVR24	12	DERIVED					Monotone missing	Y	TRD=F
38	1111_00001	Sustained Viral Response 24 Weeks After End of Treatment (SVR24)	SVR24	12	DERIVED					Monotone missing	Y	M=F

An Example from HCV Study

1	USUBJID	EOSSTT	EOSDT	EOSDY	DCSREAS	EOTSTT	EOTDT	EOTDY	DCTREAS
2	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
3	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
4	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
5	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
6	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
7	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
8	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
9	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
10	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
11	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
12	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
13	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
14	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
15	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
16	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
17	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
18	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
19	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
20	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
21	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
22	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
23	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
24	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
25	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
26	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
27	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
28	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
29	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
30	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
31	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
32	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
33	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
34	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
35	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
36	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
37	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	
38	1111_00001	DISCONTINUED	7-Sep-2014	119	WITHDRAWAL BY SUBJECT	COMPLETED	3-Aug-2014	84	

An Example from HCV Study

BARDS
Biostatistics and Research Decision Sciences

1	USUBJID	LBORRES	LBORRESU	AVAL	AVALC	BASE	ABLFL	CHG	ANL01FL	SAVISIT	SRCSEQ	SRCDOM	SRCVAR
2	1111_00001	5000000	IU/mL	5000000	TDq						1	LB	LBORRES
3	1111_00001	3400000	IU/mL	3400000	TDq	3400000	Y	0	Y		2	LB	LBORRES
4	1111_00001	300	IU/mL	300	TDq	3400000		-3399700	Y		3	LB	LBORRES
5	1111_00001	HCV RNA not detected	IU/mL	1	TND	3400000		-3399999	Y		4	LB	LBORRES
6	1111_00001				MISSING				Y				
7	1111_00001	HCV RNA not detected	IU/mL	1	TND	3400000		-3399999	Y		5	LB	LBORRES
8	1111_00001	HCV RNA not detected	IU/mL	1	TND	3400000		-3399999	Y		6	LB	LBORRES
9	1111_00001	HCV RNA not detected	IU/mL	1	TND	3400000		-3399999	Y		7	LB	LBORRES
10	1111_00001	HCV RNA not detected	IU/mL	1	TND	3400000		-3399999	Y		8	LB	LBORRES
11	1111_00001	HCV RNA not detected	IU/mL	1	TND	3400000		-3399999	Y		9	LB	LBORRES
12	1111_00001	HCV RNA not detected	IU/mL	1	TND	3400000		-3399999	Y		10	LB	LBORRES
13	1111_00001				MISSING				Y				
14	1111_00001				MISSING				Y				
15	1111_00001	5000000	IU/mL	6.69897									
16	1111_00001	3400000	IU/mL	6.53148		6.53148	Y	0	Y				
17	1111_00001	300	IU/mL	2.47712		6.53148		-4.05436	Y				
18	1111_00001	HCV RNA not detected	IU/mL	0		6.53148		-6.53148	Y				
19	1111_00001	HCV RNA not detected	IU/mL	0		6.53148		-6.53148	Y				
20	1111_00001	HCV RNA not detected	IU/mL	0		6.53148		-6.53148	Y				
21	1111_00001	HCV RNA not detected	IU/mL	0		6.53148		-6.53148	Y				
22	1111_00001	HCV RNA not detected	IU/mL	0		6.53148		-6.53148	Y				
23	1111_00001	HCV RNA not detected	IU/mL	0		6.53148		-6.53148	Y				
24	1111_00001	HCV RNA not detected	IU/mL	0		6.53148		-6.53148	Y				
25	1111_00001	HCV RNA not detected	IU/mL	1	SUCCESS				Y				
26	1111_00001	HCV RNA not detected	IU/mL	1	SUCCESS				Y				
27	1111_00001	HCV RNA not detected	IU/mL	1	SUCCESS				Y				
28	1111_00001	HCV RNA not detected	IU/mL	1	SUCCESS				Y				
29	1111_00001	HCV RNA not detected	IU/mL	1	SUCCESS				Y				
30	1111_00001	HCV RNA not detected	IU/mL	1	SUCCESS				Y				
31	1111_00001	HCV RNA not detected	IU/mL	1	SUCCESS				Y				
32	1111_00001	HCV RNA not detected	IU/mL	1	SUCCESS				Y				
33	1111_00001				MISSING				Y				
34	1111_00001				MISSING				Y				
35	1111_00001			2	FAILURE				Y				
36	1111_00001				MISSING				Y				
37	1111_00001				MISSING				Y				
38	1111_00001			2	FAILURE				Y				

HCV Resistance Dataset

BARDS
Biostatistics and Research Decision Sciences

- FDA recommends to create the HCV Resistance analysis dataset by following the Guidance for Submitting HCV Resistance Data.
  - The general data format
  - Standardization of column headings and variables
  - Recommended definitions
  - Recommended data contents
    - Subject level data (Patient Data)
    - Endpoint Data
    - Genotypic Data
- Consult with the Division of Antiviral Products (DAVP) in advance when more detailed guidance is needed

HCV Resistance Dataset

BARDS
Biostatistics and Research Decision Sciences

- Standardization of column headings and variables
  - Subject level data (Patient Data)
    - Variable naming, label, definition and control terminology

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).

HCV Resistance Dataset

- Standardization of column headings and variables
  - Subject level data (Patient Data)
    - Variable naming, label, definition and control terminology

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.

HCV Resistance Dataset

BARDS Biostatistics and Research Decision Sciences

- Standardization of column headings and variables
  - Endpoint Data
    - Variable naming, label, definition and control terminology

Variable	Definition and control terminology
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 (log10 IU/mL) at baseline
HCVVL	HCV RNA (IU/mL) at all time points from protocol, one row for each time point
LOGHCVVL	HCV RNA (log10 IU/mL) at all time points from protocol, one row for each time point
SVRxxFL (e.g., 4,12,24)	Sustained virologic response at Week 4,12,24 after end-of-treatment (Y or N, or NULL).
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

HCV Resistance Dataset

- Standardization of column headings and variables
  - Genotypic Data (In General)
    - 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.
    - Subject sequence data should be reported using subtype-specific reference strains

HCV Genotype	Reference Strain
GT 1a	H77
GT 1b	Con1
Other genotype 1 subtypes, mixed subtypes, or subtype unknown	H77
GT 2	JFH-1
GT 3	S52
GT 4	ED43
GT 5	SA13
GT 6	EUHK2

6.docx

HCV Resistance Dataset

BARDS
Biostatistics and Research Decision Sciences

- Standardization of column headings and variables
  - Genotypic Data
    - **Variables Format Example**: N30XXX (e.g., N30155, N4A0030, N5A0002, N5B0200)
    - Changes from the prototypic reference sequence 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**)
    - For insertions in subject sequence, additional columns should be added where appropriate, e.g., 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
    - For 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.
    - A composite of all substitutions emerging on treatment should be reported (i.e., POST-BL ALL).

An Example for HCV Resistance Dataset

BARDS
Biostatistics and Research Decision Sciences

Source data

USUBJID	PFTESTCD	PFTEST	VISIT	PFORRES	PFLOC
A001	GENEGAP	Gene Gap	BASELINE	4	NS3
A001	MUTID	Mutation Identified	WEEK 8	A1F	NS3
A001	MUTID	Mutation Identified	WEEK 8	I3Y	NS3
A001	MUTID	Mutation Identified	WEEK 12	P2S	NS3
A001	MUTID	Mutation Identified	WEEK 12	P3Y	NS3
A001	MUTID	Mutation Identified	FOLLOWUP WK 8	A1R/H	NS3
A001	MUTID	Mutation Identified	FOLLOWUP WK 8	I3Y	NS3
A001	GENEINS	Gene Insertion	FOLLOWUP WK 8	3SRK	NS3
A001	MUTID	Mutation Identified	FOLLOWUP WK 12	A1R	NS3
A001	MUTID	Mutation Identified	FOLLOWUP WK 12	I3Y	NS3

Resistance data

USUBJID	GENORF	VISIT	N30001	N30002	N30003	N30003A	N30003B	N30003C	N30004
H77 1A REFERENCE			A	P	I				V
A001	H77	BASELINE							?
A001	H77	WEEK 8	F		Y				
A001	H77	WEEK 12		S	Y				
A001	H77	FOLLOWUP WK 8	R/H		Y	S	R	K	
A001	H77	FOLLOWUP WK 12	R		Y				
A001	H77	POST-BL ALL	F/R/H	S	Y	S	R	K	

An Example for HCV Resistance Dataset

BARDS
Biostatistics and Research Decision Sciences

USUBJID	PFTESTCD	PFTEST	VISIT	PFORRES	PFLOC
A001	GENEGAP	Gene Gap	BASELINE	4	NS3
A001	MUTID	Mutation Identified	WEEK 8	A1F	NS3
A001	MUTID	Mutation Identified	WEEK 8	I3Y	NS3
A001	MUTID	Mutation Identified	WEEK 12	P2S	NS3
A001	MUTID	Mutation Identified	WEEK 12	P3Y	NS3
A001	MUTID	Mutation Identified	FOLLOWUP WK 8	A1R/H	NS3
A001	MUTID	Mutation Identified	FOLLOWUP WK 8	I3Y	NS3
A001	GENEINS	Gene Insertion	FOLLOWUP WK 8	3SRK	NS3
A001	MUTID	Mutation Identified	FOLLOWUP WK 12	A1R	NS3
A001	MUTID	Mutation Identified	FOLLOWUP WK 12	I3Y	NS3

USUBJID	GENORF	VISIT	N30001	N30002	N30003	N30003A	N30003B	N30003C	N30004
H77 1A REFERENCE			A	P	I				V
A001	H77	BASELINE							?
A001	H77	WEEK 8	F		Y				
A001	H77	WEEK 12		S	Y				
A001	H77	FOLLOWUP WK 8	R/H		Y	S	R	K	
A001	H77	FOLLOWUP WK 12	R		Y				
A001	H77	POST-BL ALL	F/R/H	S	Y	S	R	K	

An Example for HCV Resistance Dataset

BARDS
Biostatistics and Research Decision Sciences

- Report 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)

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

Efficacy Outcomes and Related Covariates Dataset (ADEFFOUT)

- Efficacy Outcomes and Related Covariates (ADEFFOUT)
  - Efficacy outcomes and related covariates dataset shall have one record only per subject and need to include at least following information
    - Demographic variables
    - Baseline characteristics (including Baseline Genotypic Data, stratification factors, etc.)
    - Exposure variables (first and last dosing date, etc.)
    - Population flags (ITT, PP, etc.)
    - Efficacy outcomes (primary, secondary, etc.)
    - Covariates and subgroup variables
    - Subject disposition variables

    - FDA gives variable naming, label, definition and control terminology
- adeffout.xls

Summary

- Follow the guidance as much as possible
- More communicate with the FDA, submit a draft data to reviewer before submitting a format data if possible
- Some TA specific data don’ t require to follow ADaM fundamental principle

Thank You

Questions?