



Computational Science Symposium

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JumpStarting the Regulatory Review Process – Clinical Reviewer's Perspective

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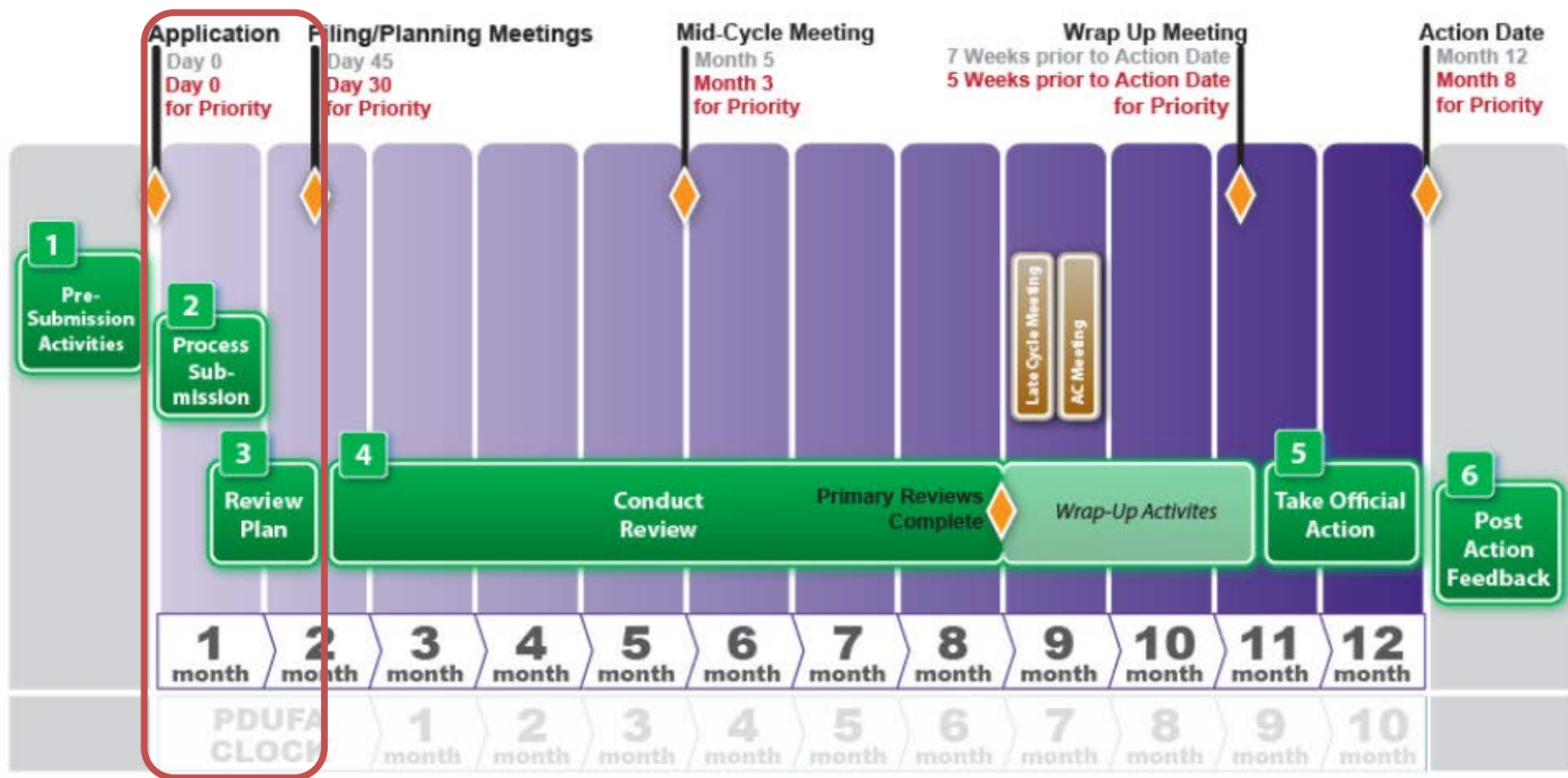
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NME/BLA Review Process and Major Steps for Completing the Review under PDUFA V



NME/BLA Submission



Impact of JumpStart on Clinical Review Process

- Very early and very quickly JumpStart provided a systematic assessment of the data fitness and data quality
 - Allowed reviewers to become familiarized with their data early on
 - Good data fitness and quality provided confidence that data could be used in reviews and helped prepare for filing

Familiarized Reviewers to Their Data

- **JUMPSTART FINDING:** The SV (subject visits) domain shows daily visits, while the TV (trial visits) domain shows subjects only have visits on certain days

STUDYID	DOMAIN	USUBJID	VISITNUM	VISITDY	SVSTDY
STUDY001-101	SV	STUDY001-101-111-001	1	1	1
STUDY001-101	SV	STUDY001-101-111-001	2	1	1
STUDY001-101	SV	STUDY001-101-111-001	3	2	2
STUDY001-101	SV	STUDY001-101-111-001	4	3	3
STUDY001-101	SV	STUDY001-101-111-001	5	4	4
STUDY001-101	SV	STUDY001-101-111-001	6	5	5
STUDY001-101	SV	STUDY001-101-111-001	7	6	6
STUDY001-101	SV	STUDY001-101-111-001	8	7	7
STUDY001-101	SV	STUDY001-101-111-001	9	8	8
STUDY001-101	SV	STUDY001-101-111-001	10	9	9
STUDY001-101	SV	STUDY001-101-111-001	11	10	10
STUDY001-101	SV	STUDY001-101-111-001	12	11	11
STUDY001-101	SV	STUDY001-101-111-001	13	12	12
STUDY001-101	SV	STUDY001-101-111-001	14	13	13
STUDY001-101	SV	STUDY001-101-111-001	15	14	14

STUDYID	DOMAIN	VISITNUM	VISIT	VISITDY	TVSTRL
STUDY001-101	TV	1	SCREENING	1	Start of Screen Epoch
STUDY001-101	TV	2	DAY 1	1	Day of study drug administration
STUDY001-101	TV	3	DAY 2	2	1 day after study drug administration
STUDY001-101	TV	4	DAY 3	3	2 days after study drug administration
STUDY001-101	TV	6	DAY 5	5	Approximately 4 days (+/- 1 day)
STUDY001-101	TV	10	DAY 9	9	Approximately 8 days (+/- 3 days)
STUDY001-101	TV	15	DAY 14/EOS	14	Approximately 13 days (+/- 3 days)
STUDY001-101	TV	16	DAY 21	21	Approximately 20 days (+/- 3 days)
STUDY001-101	TV	17	DAY 28	28	Approximately 27 days (+/- 3 days)

Good Data Fitness/Quality Provided Confidence Data Could Be Used

SDTM Domain: AE

Randomly Sampled Term Matching

Random Sample %: 100

Low Match Score: 100

Total Terms: 171

Total Matches: 29

AETERM	AEDECOD	Average Match Score
PLATELET COUNT DECREASED	Platelet count decreased	100
BLOOD PRESSURE INCREASED	Blood pressure increased	100
INSOMNIA	Insomnia	100
ORAL PRURITUS	Oral pruritus	100
CHEST DISCOMFORT	Chest discomfort	100
TOTAL PROTEIN INCREASED	Protein total increased	100
MYALGIA	Myalgia	100
BLOOD GLUCOSE INCREASED	Blood glucose increased	100
HEADACHE	Headache	100
WHITE BLOOD CELL COUNT DECREASED	White blood cell count decreased	100
BLOOD GLUCOSE DECREASED	Blood glucose decreased	100
ABDOMINAL PAIN	Abdominal pain	100
LOWER ABDOMINAL PAIN	Abdominal pain lower	100
WHITE BLOOD CELL COUNT INCREASED	White blood cell count increased	100
HERPES SIMPLEX	Herpes simplex	100
ECZEMA	Eczema	100
DECREASED APPETITE	Decreased appetite	100

Impact of JumpStart on Clinical Review Process

- Where JumpStart analyses matched Applicant's results:
 - Provided confidence that Applicant's results were reliable and reproducible
 - Demonstrated data was amenable to standard reviewer tools for conducting analyses
 - Could potentially paste JumpStart-generated tables directly into the Clinical Review

Impact of JumpStart on Clinical Review Process

- JumpStart identified inconsistencies or anomalies in the data that required:
 - Additional manipulation of datasets so they could be used with standard reviewer tools
- OR
 - Information request be sent to the Applicant for clarification/corrections

Identified Inconsistencies or Anomalies in Datasets

- **JUMPSTART FINDING:** LBTEST and LBTESTCD values not consistent with the required CDISC CT codes and lab names not consistently used across studies

LBTEST	LBTESTCD	Failures	NCI Code	Correct LBTESTCD
Hemoglobin	HB	8,475	C64848	HGB
Bicarbonate	HCO3	1,160	C74667	BICARB
Haptoglobin	HAPT	755	C74740	HAPTOG
Insulin	INSU	252	C74788	INSULIN
Anion Gap	ANGP	6	C74685	ANIONG
Globulin	GLOB	5	C74738	GLOBUL
Calcium, Ionized	ICAL	2	C81948	CAION

Identified Inconsistencies or Anomalies in Datasets

- REVIEWER ACTION: Manually adjusted variables so analysis tools could be used
 - Knowing this very early on saved considerable review time (and frustration) later when performing automated analyses; e.g. JReview Catalog analyses
 - Probably would not have discovered this issue otherwise until later in the review

Identified Inconsistencies or Anomalies in Datasets

- JumpStart Identified issues that required clarification from the Applicant
 - JumpStart team facilitated crafting comments so review team could rapidly communicate these to the Applicant and get a fast response

Identified Inconsistencies or Anomalies in Datasets

- **JUMPSTART FINDING:** For the neutrophils/leucocytes test, a few patients had two results (i.e., same date/time stamp); however, results and the reference ranges are very different
 - Could throw off means calculations, etc.
 - No easy way for a reviewer to identify these repeats
- **JUMPSTART FINDING:** In a different study, AE domain contains investigations related to Neutrophil counts but no Neutrophil lab test results provided in LB domain.

Identified Inconsistencies or Anomalies in Datasets

- REVIEWER ACTION: JumpStart provided Excel spreadsheet with list of laboratory tests that had duplicate results (by subject ID and trial) – this was sent directly to the Applicant
 - Applicant responded that certain lab tests had been mapped incorrectly and subsequently submitted new LB datasets with modified mapping to include correct test codes.
 - Reviewer did not need to waste time with bad datasets

Impact of JumpStart on Clinical Review Process

- Provided safety information overview
 - Helped identify safety signals early on
 - Helped prioritize safety review
 - Allowed reviewers to conduct focused in-depth analyses where safety signals identified
 - Allowed reviewers to request customized analyses as needed; e.g. box-whisker plots for changes over time or shift tables for parameters of interest

Provided Safety Information Overview

MedDRA at a Glance Comparison Analysis

Treatment arm:

Control arm:

Risk difference threshold (%): 2

Relative risk threshold: 2

Negative log p-value threshold:

Choose your arms and type in your thresholds in the yellow input cells
Look below to see which terms have signals; you may have to scroll down
The colors in the signal columns tell you about the signal:



This term shows a signal

A term above or below in MedDRA shows a signal

Level	System Organ Class	High-Level Group Term	High-Level Term	Preferred Term	DME	Signal	Signal At					Treatment:		Control:		Risk Difference	Relative Risk*	Cont Corr	Negative Log P-value
							SOC	HLGT	PT	N=99		N=100							
										Subject Count	%	Subject Count	%						
2	Ear and labyrinth disorders										0	0.0	0	0.0	0.0	1.0	*		
2	Ear and labyrinth disorders	Aural disorders NEC									0	0.0	0	0.0	0.0	1.0	*		
3	Ear and labyrinth disorders	Aural disorders NEC	Ear disorders NEC								0	0.0	0	0.0	0.0	1.0	*		
4	Ear and labyrinth disorders	Aural disorders NEC	Ear disorders NEC	Ear pain							0	0.0	0	0.0	0.0	1.0	*		
1	Eye disorders										0	0.0	0	0.0	0.0	1.0	*		
2	Eye disorders	Eye disorders NEC									0	0.0	0	0.0	0.0	1.0	*		
3	Eye disorders	Eye disorders NEC	Ocular disorders NEC								0	0.0	0	0.0	0.0	1.0	*		
4	Eye disorders	Eye disorders NEC	Ocular disorders NEC	Eye pain							0	0.0	0	0.0	0.0	1.0	*		
2	Eye disorders	Ocular infections, irritations and inflammations									0	0.0	0	0.0	0.0	1.0	*		
3	Eye disorders	Ocular infections, irritations and inflammations	Conjunctival infections, irritations and inflammations								0	0.0	0	0.0	0.0	1.0	*		
4	Eye disorders	Ocular infections, irritations and inflammations	Conjunctival infections, irritations and inflammations	Conjunctivitis allergic							0	0.0	0	0.0	0.0	1.0	*		
1	Gastrointestinal disorders										23	23.2	22	22.0	1.2	1.1		0.1	
2	Gastrointestinal disorders	Gastrointestinal inflammatory conditions									1	1.0	0	0.0	1.0	3.0	*	0.7	
3	Gastrointestinal disorders	Gastrointestinal inflammatory conditions	Gastritis (excl infective)								0	0.0	0	0.0	0.0	1.0	*		
4	Gastrointestinal disorders	Gastrointestinal inflammatory conditions	Gastritis (excl infective)	Gastritis							0	0.0	0	0.0	0.0	1.0	*		
3	Gastrointestinal disorders	Gastrointestinal inflammatory conditions	Gastrointestinal inflammatory disorders NEC								1	1.0	0	0.0	1.0	3.0	*	0.7	
4	Gastrointestinal disorders	Gastrointestinal inflammatory conditions	Gastrointestinal inflammatory disorders NEC	Enterocolitis							1	1.0	0	0.0	1.0	3.0	*	0.7	
2	Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions									15	15.2	17	17.0	-1.8	0.9		0.2	
3	Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	Diarrhoea (excl infective)								15	15.2	17	17.0	-1.8	0.9		0.2	
4	Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	Diarrhoea (excl infective)	Diarrhoea							15	15.2	17	17.0	-1.8	0.9		0.2	
2	Gastrointestinal disorders	Gastrointestinal signs and symptoms									10	10.1	4	4.0	6.1	2.5		2.3	
3	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Flatulence, bloating and distension								0	0.0	0	0.0	0.0	1.0	*		
4	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Flatulence, bloating and distension	Abdominal distension							0	0.0	0	0.0	0.0	1.0	*		
3	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Gastrointestinal and abdominal pains (excl oral and throat)								2	2.0	2	2.0	0.0	1.0	*	0.0	
4	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Gastrointestinal and abdominal pains (excl oral and throat)	Abdominal pain							1	1.0	2	2.0	-1.0	0.5	*	0.0	
4	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Gastrointestinal and abdominal pains (excl oral and throat)	Abdominal pain low er							0	0.0	0	0.0	0.0	1.0	*		
4	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Gastrointestinal and abdominal pains (excl oral and throat)	Abdominal pain upper							1	1.0	0	0.0	1.0	3.0	*	0.7	
3	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Gastrointestinal signs and symptoms NEC								1	1.0	0	0.0	1.0	3.0	*	0.7	

Impact of JumpStart on Clinical Review Process

- By uploading datasets to the standard reviewer tools, confirmed usability of these tools in the review process
 - Some of these review tools, e.g. JReview and MAED, are relatively new to CDER
 - Because of the efficiency and comfort with the data quality and data fitness, JumpStart allowed reviewers to also become comfortable with these new review tools

Impact of JumpStart on Clinical Review Process

- Through JumpStart, there may potentially be a critical mass of clinical reviewers who will become comfortable and proficient with these newer review tools and will be able to coordinate analyses in real time, which will be a real advantage to CDER reviewers

Summary

JumpStart:

- Was user-friendly (easy to register, helpful staff)
- Familiarized reviewers to their data quickly and provided instant understanding of the quality of their submission
- Saved time by identifying areas where data fitness/quality were good and useable, and where there were anomalies that required further immediate action
- Provided high-level overview of safety and identified signals that might not have been obvious at first glance and that merited further exploration
 - Provided assistance in crafting customized safety analyses
- Uploaded datasets to standard reviewer tools, thus demonstrating their use and increasing comfort level among reviewers with newer tools