

The Impact of SEND Data on FDA Review of Nonclinical Studies

PhUSE Computational Science Symposium

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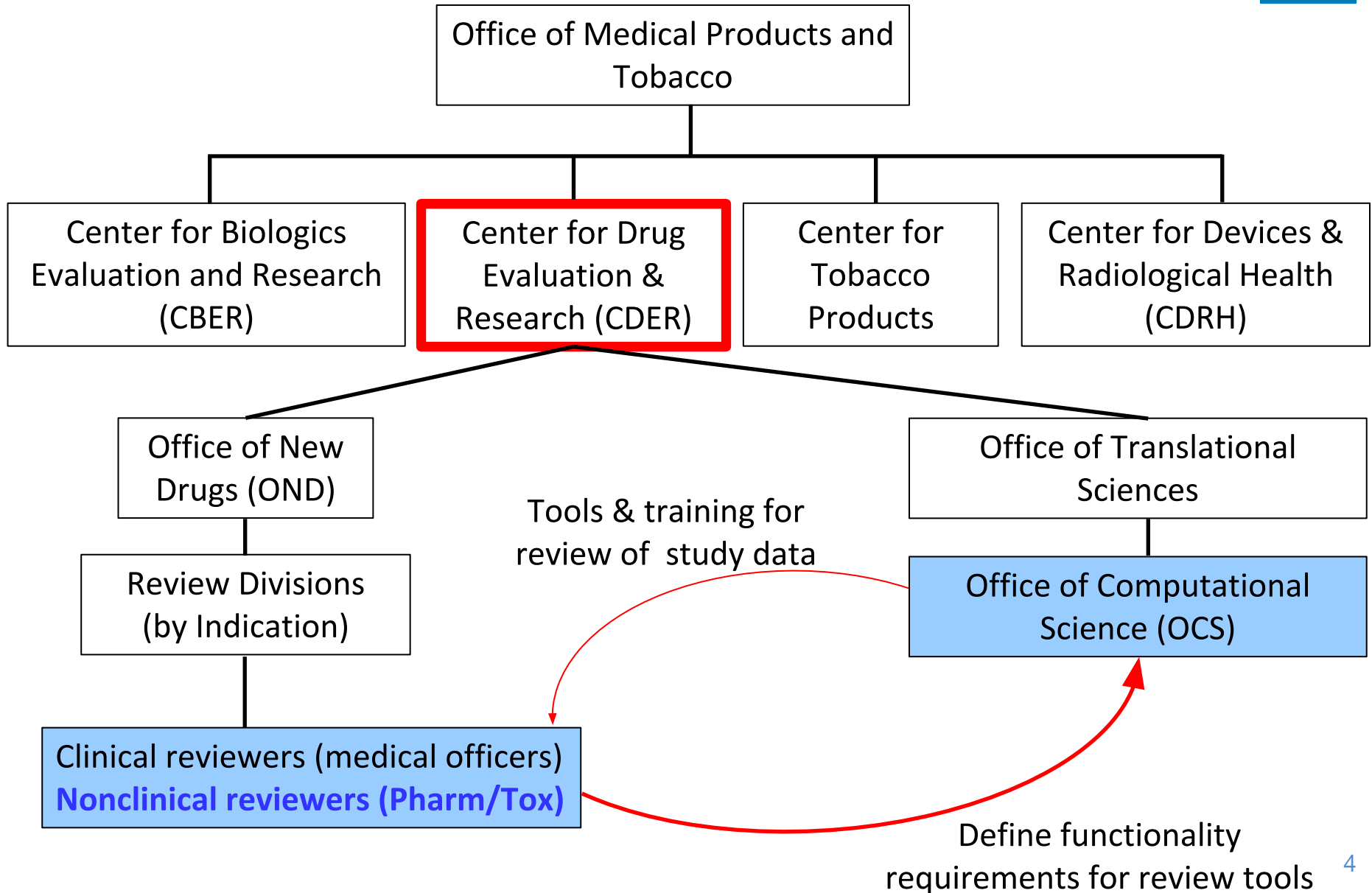
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Outline

- Overview of nonclinical review at FDA
- Janus Nonclinical
- Impact of SEND on nonclinical review
- Ongoing and future development initiatives

FDA: OND & OCS Relationship



Typical FDA Review Team for IND/NDA



Discipline	Role	Office
Regulatory project manager	Project management-communicate with sponsor	Office of New Drugs
Clinical	Primary reviewer	Office of New Drugs
	Team Leader	
Nonclinical	Primary reviewer	Office of New Drugs
	Team Leader	
Chemistry, Manufacturing & Controls (CMC)	Primary Reviewer	Office of Pharmaceutical Quality
	Team Leader	
Clinical Pharmacology	Primary Reviewer	Office of Translational Sciences – Office of Clinical Pharmacology
	Team Leader	
Biostatistics	Primary Reviewer	Office of Translational Sciences – Office of Biostatistics
	Team Leader	

Nonclinical Reviewers in OND



- 247 Reviewers
- 17 review divisions
- All are Ph.D.s
 - Pharmacology (areas of research vary widely)
 - Toxicology
- Come from post-docs, academic research, or industry positions

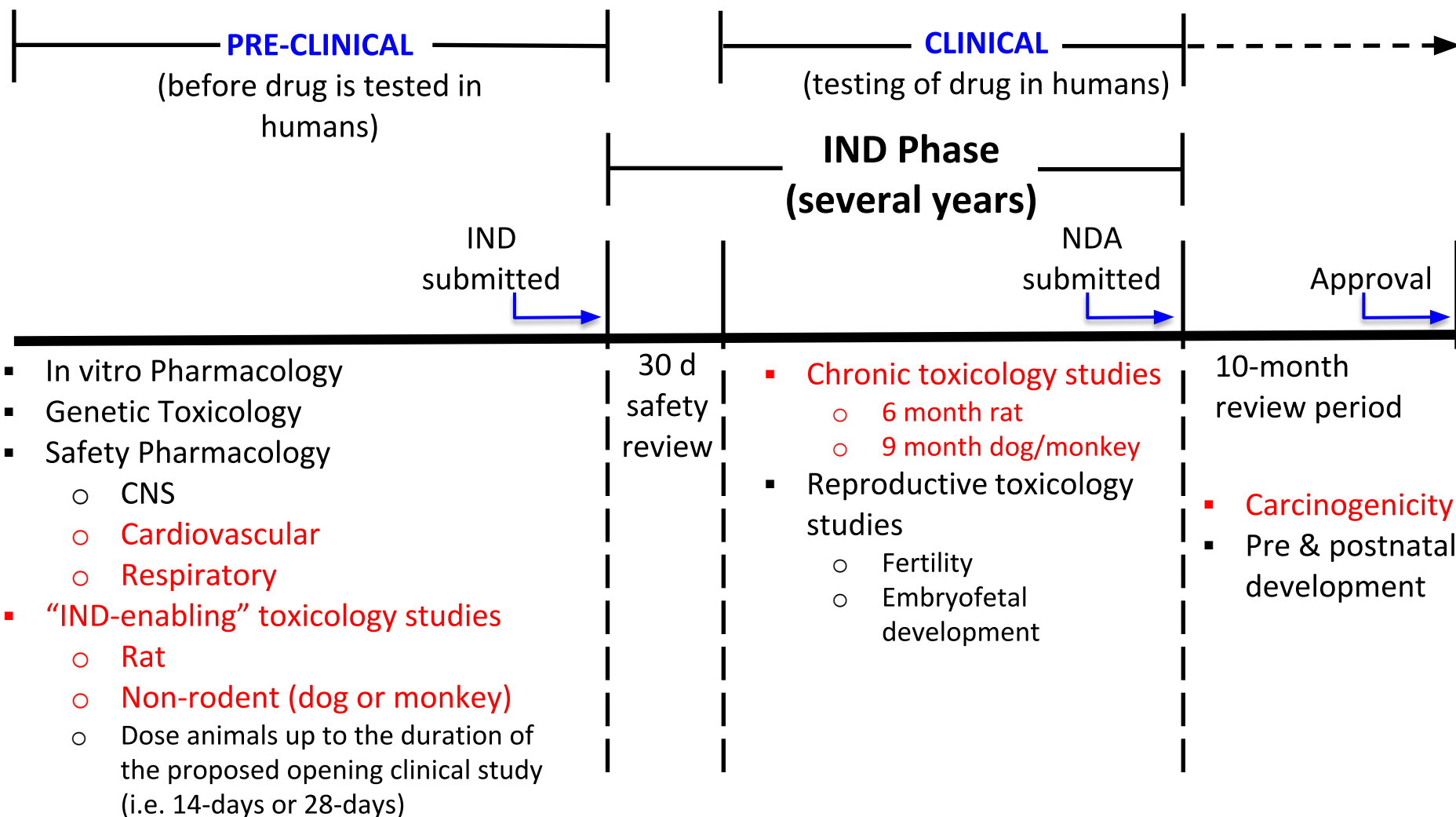
Nonclinical toxicology studies



- Objectives

- Define toxic effects of a drug that could potentially be seen in **humans**
- Define the doses/exposures at which these effects might be expected to occur

Nonclinical studies in support of clinical development



Major review principles

- (1) Look for findings that show a **dose-response relationship**
- (2) Of those findings, which ones are considered **adverse**?
 - These 2 components are main factors in limit-dose determination

Challenges with current approach to review of nonclinical studies



- Nonclinical study reports (NCSRs) submitted in pdf format
 - Data analysis requires re-typing of values from summary tables into Excel
 - Variable formats used for organization of NCSRs - 1000+ page documents very difficult to navigate
 - Nonclinical study data is not readily searchable across studies
- SEND datasets can address each of these issues

Electronic study data regulations

- FD&C Act Section 745A(a): Sponsors must use the data standards defined in the **FDA Data Standards Catalog** starting 24-months after final guidance is issued for a specific submission type

Standard	Application type	Dates that standard is <u>accepted</u> *	Dates that standard is <u>required</u> *
SEND 3.0	NDA/BLA/ANDA	6/13/11 – 3/15/19	12/17/16
	Commercial IND	6/13/11 – 3/15/20	12/17/17
SEND 3.1	NDA/BLA/ANDA	8/21/17 -	3/15/19
	Commercial IND	8/21/17-	3/15/20

* Dates refer to the nonclinical study *initiation* date (not the date that the study is submitted to the Agency)

SEND studies in Janus database

Application type	# of SEND Studies (# of applications)				Total
	2016	2017	2018	2019*	
Commercial IND	3 (2)	42 (25)	295 (136)	222 (106)	562 (269)
NDA	8 (3)	5 (3)	34 (20)	20 (7)	67 (33)
BLA	0	1 (1)	2 (2)	0	3 (3)

*As of 4/12/19

Janus Nonclinical

Janus Nonclinical

- FDA-specific, web-based application that allows users to analyze and visualize SEND datasets
- Pharm/tox reviewers from OND are guiding development of Janus NC by OCS

■ Why?

Janus Nonclinical

■ **Current**

- Table & figure format – consistent with general FDA reviewer practices
 - Review documents – consistent formatting across reviewers & review divisions

■ **Ongoing**

- Interface with IND Smart Template

■ **Future**

- Cross-study analysis (nonclinical)
- Nonclinical – clinical data correlation

Janus NC Dashboard



- User assigns group alias, control group, **set type** in the Study Sets Table
 - 5 possible Set Types: interim, terminal, recovery, toxicokinetic, satellite



Study Group	Group Label	Group Alias	Control Group	Set Code	Set Description	TK Description	Set Type
1	Group 1 - Reference Item	Control	☒				
				1N	0 mg/kg/day Reference Item Main		Terminal
				1R	0 mg/kg/day Reference Item Recovery		Recovery
				1TK	0 mg/kg/day Reference Item Toxicokinetic		TK
2	Group 2 - 1 mg/kg/day Low dose		☐				
				2N	1 mg/kg/day Main		Terminal
				2TK	1 mg/kg/day Toxicokinetic		TK
3	Group 3 - 3 mg/kg/day Mid dose		☐				
				3N	3 mg/kg/day Main		Terminal
				3TK	3 mg/kg/day Toxicokinetic		TK
4	Group 4 - 10 mg/kg/day High dose		☐				
				4N	10 mg/kg/day Main		Terminal
				4R	10 mg/kg/day Recovery		Recovery
				4TK	10 mg/kg/day Toxicokinetic		TK

Janus NC Summary Table - BW



Group / Sex		-9	-1	4	7
1M	Mean	285.3	352.8	388.5	411.9
	SD	9.6	15.2	21.3	24.5
	N	15	15	15	15
2M	Mean	286.1	352.1	386.1	407.6
	SD	5.5	15.4	21.7	25.8
	N	10	10	10	10
	%Diff G1	0.3	-0.2	-0.6	-1.1
3M	Mean	285.6	354.0	387.2	406.9
	SD	6.1	10.7	17.1	16.7
	N	10	10	10	10
	%Diff G1	0.1	0.3	-0.3	-1.2
4M	Mean	284.9	353.9	381.2	395.5
	SD	9.3	14.0	14.5	18.1
	N	15	15	15	15
	%Diff G1	-0.1	0.3	-1.9	-4.0

T Sex	Group	T Test	Unit of the blon... Results	Day -9			Day -1			Day 4			Day 7		
				Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev	N
Male	☒ Control [Terminal, Recovery]	Body Weight	g	285.27	±9.61	15	352.00	±15.17	15	388.47	±21.32	15	411.93	±24.47	15
Male	☐ Low dose - Terminal	Body Weight	g	286.10	±5.49	10	352.10	±15.38	10	386.10	±21.69	10	407.60	±25.81	10
Male	☐ Mid dose - Terminal	Body Weight	g	285.60	±6.08	10	354.00	±10.72	10	387.20	±17.14	10	406.90	±16.63	10
Male	☐ High dose [Terminal, Recovery]	Body Weight	g	284.93	±9.34	15	353.87	±13.96	15	381.20	±14.52	15	395.53	±18.07	15

Janus NC Summary Table - Histopathology

Nonclinical study report (pdf)

Tissue/ Observation	Group/Subgroup/Sex:	1/1/M	2/1/M	3/1/M	4/1/M
	Number of Animals:	10	10	10	8
Lung	Number Examined:	10	10	10	8
	Unremarkable:	9	8	9	1
Infiltrate, macrophages, alveolus					
finding not present -	10	8	1	3	
minimal 1	0	2	0	2	
slight 2	0	0	0	3	
Total Incidence:		0	2	9	5

Janus Nonclinical

STUDY LIST > DASHBOARD > MI-GROUPED SUMMARY

GROUPED SUMMARY | DAILY BY ANIMAL | ANIMAL DETAILS

Filter table data by term...

Organ/Tissue	Finding	Severity	Male			
			Control - Terminal S	Low Dose - Terminal S	Mid dose - Terminal S	High Dose - Terminal S
LUNG		#Examined	10	10	10	8
	Infiltrate, macrophages, alveolus	MINIMAL		2 (20.0%)	9 (90.0%)	2 (25.0%)
	Infiltrate, macrophages, alveolus	MILD				3 (37.5%)
	Infiltrate, macrophages, alveolus	Total		2 (20.0%)	9 (90.0%)	5 (62.5%)

Janus Nonclinical: Now



- **Janus NC summary tables reflect summary tables in NCSR**
 - Mean calculations based on Set Types defined in Dashboard
 - Highly customizable
- **Dynamically filter & sort summary table data**
 - Greatest impact: LB & MI
 - Allows for much faster identification of dose-related findings
- **Switch from Mean $\pm$ SD view to % change from control in 2 clicks**
 - Eliminates need for re-typing & analysis in Excel
- **Individual animal data available from summary table (click on mean)**

Impact of SEND data on nonclinical review

Current impact: Time Savings



- Summary table preparation time

Data table	Traditional methods – pdf	Janus NC
Clinical Chemistry	3+ hrs	30 – 45 mins
Histopathology	6 – 8 hrs	1 – 2 hrs

- Tables are exportable from Janus NC – can be added directly to review documents

Improved review efficiency: benefits



- More time to critically consider observed findings in tox studies
 - Risk assessment
 - Sponsor's perspective & potential explanations for findings
- **Potentially earlier engagement with sponsors on specific review issues (rather than at the last minute before the 30 d review clock is about to expire)**

Improved review efficiency: benefits



- P/T Reviewers: 50+ INDs/NDAs/BLAs in their portfolio at any given time
 - Submissions are constantly coming in to each IND
 - P/T reviewers: Must keep up with new clinical protocols, clinical protocol amendments, nonclinical inquiries, new study reports...
- Reality: Prioritize PDUFA deadline-related assignments
- **More efficient review of tox studies □ more time to keep up with ongoing portfolio**
 - More timely responses to inquiries with non-PDUFA mandated timelines?

Improved review efficiency: benefits



- More time to engage in non-review activities
 - Subcommittees within FDA
 - Examine topics of scientific interest
 - Engagement with industry/academic community

Future impact

- More informed regulatory decision-making
 - Janus: Warehouse of nonclinical datasets
 - Robust historical control databases
 - Within a single product
 - Follow specific findings across studies of different durations
 - Compare specific findings across species
 - Across products
 - Understand effects of drug classes (i.e. products targeting the same molecular pathway) on different nonclinical species
 - SEND dataset quality from sponsors is critical
 - Variability across datasets is an obstacle
 - Biocelerate initiatives

OCS Support for Pharm/tox Reviewers

Integrated approach



■ Tools

- For analysis and visualization of SEND data
 - Janus Nonclinical
 - Other commercially available software applications for specific uses

■ Training

- SEND standard (how nonclinical study data is modeled in SEND)
- Practical use of Janus Nonclinical
- Formats: Videos, instructor-led seminars, text documents

■ Resources

- KickStart Service
 - Conducted at the request of pharm/tox reviewer
 - In-person seminar
 - Data quality assessment of SEND datasets
 - Orient reviewer to how their SEND submissions are organized
 - Instruction on use of Janus Nonclinical to identify key findings
- OCS Service Desk

Ongoing & future development initiatives



- Training – for all nonclinical reviewers in OND
 - SEND standard (how nonclinical study data is modeled in SEND)
 - Practical use of Janus Nonclinical
- Data fitness report development for all SEND submissions
 - Need to be able to convey to reviewers issues that exist with the SEND dataset relative to the pdf study report
- Janus Nonclinical
 - Optimize summary table displays for all domains
 - Graphing/ data visualization enhancements
 - Cross-study analyses

Summary



- Nonclinical reviewers in OND work closely with staff in OCS to guide development of Janus Nonclinical (FDA-specific software application for visualization/analysis of SEND data)
- Janus Nonclinical – increased review efficiency
 - Much faster identification of treatment-related findings than traditional methods with pdf NCSRs
- Increased review efficiency - expected to benefit both FDA and Sponsors



SEND submissions to FDA



- Nonclinical studies initiated after 12/18/17 that did NOT include SEND datasets
 - Difficult to quantify this (no automated flag to identify studies by study initiation date)
 - 3-week sample size: 9/13/18 – 10/6/18; Stephanie Leuenroth-Quinn, (FDA/OND/IO)
 - **16% (15/96 INDs) of INDs during this time period failed to follow SEND requirement**
 - 26 total studies that should have had SEND (as defined by study initiation date) did not
 - Studies submitted to modules 4.2.3.1, 4.2.3.2, and 4.2.3.4
 - Draft, interim, final, GLP, Non-GLP studies
 - Companies were both small and large
 - CROs (both in US and outside of US)
 - Technical rejection criteria are not yet turned on

Major review principles

- **Additional Factors contribute to determination of the Limit Dose**

(1) Can the finding(s) be monitored clinically?

- So: could doctors see evidence of this toxicity during regular examinations and stop treatment if necessary?
 - Toxicity to brain cells: not clinically monitorable
 - Skin inflammation: clinically monitorable

(3) Is the finding reversible if you stop treatment?

(4) What level of risk is considered acceptable based on the indication?

- This is established in collaboration with the clinical review team
- Example: Lupus (severe disease, no available treatments) vs. Seasonal allergic rhinitis (many available treatments).
 - **Review division may allow clinical dosing beyond the NOAEL dose under certain circumstances**