PINNACLE 21 BY CERTARA

FDA VALIDATOR RULES V1.6 EXPLAINED

Overview of changes from previous version 1.5

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DISCLAIMER

- The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the regulatory agencies or standards development organizations.

AGENDA

- Introduction
  - Study Data Validation Definition
  - Types of Validation Rules
  - Location of FDA Validator Rules
- Details of Changes in v1.6
- Ensuring Compliance
- Dispositioning Data Validation Issues

INTRODUCTION

Study Data Validation Definition and Types of Validation Rules

DEFINITION OF STUDY DATA VALIDATION

8. Study Data Validation and Traceability

8.1 Definition of Study Data Validation

Study data validation helps to ensure that the study data are compliant, useful, and will support meaningful review and analysis. Validation activities occur at different times during submission and review of study data, including submission receipt and at the beginning of the regulatory review. Validation of study data that occurs upon receipt of a submission follows the process for Technical Rejection Criteria for Study Data (See Appendix F).

*FDA's Study Data Technical Conformance Guide, October 2022

TYPES OF VALIDATION RULES

8.2 Types of Study Data Validation Rules

1. Standards Development Organizations (e.g., CDISC) provide rules that assess conformance to its published standards (See www.CDISC.org).

2. FDA eCTD Technical Rejection Criteria for Study Data that assess conformance to the standards listed in the Catalog (See section 7.1, section 8.2.2, and Appendix F).

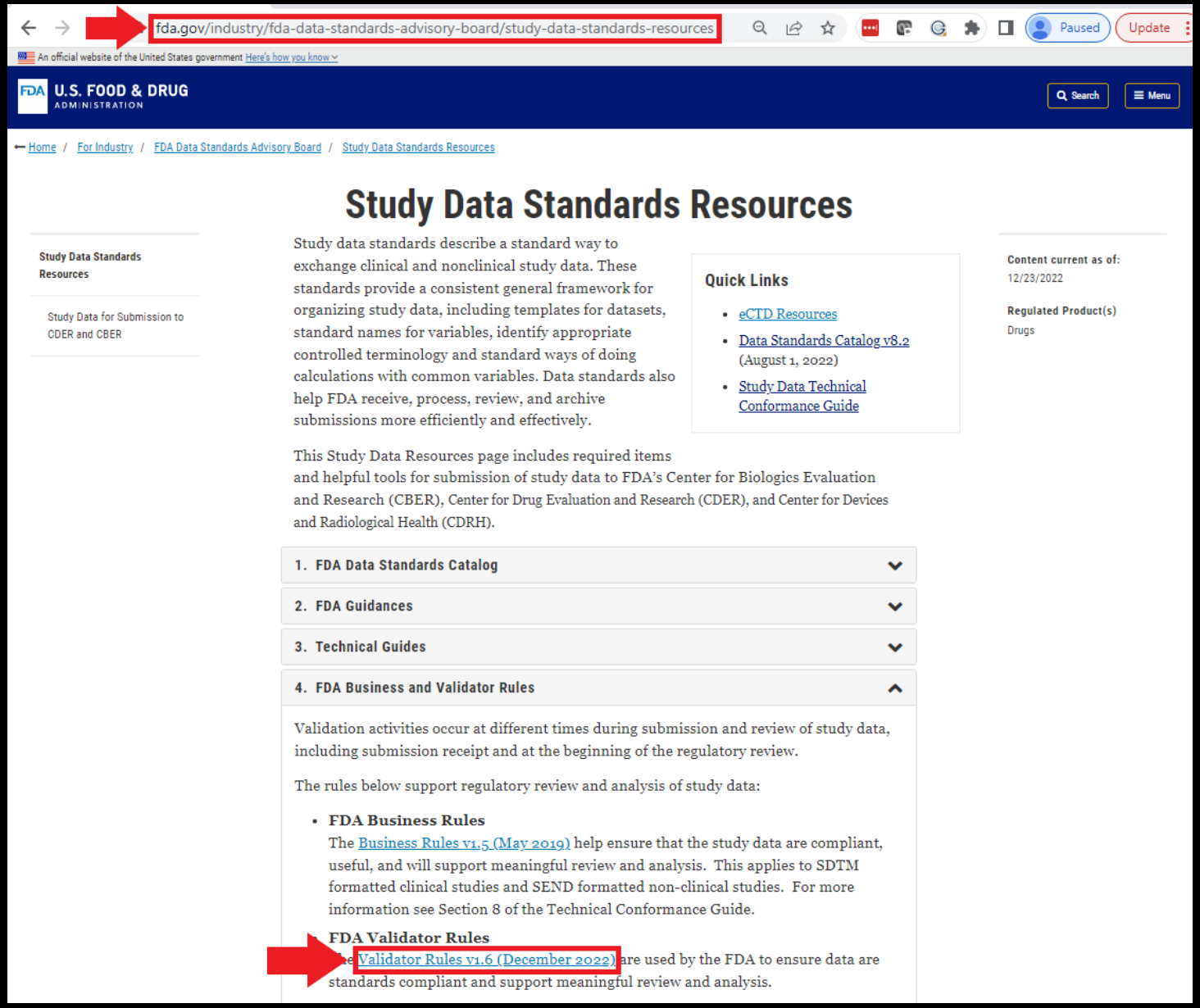
3. FDA Business and Validator rules to assess that the data support regulatory review and analysis.

8.2.1 FDA Business and Validator Rules

FDA Business Rules describe the business requirements for regulatory review to help ensure that study data are compliant and useful and support meaningful review and analysis. The list of business rules will grow and change with experience and cross-center collaborations. All business rules should be followed where applicable. The business rules are accompanied with validator rules which provide details regarding FDA's assessment of study data for purposes of review and analysis. The FDA Validator Rules also represent the latest understanding of what best supports regulatory review. The Study Data Standards Resources webpage page provides links to the currently available FDA Business and Validator rules.[67]

*FDA's Study Data Technical Conformance Guide, October 2022

LOCATION OF FDA VALIDATOR RULES



FDA VALIDATOR RULES V1.6

Changes from previous version 1.5 (published in March 2021)

NEW VERSIONS OF STANDARDS SUPPORTED

3 new versions of CDISC standards were added

version 1.6, finalized December 2022

FDA Validator Rule ID	Publisher	Publisher ID	FDA Validator Rule Message	FDA Validator Rule Description	Domains	SDTMIG 3.1.2	SDTMIG 3.1.3	SDTMIG 3.2	SDTMIG 3.3	SENDIG 3.0	SENDIG 3.1	SENDIG 3.1.1	SENDIG-AR 1.0	SENDIG-DART 1.1

SENDIG v3.1.1

- Added to FDA Data Standards Catalog v8.0 (2022-02-15)
  - Date Support Begins: 2022-02-15
- Corresponds to CDISC SEND Conformance Rules v4.0
  - Published 2021-07-29

SENDIG-AR v1.0

- Added to FDA Data Standards Catalog v6.2 (2020-04-10)
  - Date Support Begins: 2020-03-15
- No corresponding CDISC Conformance Rules

SENDIG-DART v1.1

- Added to FDA Data Standards Catalog v7.0 (2021-03-15)
  - Date Support Begins: 2021-03-05
- Corresponds to CDISC SEND Conformance Rules v4.0
  - Published 2021-07-29

NEW VALIDATOR RULES ADDED

118 new validator rules were added:

- 4 new rules added specific to SENDIG v3.1.1
- 61 new rules added specific to SENDIG-AR v1.0
  - Note: most have no Publisher ID (no corresponding CDISC Conformance Rules)
- 20 new rules added specific to SENDIG-DART v1.1

NEW VALIDATOR RULES ADDED

- 33 new rules added for a specific need or rules not previously included (medical device rules, etc.)

Rules for SDTM:

Rule ID	Publisher ID	Message
SD1233		Device is not present in DI domain
SD1234		Missing DEVTYPE Parameter for Device
SD1237		Duplicate records in Device Property
SD1449	FDAB003, TCG 6.3.1.1	Missing values for one or more variables subject to MedDRA: --LLT, --LLTCD, --DECOD, --PTCD, --HL
SD1453	CG0028	Duplicate value for --SEQ variable

Rules for both SDTM and SEND:

Rule ID	Publisher ID	Message
SD1446	FDAB034	Exposure start date is after the latest Disposition date
SD1448	FDAB031	--STRESN is populated when --STRESC value is not numeric
SD1450	FDAB044	Missing --ENINT variable, when --STINT variable is present
SD1451	FDAB044	Missing --STINT variable, when --ENINT variable is present
SD1452	FDAB040	Negative value for --VAMT

Rules for SEND:

Rule ID	Publisher ID	Message
SE0070	131.131.1	No Exposure record found for subject
SE2239	161	--RESCAT value is redundant with other variable values
SE2240		--ENDTC is after the latest Disposition date
SE2241		--DTC is after the latest Disposition date
SE2242	177	Missing value for --SPEC, when --TESTCD equals 'GROSPATH'
SE2243	178	--SPEC variable is populated, when --TESTCD equals 'CLSFUP'
SE2244	159, 394	--STRESC is the same as --ORRES when --STRESC is not 'NORMAL' or
SE2245		Missing TSNAM Trial Summary Parameter when TSCNTRY and/or TSLOC
SE2265	320	--DTC is before the latest Disposition date
SE2266		Negative value for --STRESN when --EXCLFL is not populated
SE2267	FDAB011	Missing STRPSTAT Trial Summary Parameter
SE2268	167	No record in DD domain for unscheduled death
SE2269	303	Unscheduled flag is populated for scheduled death
SE2270	320	--DY value does not equal DSSTDY value
SE2271	320	--DY value when BWTESTCD = 'TERMBW' does not equal DSSTDY value
SE2272	FDAB011	Multiple SDESIGN records
SE2273	FDAB011	Multiple STCAT records
SE2274	FDAB011	Multiple SSTYP records
SE2275	FDAB011	Multiple STDIR records
SE2276	320	--DTC does not equal DSSTDTC
SE2277	95, 95.1, 119, 281	Variable length exceeds 200 characters
SE2282	262, 262.1	Duplicate USUBJID within a POOLID
SE2355	244	Invalid --VAL value for ENVTEMPU

CHANGES TO PUBLISHER IDS

Publisher IDs updated for 11 rules

- CDISC Conformance Rule IDs added to existing rules
  - 2 are due to new rules added in CDISC SEND Conformance Rules v4.0 (but a rule already covered it)
  - 7 are due to new rules added in CDISC SDTMIG Conformance Rules v2.0 (but a rule already covered it)
  - 1 is due to a rule being deprecated in CDISC SDTMIG Conformance Rules v2.0
  - 1 appears to be due to a missed CDISC Conformance Rule ID that has been corrected

CHANGES TO RULE MESSAGES

Rule Message updated for 3 rules

Rule ID	New Message	Old Message
SD1105	EPOCH variable is populated, when DSCAT equals 'PROTOCOL MILESTONE'	EPOCH variable is populated, when DSCAT does not equal 'DISPOSITION EVENT'
SD1358	ARMNRS is not populated, when ACTARMCD or ACTARM is NULL	ACTARMCD/ACTARM are populated but ARMNRS is not populated
SD1359	ARMNRS is not populated when ARMCD/ARM are not provided	ARMCD/ARM are populated but ARMNRS is not populated

- Updated to format in consistent way with other rules

CHANGES TO RULE DESCRIPTIONS

Rule Description updated for 14 rules

Rule ID	Message	New Description	Old Description
SD0005	Duplicate value for --SEQ variable	The value of Sequence Number (--SEQ) variable must be unique for each record within a domain and within each Unique Subject Identifier (USUBJID) or Pool Identifier (POOLID) variables value when they are present in the domain. Exclusions are DO, DT, DU and DX domains.	The value of Sequence Number (--SEQ) variable must be unique for each record within a domain and within each Unique Subject Identifier (USUBJID), Pool Identifier (POOLID) or Sponsor Device Identifier (SPDEVID) variables value when they are present in the domain.
SD0007	Inconsistent value for Standard Units	Standard Units (--STRESU) must be consistent for all records with the same Short Name of Measurement, Test or Examination (--TESTCD), Object of the Observation (--OBJ), Measurement,Test, or Examination Detail (--TSTDTL), Category (--CAT), Subcategory (--SCAT), Specimen Type (--SPEC) and Method of Test or Examination (--METHOD).	Standard Units (--STRESU) must be consistent for all records with the same Short Name of Measurement, Test or Examination (--TESTCD), Category (--CAT), Subcategory (--SCAT), Specimen Type (--SPEC) and Method of Test or Examination (--METHOD).
SD0026	Missing value for --ORRESU, when --ORRES is provided	Original Units (--ORRESU) should not be NULL, when Result or Finding in Original Units (--ORRES) is provided is a numeric result.	Original Units (--ORRESU) should not be NULL, when Result or Finding in Original Units (--ORRES) is provided.
SD0029	Missing value for --STRESU, when --STRESC is provided	Standard Units (--STRESU) should not be NULL, when Character Result/Finding in Std Units (--STRESC) is provided as a numeric result.	Standard Units (--STRESU) should not be NULL, when Character Result/Finding in Std Units (--STRESC) is provided.
SD0095	Invalid usage of SUPPQUAL for non-general-observation-class Domain	Supplemental Qualifiers special purpose dataset (SUPP--) can only be used to capture non-standard variables and their association to parent records in general-observation-class datasets (Events, Findings, Interventions) and Demographics. Another exception is Subject Visits domain in SDTM-IG prior v3.4	Supplemental Qualifiers special purpose dataset (SUPP--) can only be used to capture non-standard variables and their association to parent records in general-observation-class datasets (Events, Findings, Interventions) and Demographics.
SD1021	Unexpected character value in variable	Character values should not have leading space ' ' characters, carriage returns, or '.' as an entire value. The only exceptions are COVALn and TSVALn variables.	Character values should not have leading space ' ' characters, or '.' as an entire value. The only exceptions are COVALn and TSVALn variables.
SD1105	EPOCH variable is populated, when DSCAT equals 'PROTOCOL MILESTONE'	Epoch (EPOCH) variable value should not be populated, when Category for Disposition Event (DSCAT) variable value equals 'PROTOCOL MILESTONE'.	Epoch (EPOCH) variable value should not be populated, when Category for Disposition Event (DSCAT) variable value does not equal 'DISPOSITION EVENT'.
SD1201	Duplicate records in domain	The structure of Events class domains should be one records per Event per subject. No Events with the same Collected Term (--TERM), Decoded Term (--DECOD), Category (--CAT), Subcategory (--SCAT), Occurrence (--OCCUR), Location (--LOC), Laterality (--LAT), Directionality (--DIR), Severity (--SEV), Toxicity Grade (--TOXGR), Visit Number (VISITNUM), Visit Day (VISITDY), and Start Reference Time Point (--STTPT) values for the same Subject (USUBJID) and the same Start Date (--STDTC) are expected.	The structure of Events class domains should be one records per Event per subject. No Events with the same Collected Term (--TERM), Decoded Term (--DECOD), Category (--CAT), Subcategory (--SCAT), Severity (--SEV), and Toxicity Grade (--TOXGR), Start Reference Time Point (--STTPT) values for the same Subject (USUBJID) and the same Start Date (--STDTC) are expected.
SD1348	Missing values for --STINT and --ENINT variables when --TEST references 'T1 to T2'	Planned Start of Assessment Interval (--STINT) and Planned End of Assessment Interval (--ENINT) variables should be present and populated when Name of Measurement, Test or Examination (--TEST) is over a time interval, 'T1 to T2', where 'T1' is represented by the value in --STINT and 'T2' is represented by the value in --ENINT.	Planned Start of Assessment Interval (--STINT) and Planned End of Assessment Interval (--ENINT) should be populated when Name of Measurement, Test or Examination (--TEST) is over a time interval, 'T1 to T2', where 'T1' is represented by the value in --STINT and 'T2' is represented by the value in --ENINT.
SD1352	Duplicate records in domain	The structure of Interventions class domains should be one record per Intervention Episode per subject. No Interventions with the same Treatment (--TRT), Decoded Term (--DECOD), Mood (--MOOD), Category (--CAT), Subcategory (--SCAT), Route (--ROUTE), Location (--LOC) and Treatment Vehicle (--TRTV) values for the same Subject (USUBJID) with the same Start Date (--STDTC), Planned Time Point Name (--TPT), and Planned Time Point Number (--TPTNUM) are expected.	The structure of Interventions class domains should be one record per Intervention Episode per subject. No Interventions with the same Treatment (--TRT), Decoded Term (--DECOD), Category (--CAT), Subcategory (--SCAT), Route (--ROUTE), Location (--LOC) and Treatment Vehicle (--TRTV) values for the same Subject (USUBJID) and the same Start Date (--STDTC) are expected.
SD1364	ACTARMCD/ACTARM is populated for a subject who wasn't treated	Actual Arm Code (ACTARMCD) and Actual Arm (ACTARM) must be null for subjects who weren't treated. This includes Screen Failure subjects, Not Assigned subjects, and Not Treated subjects.	Actual Arm Code (ACTARMCD) and Actual Arm Code (ACTARMCD) must not be null for subjects who weren't treated. This includes Screen Failure subjects, Not Assigned subjects, and Not Treated subjects.
SD1439	Multiple BASELINE records for the same test	By its definition clinical baseline flags (e.g., last non-missing value prior to first dose) should have only a single record for the same test for subject. Therefore, each subject (USUBJID) should have no more than one record with Baseline Flag (--BLFL) equals 'Y' for the same assessment which is defined by Test (--TESTCD), Category (--CAT), Subcategory (--SCAT), Method (--METHOD), Specimen (--SPEC), Location (--LOC), Laterality (--LAT) and Directionality (--DIR).	By its definition clinical baseline flags (e.g., last non-missing value prior to first dose) should have only a single record for the same test for subject. Therefore, each subject (USUBJID) should have no more than one record with Baseline Flag (--BLFL) equals 'Y' for the same assessment which is defined by Test (--TESTCD), Category (--CAT), Subcategory (--SCAT), Method (--METHOD), Specimen (--SPEC), Location (--LOC) and Laterality (--LAT)
SD1442	Inconsistent value for --HLGT within --TERM	MedDRA coding High Level Group Term (--HLGT) should be consistent for the same collected term (--TERM)	MedDRA coding High Level Group Term (--HLT) should be consistent for the same collected term (--TERM)
SD1445	Multiple --LOBXFL records for the same test	By its definition Last Observation Before Exposure Flag (--LOBXFL) should have only a single record for the same test for subject. Therefore, each subject (USUBJID) should have no more than one record with Last Observation Before Exposure Flag (--LOBXFL) equals 'Y' for the same assessment which is defined by Test (--TESTCD), Category (--CAT), Subcategory (--SCAT), Position of Subject During Observation (--POS), Method (--METHOD), Specimen (--SPEC), Location (--LOC) and Laterality (--LAT).	By its definition Last Observation Before Exposure Flag (--LOBXFL) should have only a single record for the same test for subject. Therefore, each subject (USUBJID) should have no more than one record with Last Observation Before Exposure Flag (--LOBXFL) equals 'Y' for the same assessment which is defined by Test (--TESTCD), Category (--CAT), Subcategory (--SCAT), Method (--METHOD), Specimen (--SPEC), Location (--LOC) and Laterality (--LAT)

- Updated to either account for reformatting or to correct minor typos

CHANGES TO SDTMIG RULE ASSIGNMENTS

Rule Assignments Added

- SD1138 (--DRVFL='Y', when --ORRES value is populated)
  - Added to all SDTMIG versions

Rule Assignments Removed

- SD1259 (Invalid value for SETCD)
  - Removed from SDTMIG v3.1.2, v3.1.3, and v3.2
- SD0063 and SD0063A (SDTM/dataset variable label mismatch)
  - Removed from SDTMIG v3.3

CHANGES TO SENDIG RULE ASSIGNMENTS

Rule Assignments Added

- SD1118 (Neither --STDTC, --DTC nor --STDY are populated)
  - Added to SENDIG v3.1

Rule Assignments Removed

- SD1008 (CODTC is populated, when comment is a child record of another domain)
  - Removed from SENDIG v3.1
- SD1138 (--DRVFL='Y', when --ORRES value is populated)
  - Removed from SENDIG v3.1

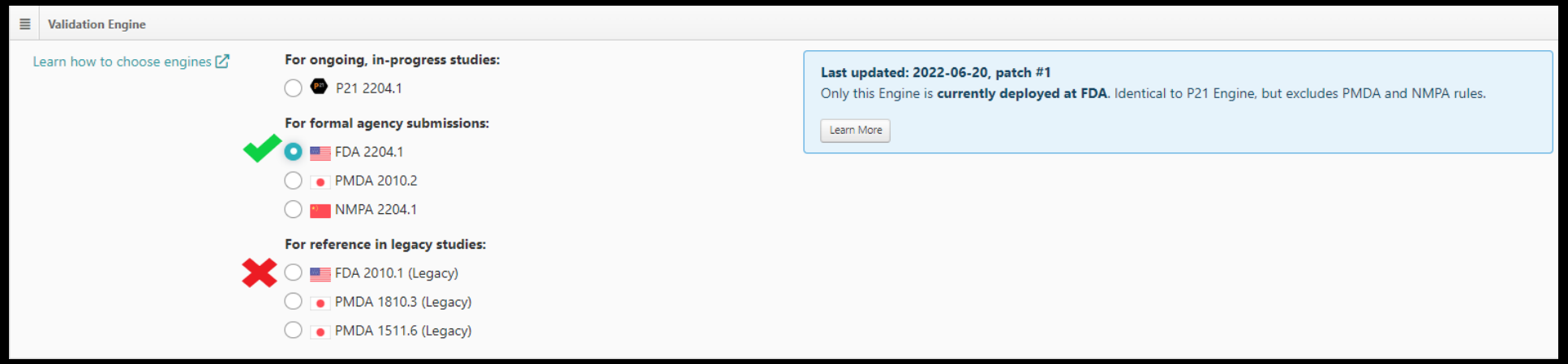
P21

ENSURING COMPLIANCE

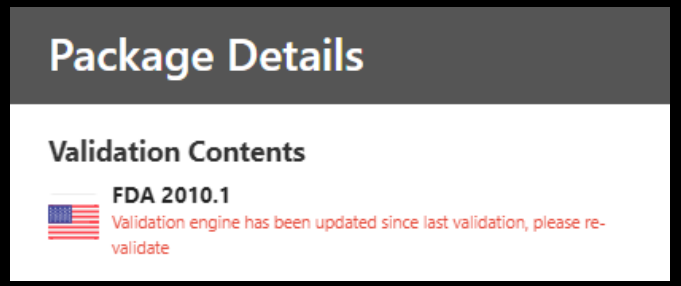
ENSURING COMPLIANCE IN ENTERPRISE

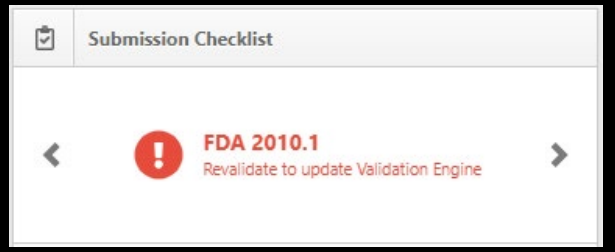
Always Use Latest Validation Engine Available

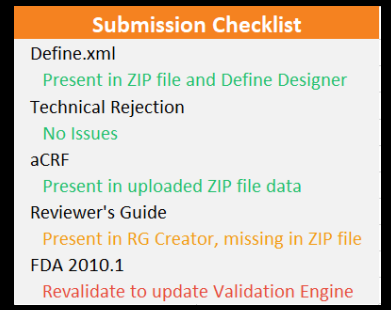
- Use P21 engine, but switch to agency-specific engine prior to submission



- Using an older (Legacy) engine will result in a warning message on multiple screens
  - Don't ignore these messages







ENSURING COMPLIANCE IN COMMUNITY

Always Use Latest Validation Engine Available

Compatible Engines

Community provides different Validation Engines so that you can stay compliant with regulatory agencies. To do this, simply select which Engine you would like to use from the dropdown. By selecting the appropriate Engine, other dropdowns will be filtered to only show the standards and configurations that are compatible with the agency. For example, you won't find SEND in the standard dropdown for any PMDA Engine because the PMDA does not support SEND.

- **FDA** - Validation engine currently deployed at FDA. Use to prepare for imminent submission.
- **FDA Legacy** - Prior version of FDA engine. Provided for reference only. Do not use for imminent submission.
- **PMDA** - Validation engine for PMDA rules v3.0. Valid for use with applications from January 1, 2022.
- **PMDA Legacy** - Validation engines for older PMDA rules v1.0 and v2.0.
- **NMPA** - Beta validation engine for NMPA. Supports datasets with UTF-8 encoded Chinese characters and displays rule messages and descriptions in Chinese translation.

Incompatible Engines

The Validation Summary tab of the Validation Report will warn you if an incompatible engine has been used. The most common reasons for validation with incompatible engines are:

- Validation was ran using an unsupported configuration file
- A depreciated engine that is no longer compatible by PMDA or FDA was used

If this happens, ensure you are connected to the Internet and that you have the latest version of Pinnacle 21 Community. To see your version, go to "About Pinnacle 21 Community". After you have verified your Internet connection and release version, re-run the validation and choose a non-depreciated Engine from the dropdown and ensure the configuration file you select has not been modified or customized.

For any additional questions, please post on the P21 Community Forum. If you are an Enterprise client, please contact your CSM or email success@pinnacle21.com

ENSURING COMPLIANCE

Dispositioning Your Data Validation Issues

8.2.2 Support on Data Validation Rules

Sponsors should evaluate their study data before submission against the conformance rules published by an SDO, the eCTD Technical Rejection Criteria for Study Data (See Appendix F), and the FDA Business Rules. Sponsors may also wish to use the FDA Validator Rules to understand what is available to the FDA reviewer. Sponsors should either correct any discrepancies between study data and the standard or the business rules or explain meaningful discrepancies in the relevant Reviewer Guide (RG). Additional information about conformance to the standard, FDA Business Rules, or FDA Validator Rules that could facilitate review of the submitted data, or establish consistency and traceability between the study data and the Study Report, should also be provided in the relevant RG.

*FDA's Study Data Technical Conformance Guide, October 2022

P21

KEEP IN TOUCH!

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You will receive an email when the slides are are posted on our blog:
www.pinnacle21.com/blog