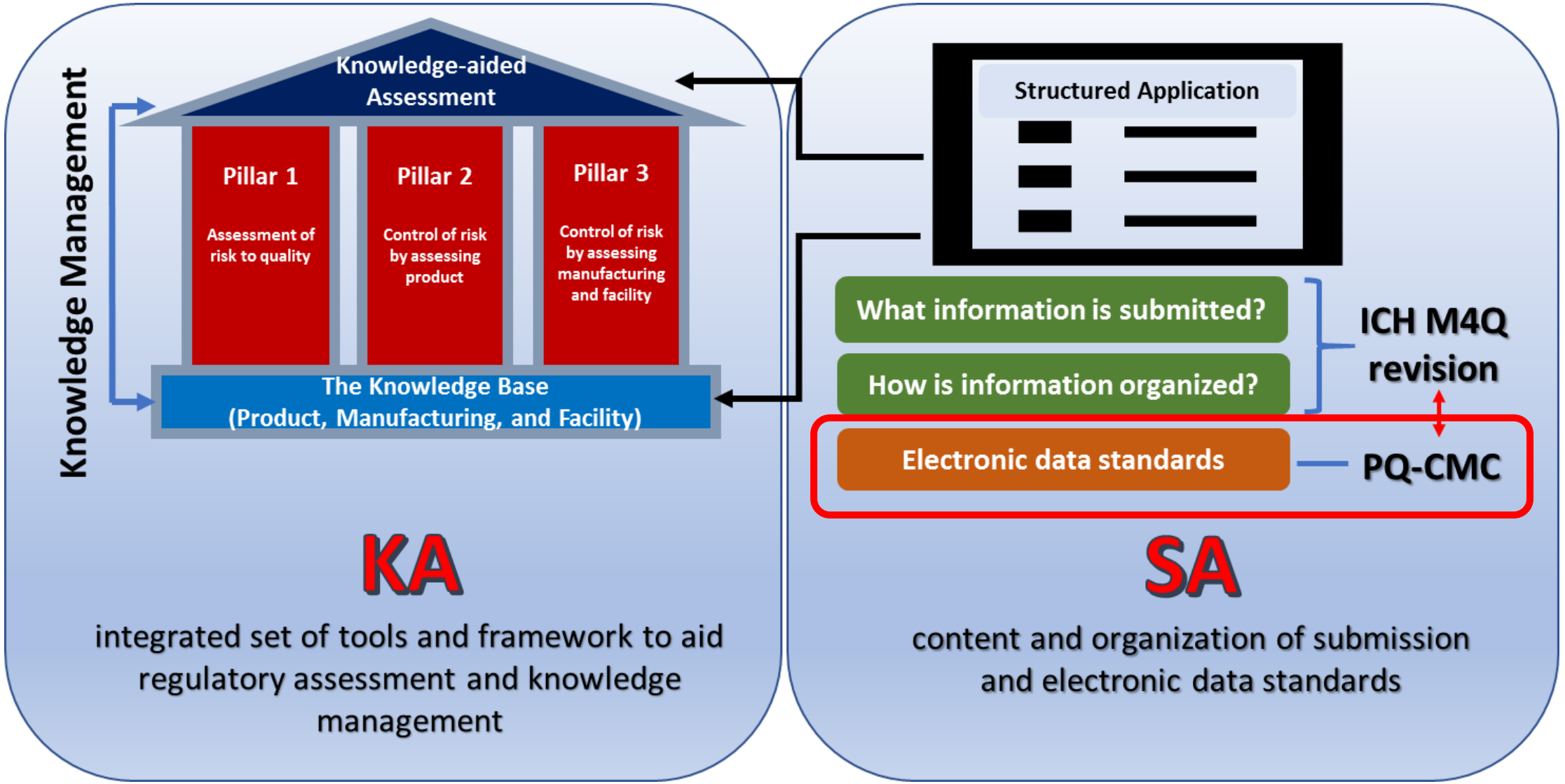
FDA Pharmaceutical Quality Electronic Data Standards (aka PQ/CMC)

Geoffrey Wu, Ph.D.
Commander, USPHS
Deputy Director
Office of Lifecycle Drug Products, OPQ
Chair, OPQ PQ/CMC Workgroup

December 3, 2021

Future KASA System



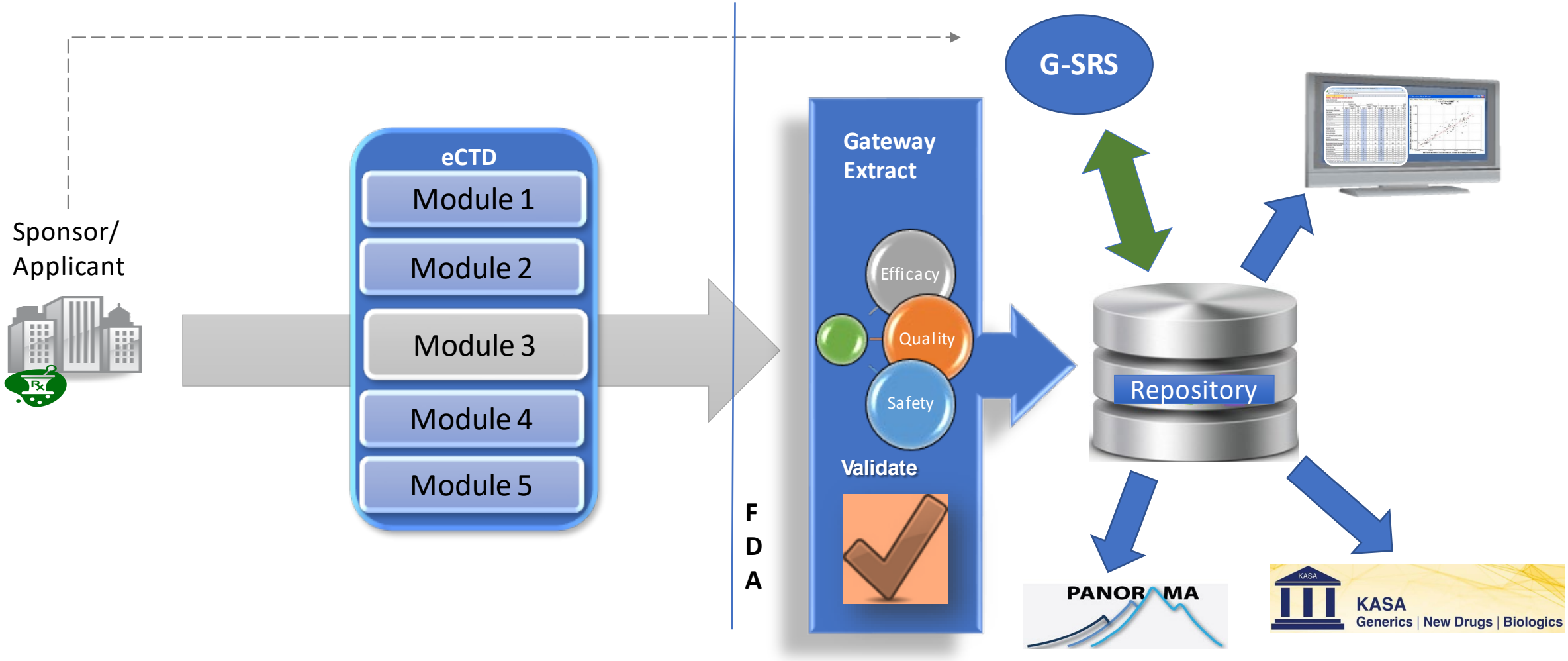
Problem Statement

- Currently Module 3 body of data submitted in PDF format with unstructured pharmaceutical quality data. Significantly hinders the efficiency of data exchange, quality assessment, and lifecycle knowledge management.

eCTD Module 3 submissions with unstructured PQ/CMC data

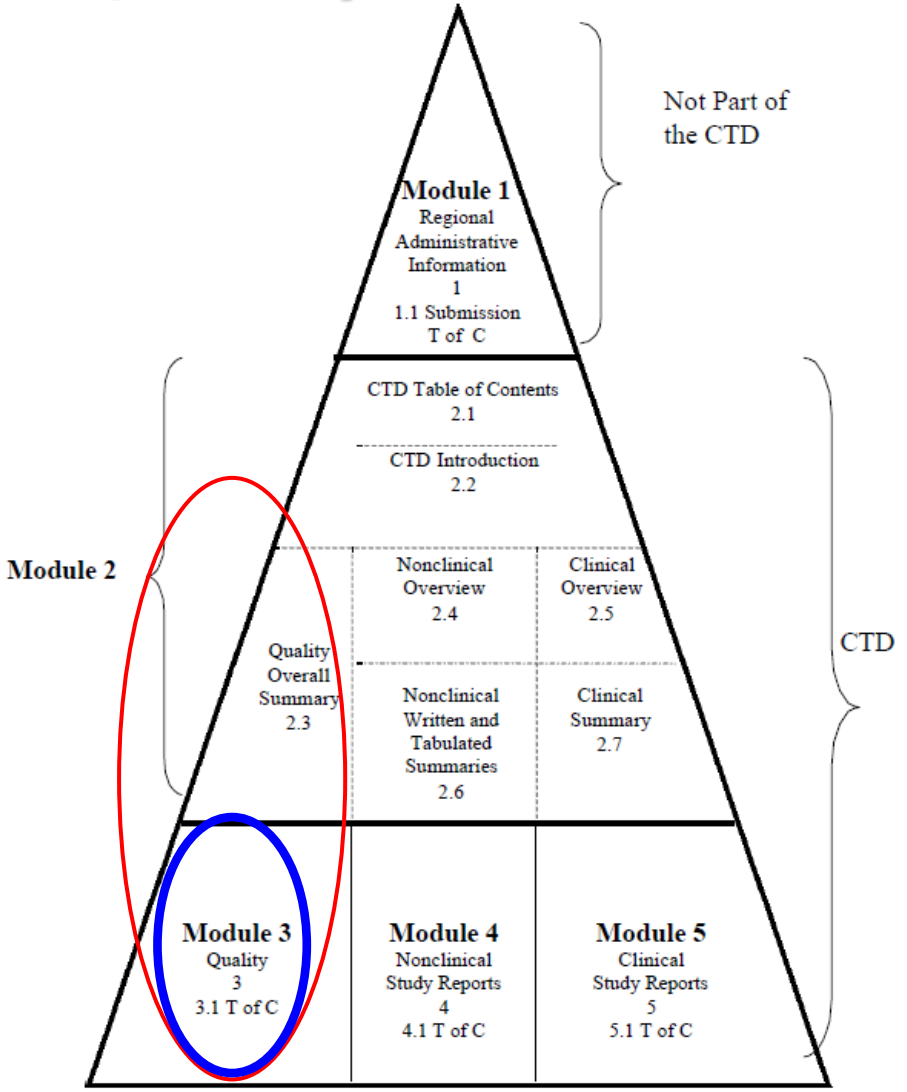
Test	*Limit*
Description	White or almost white, crystalline powder.
Identification . *Test A:* . *Test B:*	The I.R. spectrum is concordant with the *reference spectrum* [redacted] It meets the requirements of the test for [redacted]
(+)-*trans* –paroxetine (corresponding to RC C of USP)	Not more than 0.1%
Related substances: **. Impurity I** (corresponding to RC B of USP) **. Impurity II** **. Impurity III** (corresponding to RC F of USP) **. Any other ind. impurity** **. Total impurities**	 Not more than 0.30% Not more than 0.15% Not more than 0.15% Not more than 0.10% Not more than 0.50%
Heavy metals	Not more than 20 ppm (Pb)
Water	2.2 – 2.7%
Residue on ignition	Not more than 0.1%
Assay	98.5 – 102.0% *(on anhydrous and solvent-free substance)*
Residual solvents: **. Isopropanol**	Not more than 0.2%
Additional test	
Particle size (laser)	D(v,0.1): NMT 10 μm D(v,0.5): NMT 30 μm D(v,0.9): NMT 60 μm
Polymorphic Form	The x-Ray powder diffractogram is consistent with the reference diffractogram of [redacted] Characteristic XRD peak positions are: 7.1, 10.8, 14.2, 16.7, 17.2, 18.5, 21.4, 21.8, 22.6, 23.2, 23.5, 24.0, 24.2, 28.5, 32.5 within ±0.3 degrees.

Our Vision with Structured Data



Pharmaceutical Quality Chemistry Manufacturing and Control (PQ/CMC)

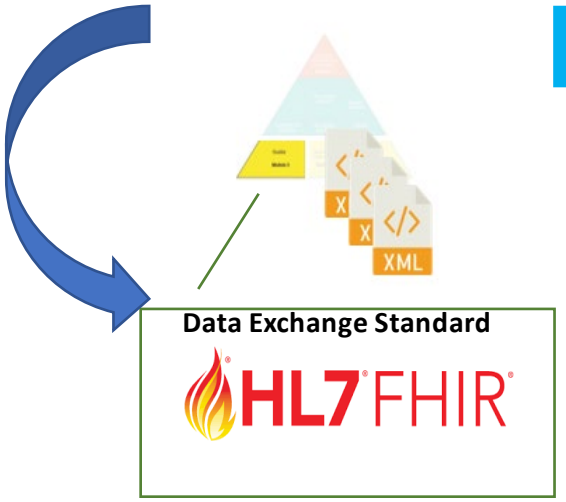
- A cross-Center effort to establish content standards and electronic exchange standards for submitting PQ/CMC data, predicated on eSubmission requirements of FD&C Act 745A(a) (NDAs, ANDAs, BLAs, and certain INDs)
- Focus on Module 3 (Body of Data) of the eCTD
- Participating Centers: **CDER**, **CBER** and **CVM**
- Led and sponsored by **CDER/Office of Strategic Program (OSP)**
- Initiated ~ 2014



Reference: [Providing Regulatory Submissions in Electronic Format – Submission Under Section 745A(a) of the Federal Food , Drug, and Cosmetic Act (Dec 2014)]

Concept: the Submission of Standardized and Structured PQ/CMC Data

eCTD Module 3 submissions with standardized, structured PQ/CMC data



eSub

Data is available via integration with FDA Systems

- ✓ Reviewer tools, e.g. KASA
- ✓ Reports
- ✓ Others, as determined

Objective 1: To develop structured and computable data standards for PQ/CMC

Objective 2: To design and develop data exchange standard for submission of PQ/CMC data

- FHIR® – Fast Healthcare Interoperability Resources – is a next generation standards framework created by Health Level Seven International (HL7).
- www.hl7.org

Data Standards Development Approach

Data Requirements Sources

DSST Report

CDER
CVM **SME Team**
CBER

SRS eCTD
FDA Initiatives
eComp IDMP

FDA Terminology Groups

Serve as foundation for data requirements

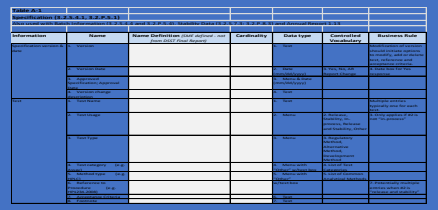
Provide additional req. and extend DSST req.

Inform representation of common touch points - Substance, Products, etc.

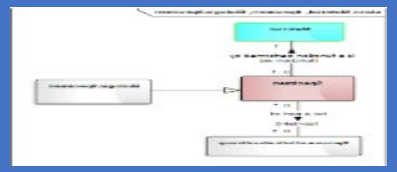
Leverage existing FDA terminology standards

Project Requirements Work Products

Data req. capture worksheet



PQ/CMC UML Model



Future Implementation Products

PQ/CMC Data Exchange Options: HL7 SPL & eStability; HL7 FHIR

PQ/CMC Database TBD

PQ/CMC Data Elements – Phase 1

(Substantially completed by end of 2020; ~ 33% of Module 3 data)

#	PQ/CMC Data Groupings	High level eCTD Reference	Total Elements
0	Application Sponsor	3.2.S.2.1, 3.2.P.3.1	6
1	Specification	(3.2.S.4.1, 3.2.P.5.1; 3.2.S.4.4 and 3.2.P.5.4; 3.2.S.7.1; 3.2.P.8.1)	7
2	Test	(3.2.S.4.1, 3.2.P.5.1)	11
3	Acceptance Criteria	3.2.S.4.1, 3.2.P.5.1)	7
4	Batch Lot Information	(3.2.S.4.4; 3.2.P.5.4; 3.2.S.7.1; 3.2.P.8.1)	29
5	Batch Analysis	(3.2.S.4.4; 3.2.P.5.4; 3.2.S.7.1; 3.2.P.8.1)	10
6	Stability Study	(3.2.S.7.3; 3.2.P.8.3) / 3.2.S.7.1,3.2.S.7.2, 3.2.P.8.1, 3.2.P.8.2	12
7	Nomenclature Drug Substance	(3.2.S.1.1; 3.2.S.1.2)	12
8	Drug Substance Characterization	(3.2.S. 3.1)	4
9	Description & Comp. Drug Product	(3.2.P.1)	18
10	Batch Formula	(3.2.P.3.2)	9
11	Drug Sub. Control of Materials	(3.2.S.2.3)	13
12	Drug Product Control of Excipients	(3.2.P.4.1)	16
13	Drug Substance Impurities	(3.2.S.3.2)	11
14	Drug Product Impurities	(3.2.P.5.5)	12
15*	Analytical Methods Validation	(3.2.S.4.3; 3.2.P.4.3; 3.2.P.5.3)	10
	Total		**181**

- Piloted with 7 industry participants
- Evaluated suitability, appropriateness of data elements and terminologies
- Continuous improvement in conjunction with KASA data structure

* SMEs developed data standards but deferred the refinement to later stage.

PQ/CMC Data Elements – Phase 2
(Initiated in January 2021)

Categories of PQ/CMC data in eCTD Module 3 and Module 2 QOS

1. Specification(drug substance/drug product/excipients)
2. Batch Analysis (drug substance/drug product)
3. Stability(drug substance/drug product)
4. Nomenclature of Drug Substance
5. Composition of Drug Product
6. Batch Formula
7. Impurities
8. Manufacturing Process
9. Annual BLA Lot Distribution Report
10. CMC Changes in Annual Report – NDA/ANDA/BLA/NADA/ANADA
11. Analytical Procedure Validation
12. Facility Information

Categories 1 -7

PHASE 1

Categories 8 -12

PHASE 2

A Demonstrative Example

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(+)-*trans* –paroxetine (corresponding to RC C of USP)	Not more than 0.1%
Related substances: . **Impurity I** (corresponding to RC B of USP) . **Impurity II** . **Impurity III** (corresponding to RC F of USP) . **Any other ind. impurity** . **Total impurities**	Not more than 0.30% Not more than 0.15% Not more than 0.15% Not more than 0.10% Not more than 0.50%
Heavy metals	Not more than 20 ppm (Pb)
Water	2.2 – 2.7%
Residue on ignition	Not more than 0.1%
Assay	98.5 – 102.0% *(on anhydrous and solvent-free substance)*
Residual solvents: . **Isopropanol**	Not more than 0.2%
Additional test	
Particle size (laser)	D(v,0.1): NMT 10 µm D(v,0.5): NMT 30 µm D(v,0.9): NMT 60 µm
Polymorphic Form	The x-Ray powder diffractogram is consistent with the reference diffractogram of [redacted] Characteristic XRD peak positions are: 7.1, 10.8, 14.2, 16.7, 17.2, 18.5, 21.4, 21.8, 22.6, 23.2, 23.5, 24.0, 24.2, 28.5, 32.5 within ±0.3 degrees.

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Identification . *Test A:*	The I.R. spectrum is concordant with the *reference spectrum* [redacted]
. *Test B:*	It meets the requirements of the test for [redacted]
(+)-*trans*-paroxetine (corresponding to RC C of USP)	Not more than 0.1%
Related substances: . **Impurity I** (corresponding to RC B of USP) . **Impurity II** . **Impurity III** (corresponc USP) . **Any other in** . **Total impurities**	Not more than 0.30%
Heavy metals	Not more than 20 ppm (Pb)
Water	2.2 – 2.7%
Residue on ignition	Not more than 0.1%
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Currently unstructured Specification Table

A Demonstrative Example

Table	Data Element Name	Data Element Name Definition	Data type	Terminology	Controlled Vocabulary	Conformance
01-Specification	**Specification Title**	The textual identification for the specification.	Text		0	M
01-Specification	**Specification Subtitle**	An additional textual identification for the spe	Text		0	O
01-Specification	**Specification Type**	A classification of specification related to the	Code	Drug ProductDrug Sul	See Controlled Terminology sheet	M
01-Specification	**Specification Version**	The alphanumeric text assigned by the sponsc	Text		0	M
01-Specification	**Specification Version Date**	The date when the sponsor assigned a date to	Date		0	M
01-Specification	**Specification Status**	The current FDA regulatory status of the spec	Code	ApprovedTentatively A	See Controlled Terminology sheet	M
01-Specification	**Specification Status Date**	The date on which the FDA approval status fo	Date		0	M
01-Specification	**Specification Additional Information**	Placeholder for providing any comments that	Text		0	O
02-Test	**Test Name**	The textual description of a procedure or anal	Text		0	M
02-Test	**Test Method Origin**	A coded value specifying the source of the me	Code	CFRProprietaryCompe	See Controlled Terminology sheet	M
02-Test	**Test Category**	A high level grouping of quality attributes for	Code	AssayBiological Prope	See Controlled Terminology sheet	M
02-Test	**Analytical Procedure**	The name of the technique used to determine	Text		0	M
02-Test	**Reference to Procedure**	A sponsor/applicant provided alphanumeric c	Text		0	M
02-Test	**Relative Retention Time**	The ratio of the retention time of a componer	Text		0	O
02-Test	**Test Additional Information**	Placeholder for providing any comments that	Text		0	O
02-Test	**Test Order**	The sequential number assigned to each Test	Numeric		0	M
02-Test	**Stage Name**	A textual description and/or a number that id	Text		0	M
02-Test	**Stage Sequence Order**	The order of the stages in regular succession.	Numeric		0	M
02-Test	Stage Additional Information	Placeholder for providing any comments that	Text		0	O
03-Acceptance Criteria	**Value**	The acceptable qualitative or text value of the	Text		0	O
03-Acceptance Criteria	**ValueNumeric**	The acceptable quantitative or numeric value	Numeric		0	O
03-Acceptance Criteria	**ValueNumeric UOM**	A named quantity in terms of which other qu	Code	http://www.fda.gov/	See Controlled Terminology sheet	O
03-Acceptance Criteria	**Original Text**	The text of the acceptance criteria as provide	Text		0	M
03-Acceptance Criteria	**Acceptance Criteria Usage**	A coded value specifying when a particular an	Code	ReleaseStability	See Controlled Terminology sheet	M
03-Acceptance Criteria	**Interpretation Code**	A code that describes how to relate the given	Code	NMT (not more than)	See Controlled Terminology sheet	M
03-Acceptance Criteria	**Additional Information**	A textual field to provide any additional infor	Text		0	O

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01-Specification	**Specification Version**	The alphanumeric text assigned by the sponsc	Text		0	M
01-Specification	**Specification Version Date**	The date when the sponsor assigned a date to	Date		0	M
01-Specification	**Specification Status**	The current FDA regulatory status of the spec	Code	ApprovedTentatively A	See Controlled Terminol	heet M
01-Specification	**Specification Status Date**	The date on which the FDA approval status fo	Date		0	M
01-Specificat						O
02-Test						M
02-Test						M
02-Test						M
02-Test						M
02-Test						M
02-Test	**Relative Retention Time**	The ratio of the retention time of a componer	Text		0	O
02-Test	**Test Additional Information**	Placeholder for providing any comments that	Text		0	O
02-Test	**Test Order**	The sequential number assigned to each Test	Numeric		0	M
02-Test	**Stage Name**	A textual description and/or a number that id	Text		0	M
02-Test	**Stage Sequence Order**	The order of the stages in regular succession.	Numeric		0	M
02-Test	Stage Additional Information	Placeholder for providing any comments that	Text		0	O
03-Acceptance Criteria	**Value**	The acceptable qualitative or text value of the	Text		0	O
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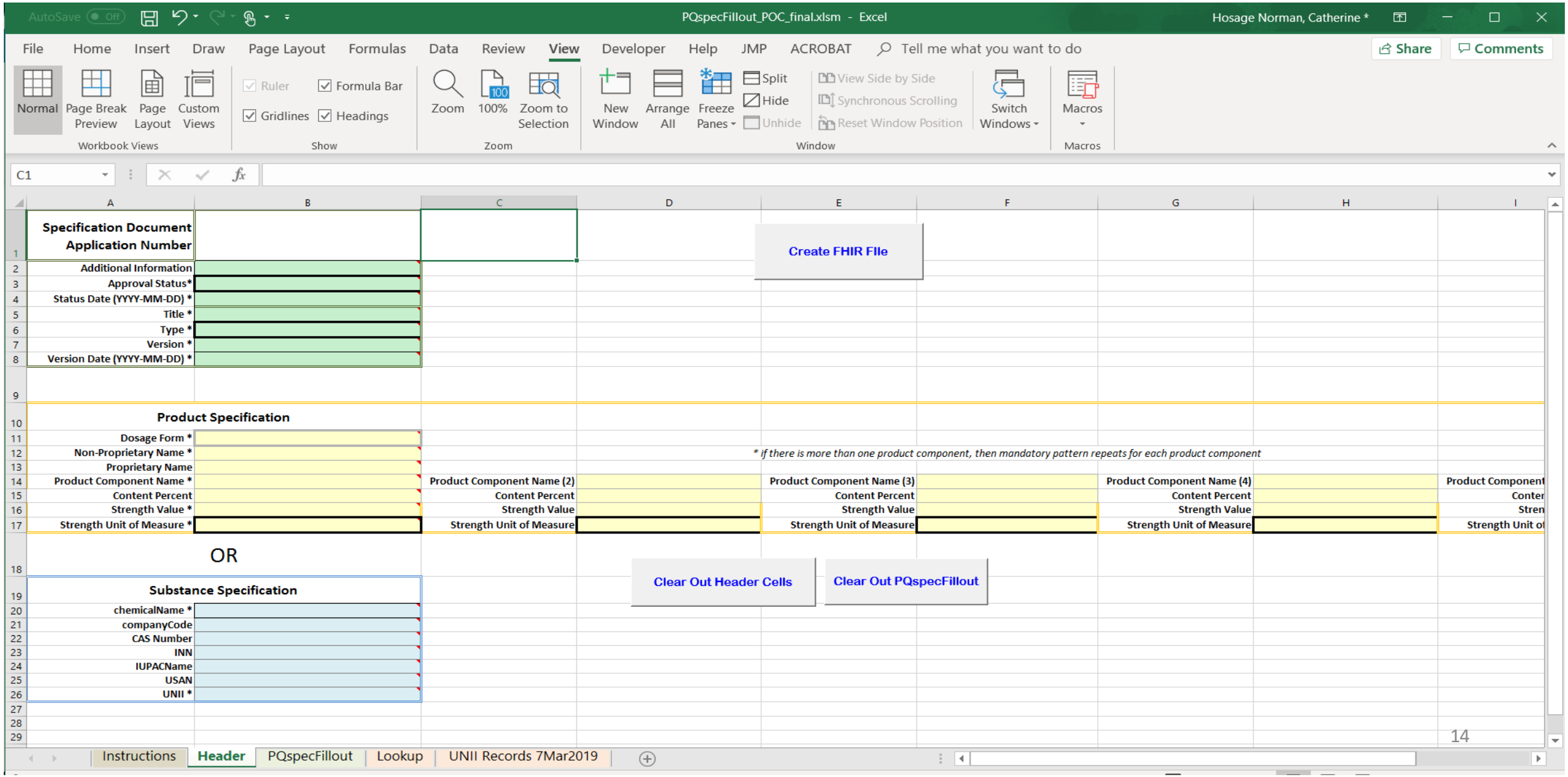
03-Acceptance Criteria	**Interpretation Code**	A code that describes how to relate the given	Code	NMT (not more than)	See Controlled Terminology sheet	M
03-Acceptance Criteria	**Additional Information**	A textual field to provide any additional infor	Text		0	O

PQ/CMC effort:
Transform into standardized and structured, discrete data elements

Reference: Federal Register Notice Draft PQ/CMC Data Elements and Terminologies; Request for Comments (07/11/2017)

A Demonstrative Example



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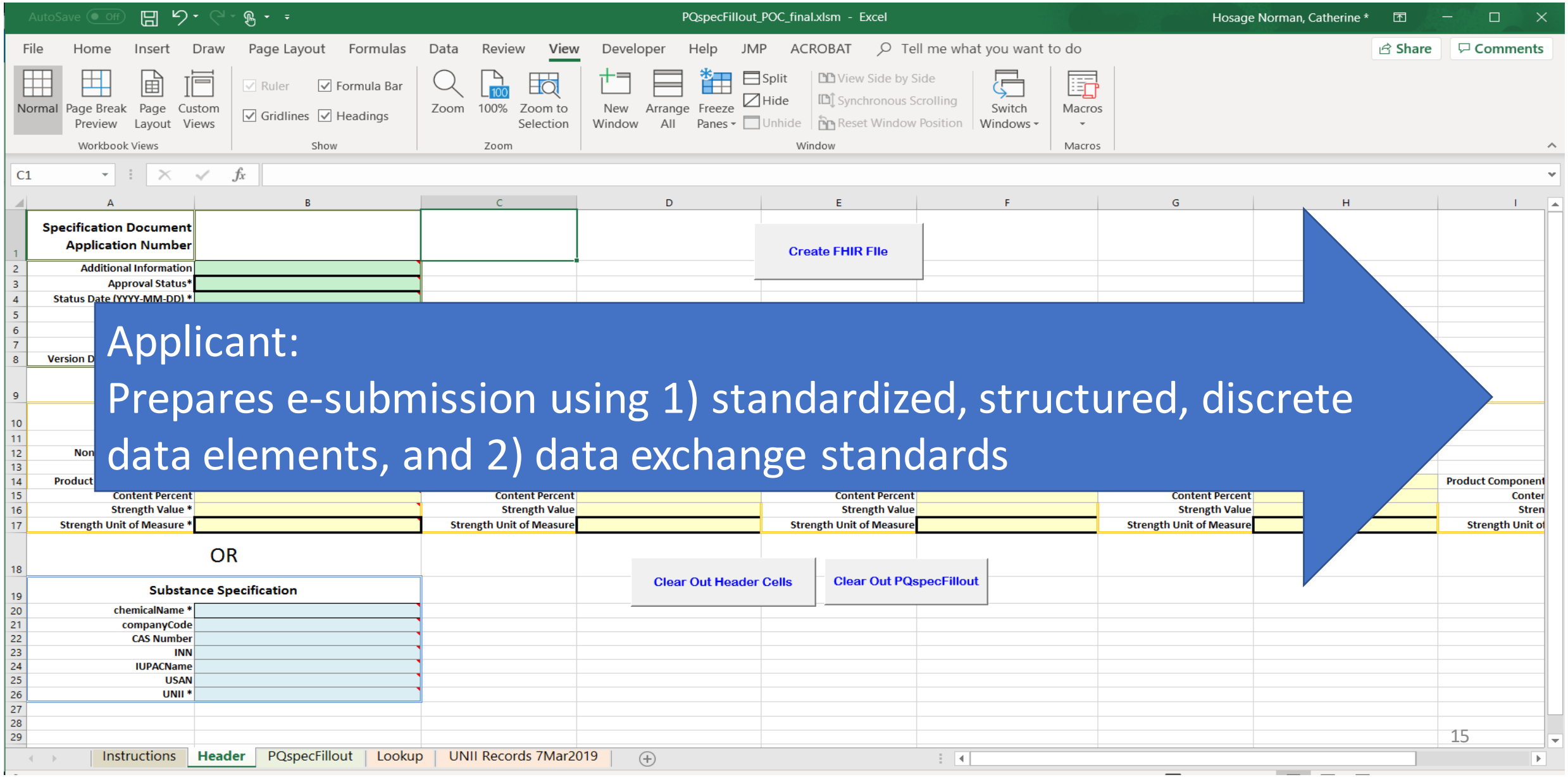


A Demonstrative Example

U.S. FOOD & DRUG ADMINISTRATION

PHARMACEUTICAL QUALITY
CHEMISTRY, MANUFACTURING, AND CONTROLS (PQ/CMC)

Application Sequence .. ATZN32801 0001 Spec. Ver...
Test Category: (All)

Drug Product Specification [redacted]
Specification .

Type: Drug Product
Approval Status: Not Approved
Additional Information: Test example specification

Version: 2.0

Version Date: 2018-04-27
Approval Date: 2019-05-23

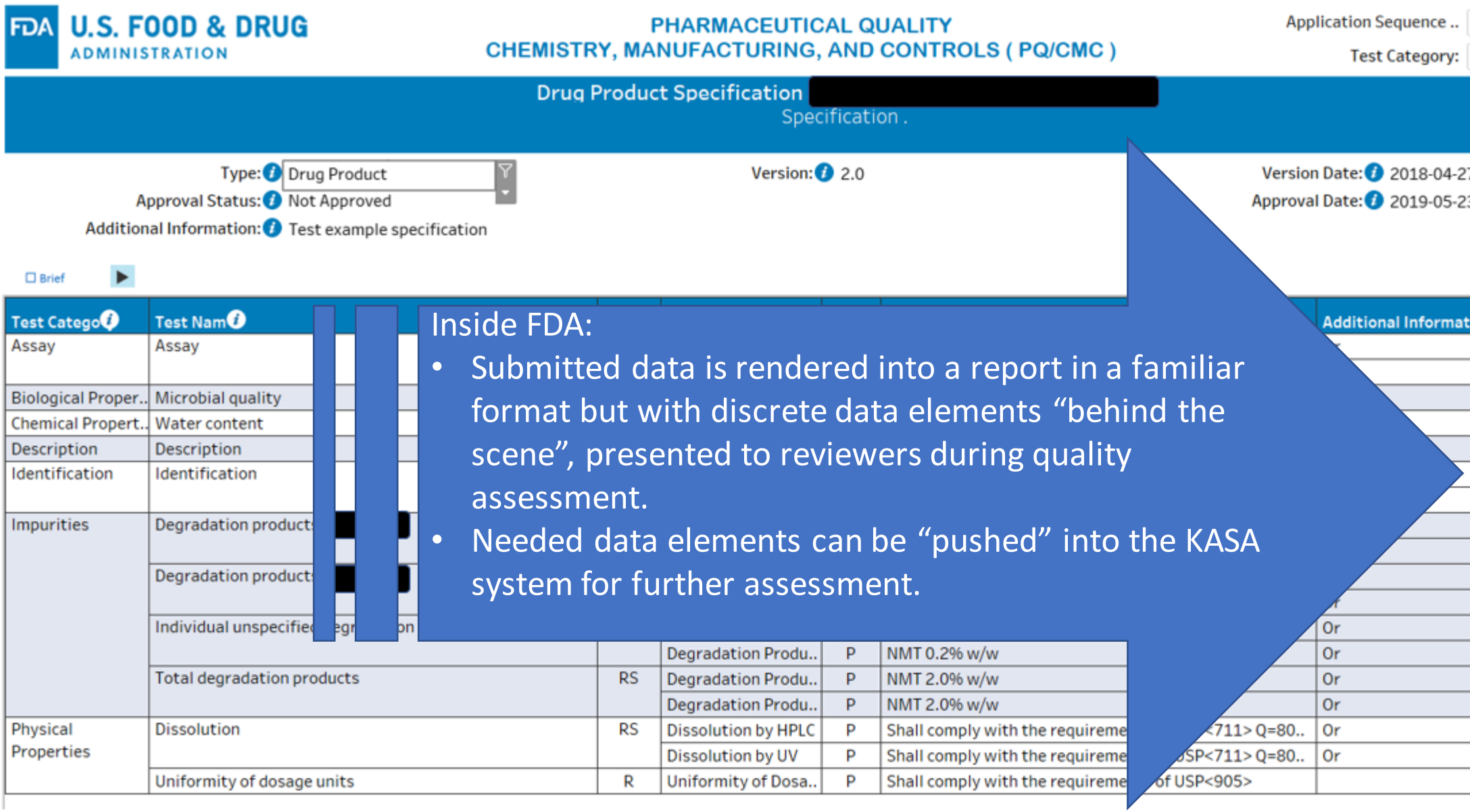
Legend (Usa..
R Release
S Stability

Legend (Type)
C Compen..
P Propriet..

☐ Brief ▶

Test Catego	Test Nam	Usag	Metho	Type	Acceptance Crite	Additional Informati
Assay	Assay	RS	Assay by HPLC	P	90% to 110% of label claim	Or
			Assay by UHPLC	P	90% to 110% of label claim	Or
Biological Proper..	Microbial quality	S	Microbial quality	C	Monitor Report	text
Chemical Propert..	Water content	S	Water Content by K..	P	Monitor Report	text
Description	Description	RS	Visual inspection	P	Size 1 hard capsule with a blue opaque cap and a yellow ..	
Identification	Identification	R	Identification by H..	P	Consistent with the retention time and UV spectrum of t..	Or
			Identification by U..	P	Consistent with the retention time and UV spectrum of t..	Or
Impurities	Degradation products [redacted]	RS	Degradation Produ..	P	NMT 0.6% w/w	Or
			Degradation Produ..	P	NMT 0.6% w/w	Or
	Degradation products [redacted]	RS	Degradation Produ..	P	NMT 0.6% w/w	Or
			Degradation Produ..	P	NMT 0.6% w/w	Or
	Individual unspecified degradation products	RS	Degradation Produ..	P	NMT 0.2% w/w	Or
			Degradation Produ..	P	NMT 0.2% w/w	Or
	Total degradation products	RS	Degradation Produ..	P	NMT 2.0% w/w	Or
			Degradation Produ..	P	NMT 2.0% w/w	Or
Physical Properties	Dissolution	RS	Dissolution by HPLC	P	Shall comply with the requirements of USP<711> Q=80..	Or
			Dissolution by UV	P	Shall comply with the requirements of USP<711> Q=80..	Or
	Uniformity of dosage units	R	Uniformity of Dosa..	P	Shall comply with the requirements of USP<905>	

A Demonstrative Example



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Version Date: 2018-04-27
Approval Date: 2019-05-23

Legend (Usa..
R Release
S Stability

Legend (Type)
C Compen..
P Propriet..

Brief

Test Catego	Test Nam						Additional Informati
Assay	Assay						
Biological Proper..	Microbial quality						
Chemical Propert..	Water content						
Description	Description						
Identification	Identification						
Impurities	Degradation product [redacted]						
	Degradation product [redacted]						
	Individual unspecifie[redacted]on						Or
			Degradation Produ..	P	NMT 0.2% w/w		Or
	Total degradation products	RS	Degradation Produ..	P	NMT 2.0% w/w		Or
			Degradation Produ..	P	NMT 2.0% w/w		Or
Physical Properties	Dissolution	RS	Dissolution by HPLC	P	Shall comply with the requireme	<711> Q=80..	Or
			Dissolution by UV	P	Shall comply with the requireme	USP<711> Q=80..	Or
	Uniformity of dosage units	R	Uniformity of Dosa..	P	Shall comply with the requireme	of USP<905>	

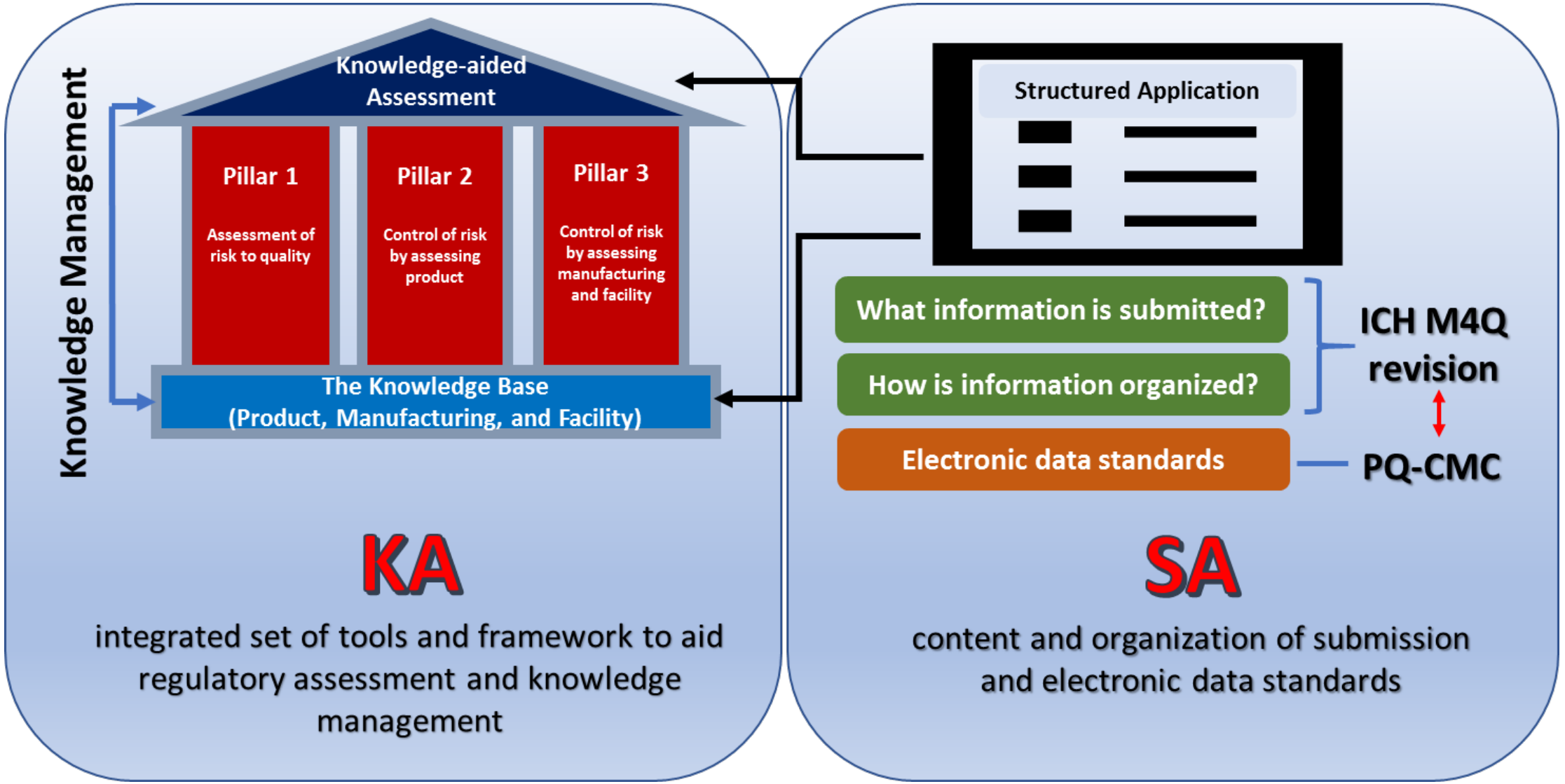
Inside FDA:

- Submitted data is rendered into a report in a familiar format but with discrete data elements "behind the scene", presented to reviewers during quality assessment.
- Needed data elements can be "pushed" into the KASA system for further assessment.

Benefits

- Ensures Industry and FDA are using the “same data”
- Industry
  - Could provide consistent formats for internal and external data management & storage (e.g. in LIMS), and data exchange with CMOs (Contract Manufacturing Organizations)
- FDA
  - Receives consistent high-quality data that can be consumed by computer systems without data entry and interpretations
  - Operationalize submitted data to enhance the effectiveness of quality assessment – a significant enabler for KASA
- Facilitates the M4Q implementation and enhances global regulatory convergence
- Accelerates the digitization efforts in both Industry and FDA, eventually enhances lifecycle knowledge management (e.g., for crisis response)

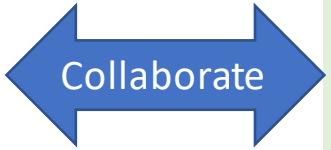
Future KASA System



Thank You!

FDA PQ/CMC SME Group:

- Norman Gregory (CVM)
- Frank Holcombe, Jr. (CDER)
- Michael Kerrigan (CVM)
- Ze Peng (CBER)
- Andre Raw (CDER – for KASA)
- Norman Schmuff (CDER)
- Chikako Torigoe (CBER)
- Geoffrey Wu (CDER)



OPQ PQ/CMC Workgroup:

- **Chair:** Geoffrey Wu
- **Technical Lead:** Norman Schmuff
- **Project Manager:** Mihir Jaiswal
- **Members:**
  - Ted Carver
  - Ee-Sunn (Joanne) Chia
  - Bazarra Damdinsuren
  - Frank Holcombe, Jr.
  - Susan Zuk

Thank You

U.S. FOOD & DRUG ADMINISTRATION

Effective leadership Collaborative relationships

Encourage innovation **Risk-based approaches**

One Quality Voice

Patients first Team-based processes

Developing and utilizing staff expertise

Scientifically-sound quality standards