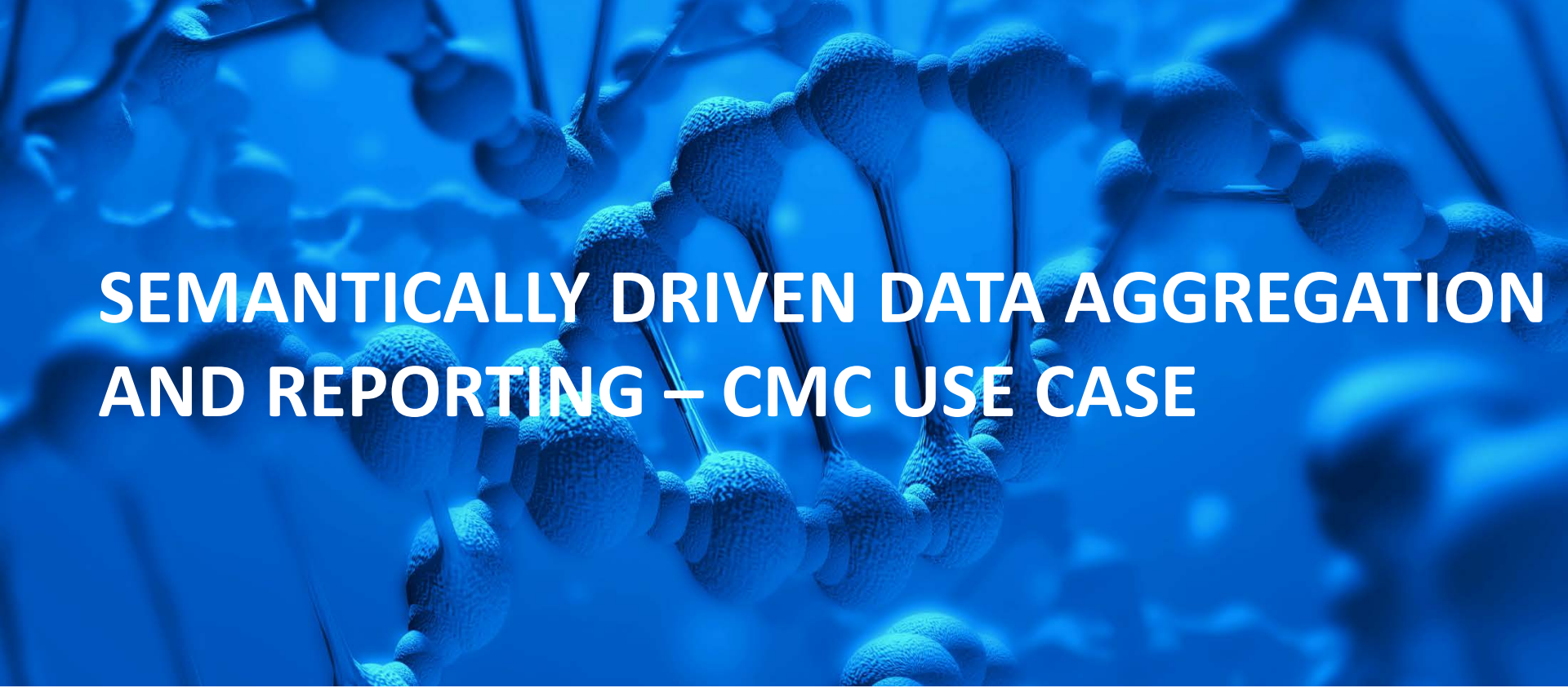

SEMANTICALLY DRIVEN DATA AGGREGATION AND REPORTING – CMC USE CASE

JANET CHEETHAM

NOV 6TH 2018, ALLOTROPE CONNECT

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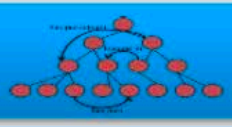
FUTURE STATE – REGULATORY KNOWLEDGE MANAGEMENT USING THE ALLOTROPE STANDARDS – INTEGRATED E-CTD CONTENT IN ADF

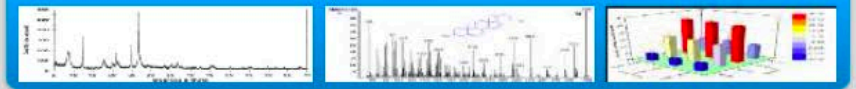
Import of structured content

Data Description

Allotrope eCTD ontologies & data models for searching and analytics



Data Cube



Data Package

Current eCTD Structure
Module 1
Module 2
Module 3
Module 4
Module 5


eCTD sections


Supporting documents

chemical structures

videos

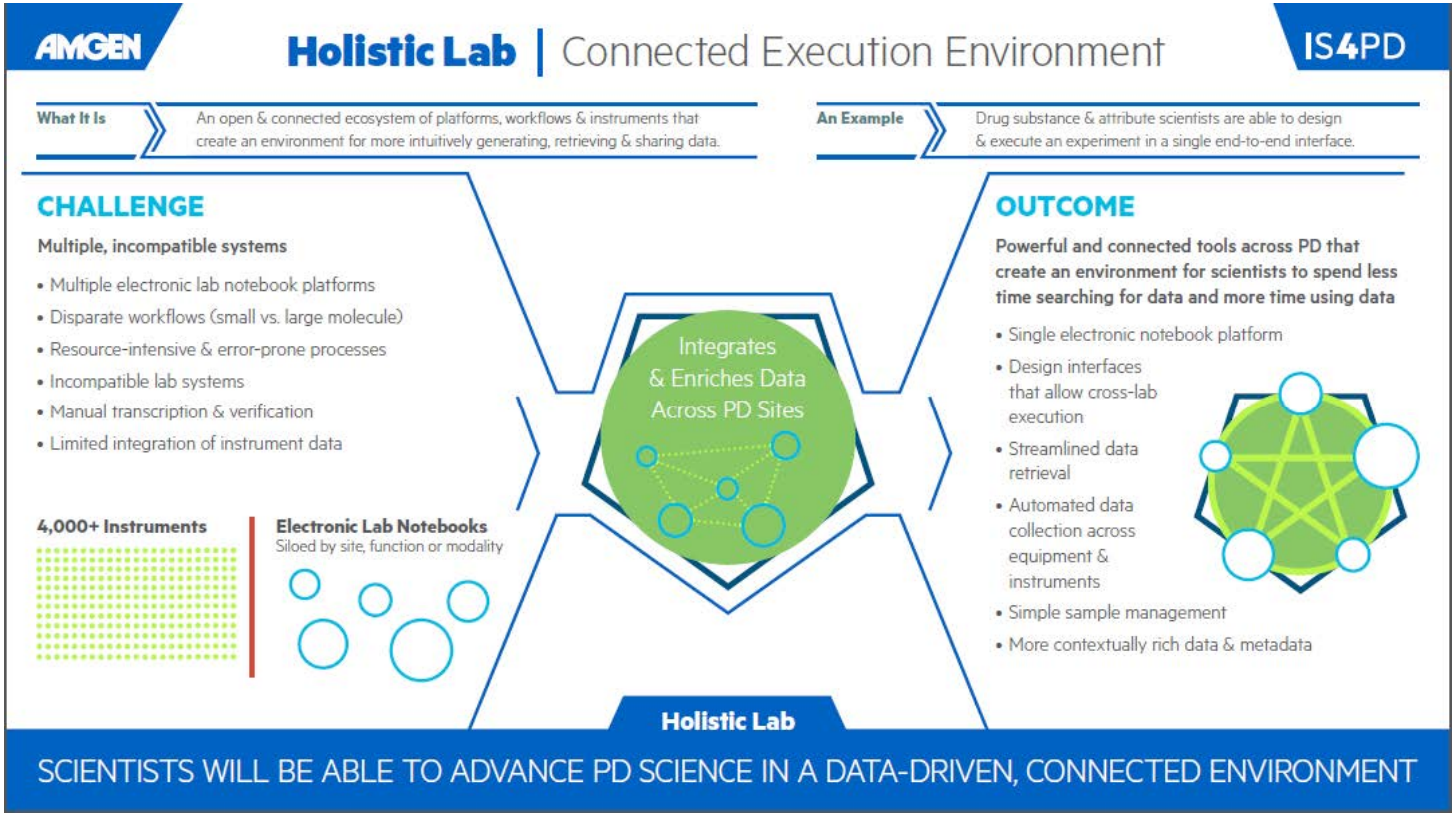

models


images

Data mining and analytics

Export of structured content

COMMUNICATING A COMPELLING VISION AT START OF THE PROJECT



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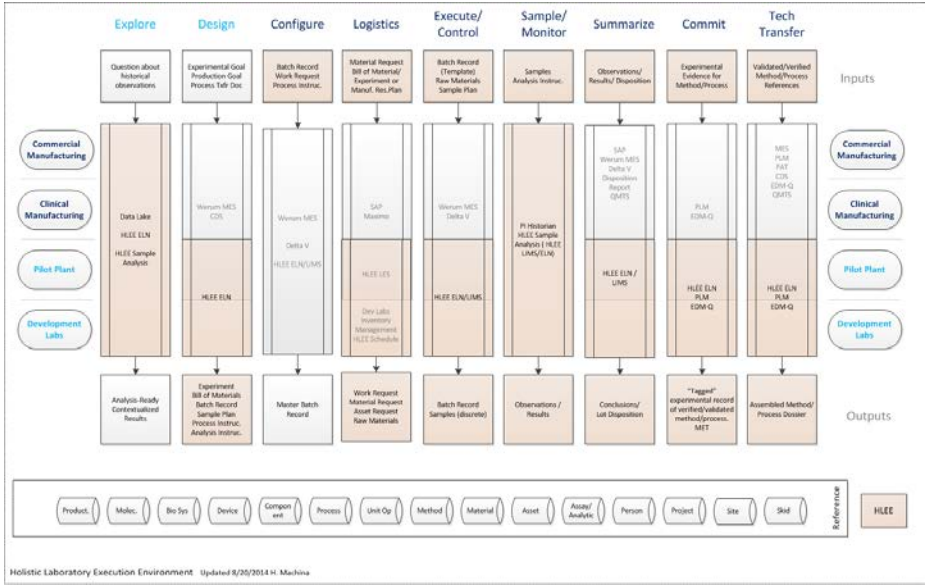
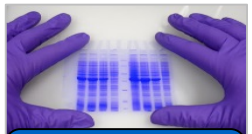
BUSINESS DRIVEN ALIGNMENT - CROSS DISCIPLINARY CAPABABILTIES



Generate & Submit Reports



Compile & Interpret Data/Results

Lab Work, Test Samples

Request for Study / Lab Work

Samples/Materials Inventory

Recipe/Method Development

Review & Confirm

Personnel

Recipe/Method Adaption

Plan, Assign & Schedule

Instrument Inventory

Recipe/Method Management

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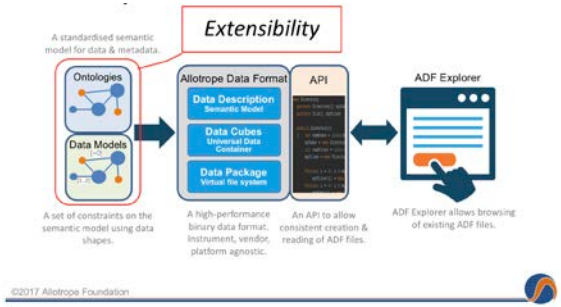
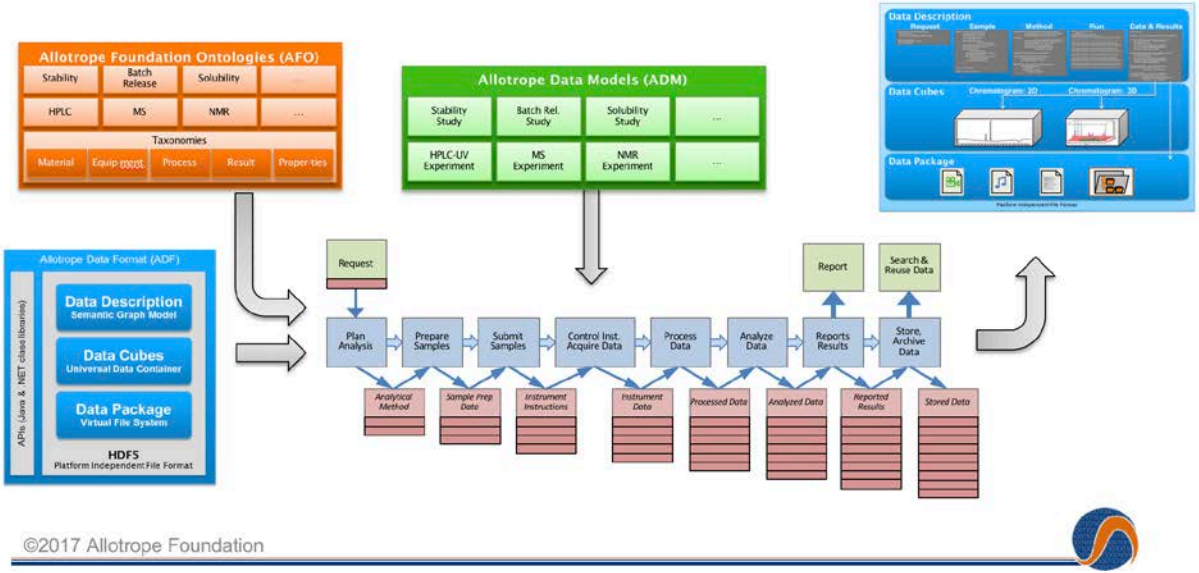
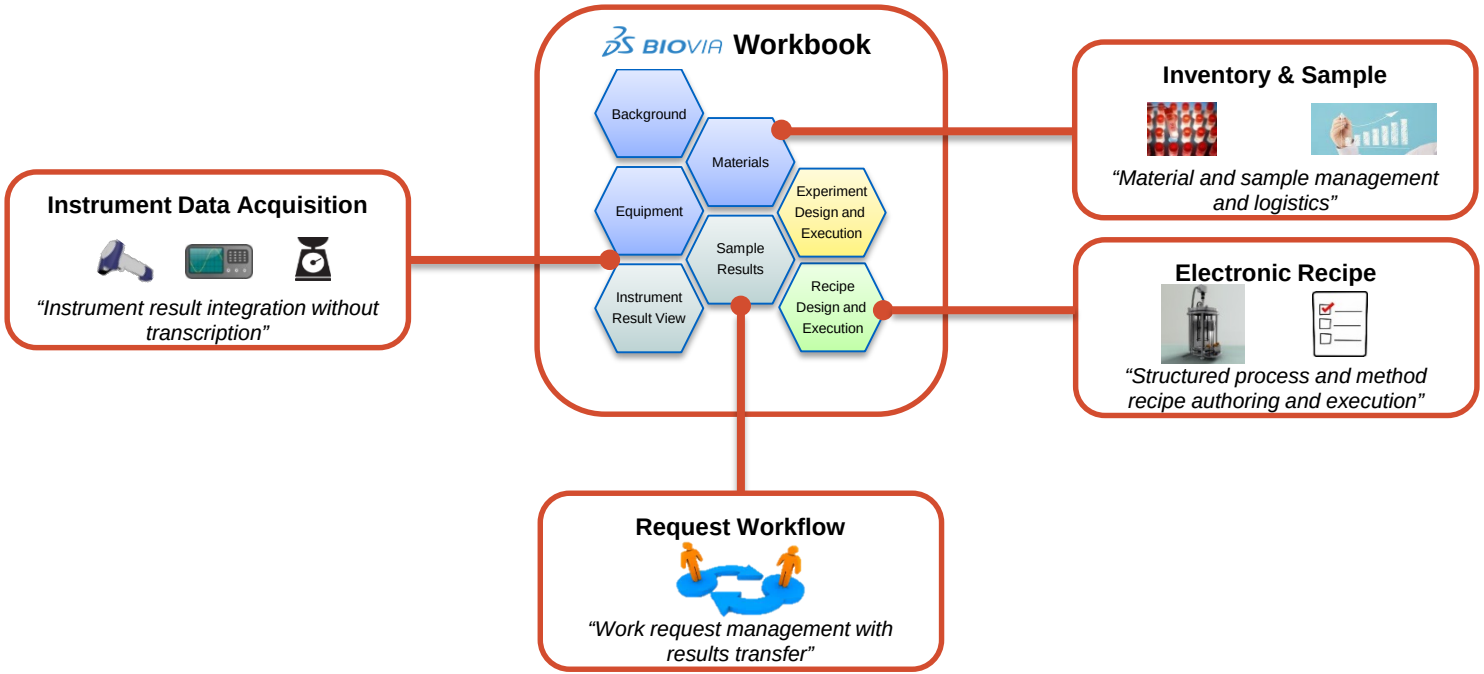
THE ALLOTROPE FRAMEWORK: THREE PRODUCTS, ONE HOLISTIC SOLUTION



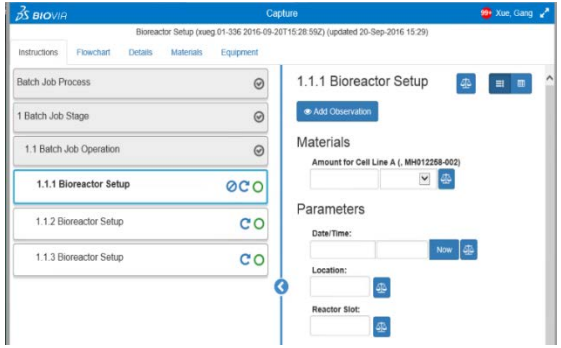


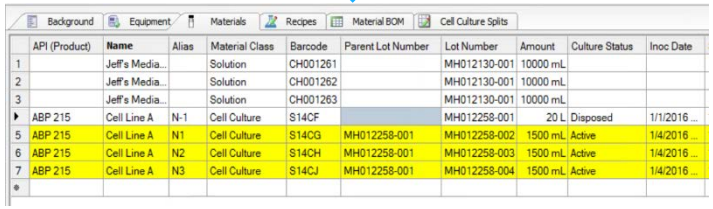
THE HOLISTIC LAB "ECOSYSTEM" – A SINGLE PD SOLUTION MODULAR ARCHITECTURE WITH DATA INTEGRITY BY DESIGN



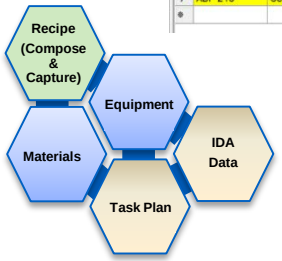
COLLABORATIVE DESIGN, EXECUTION & RESULTS CAPTURE IN HL

DST, DPT

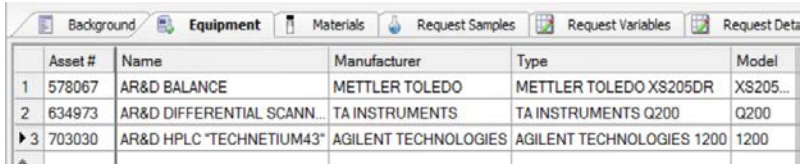




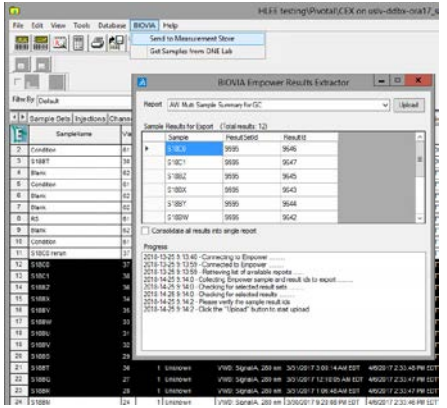
	API (Product)	Name	Alias	Material Class	Barcode	Parent Lot Number	Lot Number	Amount	Culture Status	Inoc Date
1		Jeff's Media...		Solution	CH001261		MH012130-001	10000 mL		
2		Jeff's Media...		Solution	CH001262		MH012130-001	10000 mL		
3		Jeff's Media...		Solution	CH001263		MH012130-001	10000 mL		
▸	ABP 215	Cell Line A	N-1	Cell Culture	S14CF		MH012258-001	20 L	Disposed	1/1/2016 ...
5	ABP 215	Cell Line A	N1	Cell Culture	S14CG	MH012258-001	MH012258-002	1500 mL	Active	1/4/2016 ...
6	ABP 215	Cell Line A	N2	Cell Culture	S14CH	MH012258-001	MH012258-003	1500 mL	Active	1/4/2016 ...
7	ABP 215	Cell Line A	N3	Cell Culture	S14CJ	MH012258-001	MH012258-004	1500 mL	Active	1/4/2016 ...



AS



	Asset #	Name	Manufacturer	Type	Model
1	578067	AR&D BALANCE	METTLER TOLEDO	METTLER TOLEDO XS205DR	XS205...
2	634973	AR&D DIFFERENTIAL SCANN...	TA INSTRUMENTS	TA INSTRUMENTS Q200	Q200
▸ 3	703030	AR&D HPLC "TECHNETIUM43"	AGILENT TECHNOLOGIES	AGILENT TECHNOLOGIES 1200	1200



SE-HPLC

Residual Solvents | AKTA | Titer | SE-HPLC

Sample ID	Sample Name	Task Id	retention time	retention time unit	Peak Name	Peak Area Percent	Peak Area Percent unit	Peak Area
S732X	Cell Line A	T8273	2.1741	min	HMW	20.480	%	25.573
S732X	Cell Line A	T8273	2.9241	min	Main	76.478	%	95.497
S732X	Cell Line A	T8273	3.1041	min	LMW	3.0413	%	3.7976
S732Y	Cell Line A	T8273	2.2609	min	HMW	11.825	%	14.479
S732Y	Cell Line A	T8273	2.9259	min	Main	85.345	%	104.50
S732Y	Cell Line A	T8273	3.1059	min	LMW	2.8297	%	3.4646

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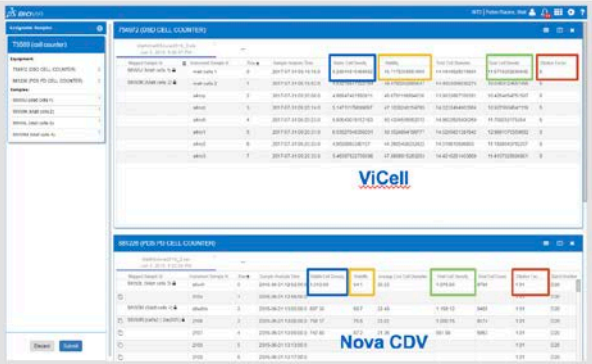
PROGRESSIVE STRATEGY TO LEVERAGE DEVELOPING STANDARDS

CONTINUOUS INTEGRATION FEED OF ALLOTROPE ONTOLOGIES FOR NEW INSTRUMENT CLASSES

- **Cell Counters**



BEYOND LC-UV: GROWING COVERAGE OF INSTRUMENT CLASSES BY ALLOTROPE STANDARDS BY YE 2018

Instrument	Use Cases	SME Input	Model built	SME/Public Review	Allotrope Governance	Artifacts Complete	Notes
Cell Counter	N/A	X	X	X	X	X	
Blood Gas Analyzer	N/A	X	X	X	X	X	
pH meter	N/A	X	X	X	In progress		
Conductivity Meter	N/A	X	X	X	In progress		
Osmolality Meter	N/A	X	X	X	In progress		
RAMAN	Raw data and identification	X	X	X	In progress		Raw data and identification use case only
AKTA	Capture of present OPC data	X					
NMR	Full capture of all data	X	X				BI/Pfizer/Bruker only, data descriptor only
Balance	N/A	X					Challenges with precision model desired by SMEs

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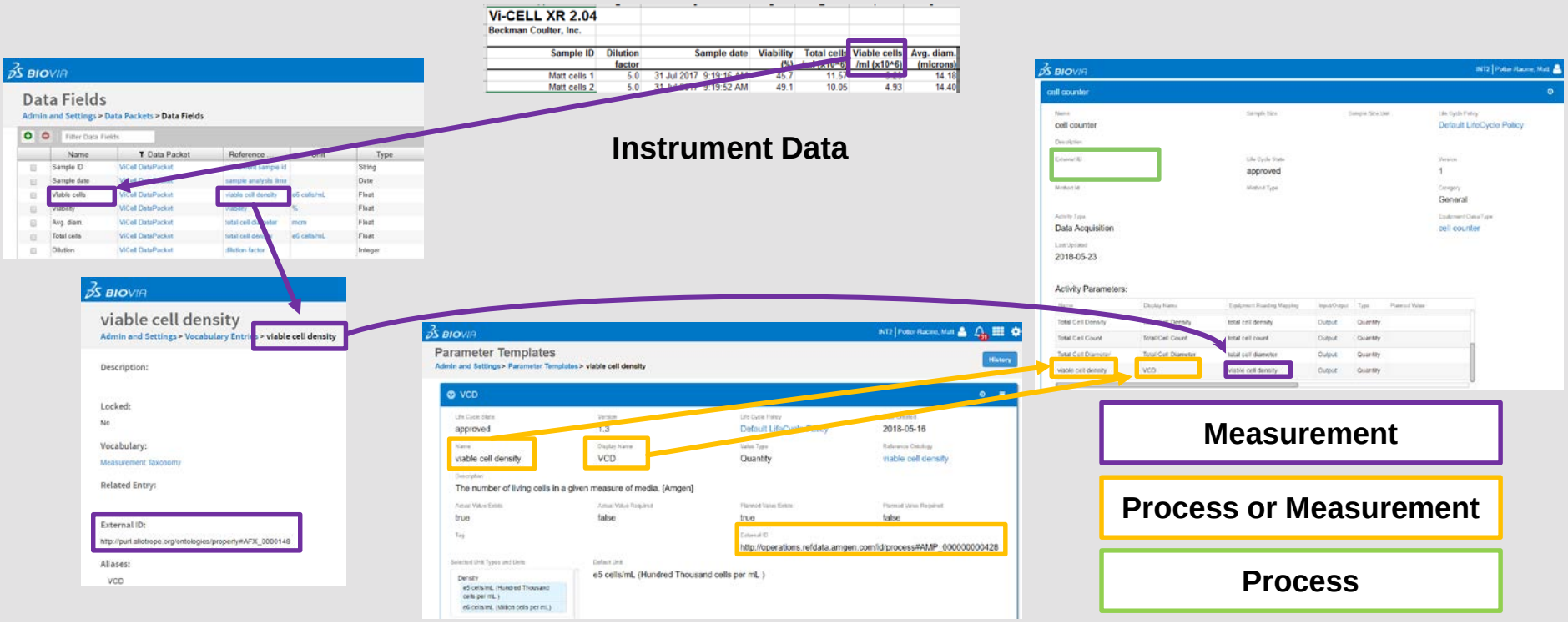
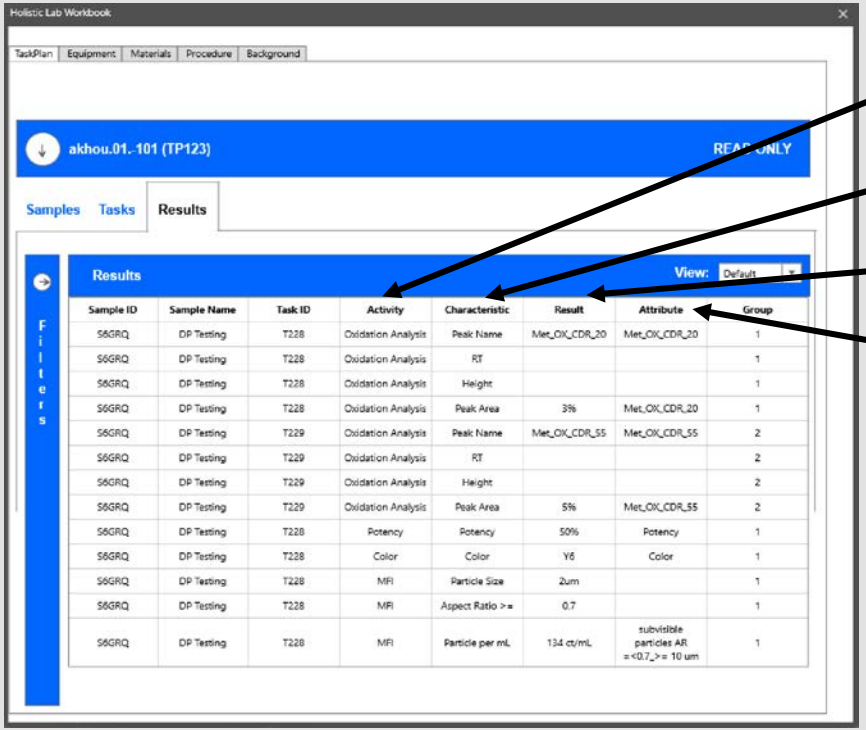
HOLISTIC URI ONTOLOGY MAPPING ACROSS LAB ECOSYSTEM



TASK PLAN EXTENDS SEMANTIC LOGIC LINKING ATTRIBUTES AND RESULTS WITHIN LAB LEVEL DATA CAPTURE SYSTEM



Process URI: Activity

Process and Measurement URI: Parameters

UoM URI: UoM

Process URI: Attribute

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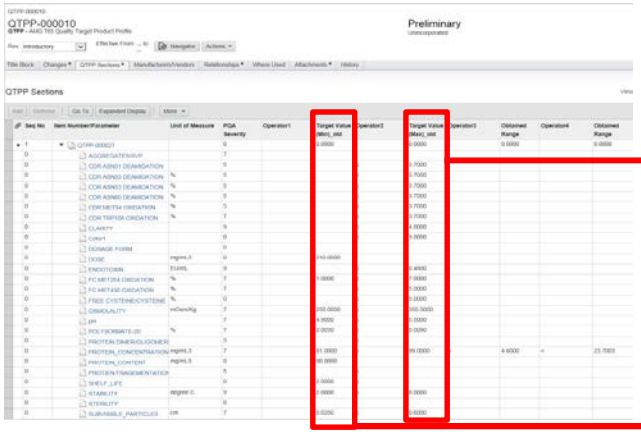
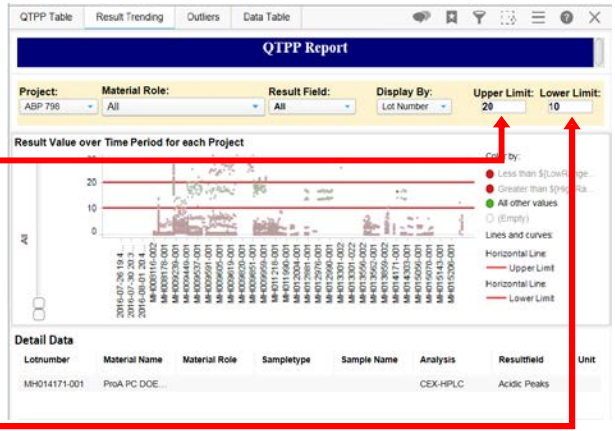
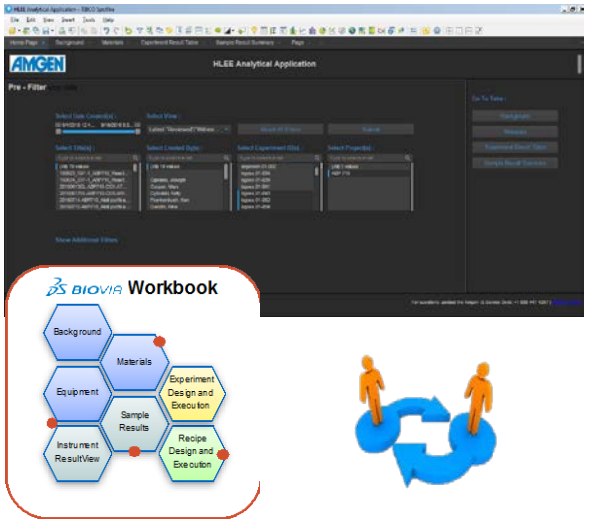
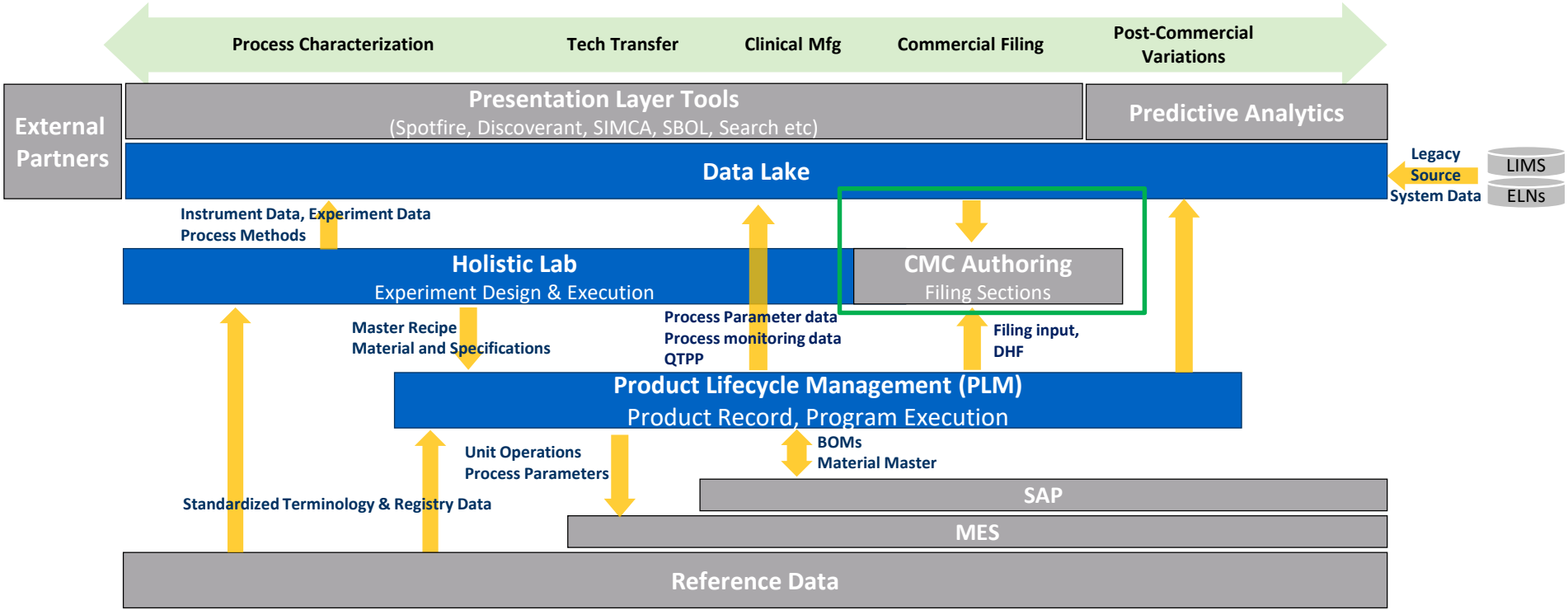
CONNECTED DATA FLOW LEVERAGING GLOBAL DATA INSIGHTS



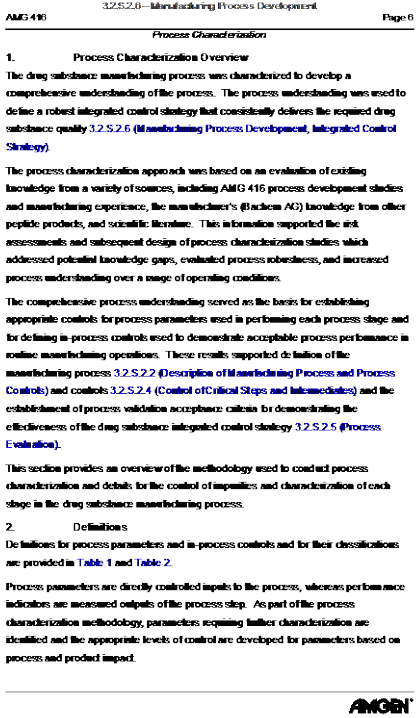




DRIVING DATA FLOW ACROSS THE PROCESS DEVELOPMENT LIFECYCLE LEVERAGING AN INTEGRATED IS SYSTEMS LANDSCAPE



DECONSTRUCTING THE E-CTD - INDUSTRIALIZING THE ASSEMBLY



3.2.S.2.6—Manufacturing Process Development

AMG 416 Page 6

Process Characterization

1. Process Characterization Overview

The drug substance manufacturing process was characterized to develop a comprehensive understanding of the process. The process understanding was used to define a robust integrated control strategy that consistently delivers the required drug substance quality 3.2.S.2.6 (Manufacturing Process Development, Integrated Control Strategy).

The process characterization approach was based on an evaluation of existing knowledge from a variety of sources, including AMG 416 process development studies and manufacturing experience, the manufacturer's (Bachem AG) knowledge from other peptide products, and scientific literature. This information supported the risk assessments and subsequent design of process characterization studies which addressed potential knowledge gaps, evaluated process robustness, and increased process understanding over a range of operating conditions.

The comprehensive process understanding served as the basis for establishing appropriate controls for process parameters used in performing each process stage and for defining in-process controls used to demonstrate acceptable process performance in routine manufacturing operations. These results supported definition of the manufacturing process 3.2.S.2.2 (Description of Manufacturing Process and Process Controls) and controls 3.2.S.2.4 (Control of Critical Steps and Intermediates) and the establishment of process validation acceptance criteria for demonstrating the effectiveness of the drug substance integrated control strategy 3.2.S.2.5 (Process Evaluation).

This section provides an overview of the methodology used to conduct process characterization and details for the control of impurities and characterization of each stage in the drug substance manufacturing process.

2. Definitions

Definitions for process parameters and in-process controls and for their classifications are provided in Table 1 and Table 2.

Process parameters are directly controlled inputs to the process, whereas performance indicators are measured outputs of the process step. As part of the process characterization methodology, parameters requiring further characterization are identified and the appropriate levels of control are developed for parameters based on process and product impact.

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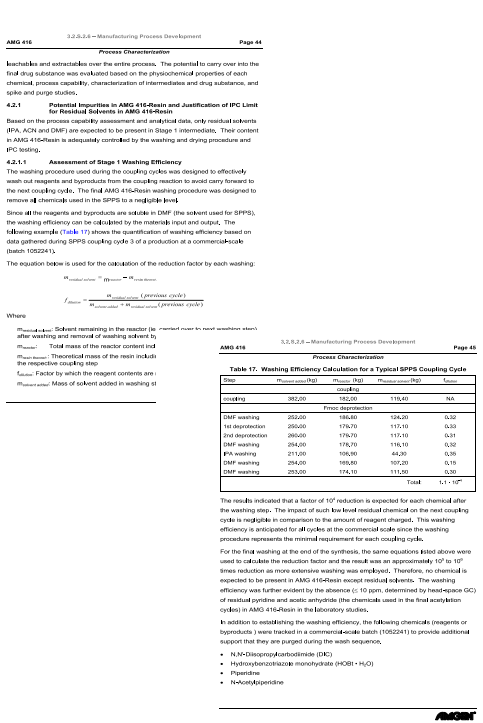

3.2.S.2.6 – Manufacturing Process Development

AMG 416 Page 44

Process Characterization

leachables and extractables over the entire process. The potential to carry over into the final drug substance was evaluated based on the physiochemical properties of each chemical, process capability, characterization of intermediates and drug substance, and spike and purge studies.

4.2.1 Potential Impurities in AMG 416-Resin and Justification of IPC Limit for Residual Solvents in AMG 416-Resin

Based on the process capability assessment and analytical data, only residual solvents (IPA, ACN and DMF) are expected to be present in Stage 1 intermediate. Their content in AMG 416-Resin is adequately controlled by the washing and drying procedure and IPC testing.

4.2.1.1 Assessment of Stage 1 Washing Efficiency

The washing procedure used during the coupling cycles was designed to effectively wash out reagents and byproducts from the coupling reaction to avoid carry forward to the next coupling cycle. The final AMG 416-Resin washing procedure was designed to remove all chemicals used in the SPPS to a negligible level.

Since all the reagents and byproducts are soluble in DMF (the solvent used for SPPS), the washing efficiency can be calculated by the materials input and output. The following example (Table 17) shows the quantification of washing efficiency based on data gathered during SPPS coupling cycle 3 of a production at a commercial-scale (batch 1052241).

The equation below is used for the calculation of the reduction factor by each washing:

$$m_{residual\ solvent} = \eta_{reactor} - m_{resin\ theoret.}$$

$$f_{dilution} = \frac{m_{residual\ solvent}\ (previous\ cycle)}{m_{solvent\ added} + m_{residual\ solvent}\ (previous\ cycle)}$$

Where

$m_{residual\ solvent}$: Solvent remaining in the reactor (as carried over to next washing step) after washing and removal of washing solvent by

$m_{reactor}$: Total mass of the reactor content incl

$m_{resin\ theoret.}$: Theoretical mass of the resin includi the respective coupling step

$f_{dilution}$: Factor by which the reagent contents are

$m_{solvent\ added}$: Mass of solvent added in washing st

AMG 416 3.2.S.2.6 – Manufacturing Process Development Page 45

Process Characterization

Table 17. Washing Efficiency Calculation for a Typical SPPS Coupling Cycle

Step	$m_{residual\ solvent}$ (kg)	$m_{reactor}$ (kg)	$m_{resin\ theoret.}$ (kg)	$f_{dilution}$
		coupling		
coupling	382,00	182,00	119,40	NA
		Fmoc-deprotection		
DMF washing	252,00	186,80	124,20	0,32
1st deprotection	250,00	176,70	117,10	0,33
2nd deprotection	265,00	176,70	117,10	0,31
DMF washing	254,20	178,70	116,10	0,32
IPA washing	211,20	106,90	44,30	0,35
DMF washing	254,20	169,80	107,20	0,19
DMF washing	253,00	174,10	111,50	0,30
			Total	$1,1 \cdot 10^{-4}$

The results indicated that a factor of 10^4 reduction is expected for each chemical after the washing step. The impact of such low level residual chemical on the next coupling cycle is negligible in comparison to the amount of reagent charged. This washing efficiency is anticipated for all cycles at the commercial-scale since the washing procedure represents the minimal requirement for each coupling cycle.

For the final washing at the end of the synthesis, the same equations listed above were used to calculate the reduction factor and the result was an approximately 10^5 to 10^6 times reduction as more extensive washing was employed. Therefore, no chemical is expected to be present in AMG 416-Resin except residual solvents. The washing efficiency was further evident by the absence (< 10 ppm, determined by head-space GC) of residual pyridine and acetic anhydride (the chemicals used in the final acetylation cycles) in AMG 416-Resin in the laboratory studies.

In addition to establishing the washing efficiency, the following chemicals (reagents or byproducts) were tracked in a commercial-scale batch (1052241) to provide additional support that they are purged during the wash sequence.

- N,N'-Diisopropylcarbodiimide (DIC)
- Hydroxybenzotriazole monohydrate (HOBt · H_2O)
- Piperidine
- N-Acetylpiperidine

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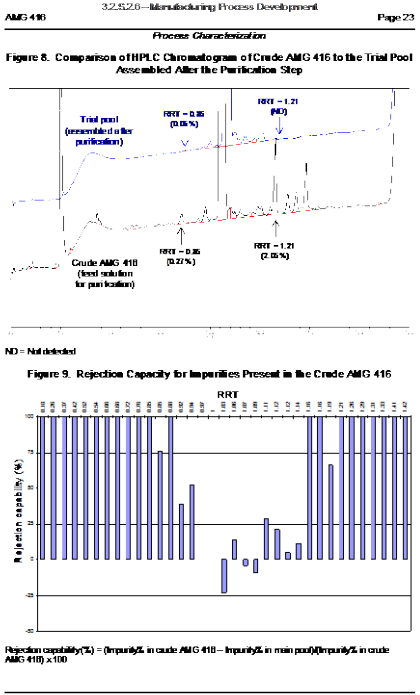

3.2.S.2.6—Manufacturing Process Development

AMG 416 Page 23

Process Characterization

Figure 8. Comparison of HPLC Chromatogram of Crude AMG 416 to the Trial Pool Assembled After the Purification Step

ND = Not detected

Figure 9. Rejection Capacity for Impurities Present in the Crude AMG 416

Rejection capability(%) = (Impurity% in crude AMG 416 – Impurity% in main pool)/Impurity% in crude AMG 416) x100

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Narrative Content

Narrative + Data

Data Content

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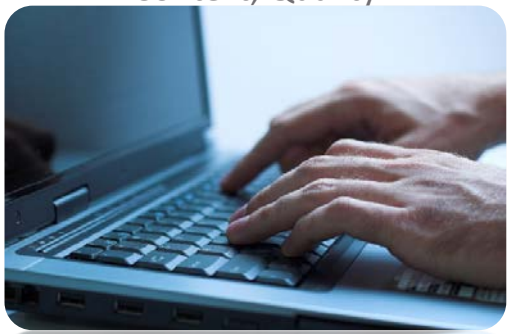
REALIZING THE BENEFITS TODAY OF A DATA CENTRIC "SMART" LAB POWERED BY THE ALLOTROPE FRAMEWORK AND DIGITAL PLATFORMS

Reduced Manual Effort & Paper

Better Scientific Reproducibility

Increased Data Integrity, Context, Quality



Streamlined Access, Sharing,

Foundation for Data Science

Consolidated Requirements Lower Innovation Barrier

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BACKUPS

HIGHLY MATRIXED CROSS FUNCTIONAL TEAM, SENIOR EXECUTIVE SPONSORSHIP, STRATEGIC LEVEL VENDOR PARTNERSHIPS