BioPharma PMI Instructions

8 November 2015

Overview

The biopharma Process Mass Intensity (PMI) metric provides a standard method for collecting mass data on the amount of water, raw material, and consumables used to produce 1 kg of biologic drug substance (API). This metric uses common parameters to define biologics manufacturing which allows for industry-wide benchmarking, increased transparency during process development, and a method to objectively compare processes.

The next series of slides provide more information on how the PMI is defined and calculated. There are example slides for each PMI calculation. An example of the summary table is given at the end.

Overview
Production Process Parameters

Process parameters that are considered in scope for the biologics PMI.

1. Upstream process (USP): seed train expansion, bioreactor
2. Isolation/Recovery: steps involved in separating the product from the cell mass and associated operations such as homogenization, centrifugation, depth filtration.
3. Downstream process (DSP): steps involved in purification such as chromatography, ultrafiltration, viral treatment.
4. Reaction: steps involving reactions post fermentation in order to modify the biomolecule such as protein refold, cleavage, or conjugation.
5. Purified Drug Substance: bulk fill, final fill

Overview
What to Include in Calculations

All water, raw materials, and consumables used in process steps should be counted including in-process cleaning steps.

Examples:

- Water used during in-line dilution of buffer concentrates
- In-process cleaning steps up to and including regeneration
- Consumable weights can include sterile packaging (do NOT include secondary/outer packaging)
- Water and raw materials for entire volume batched
- Water for flushing or rinsing that is consumed in-process

Overview
Defining PMI

Here we define the biopharma PMI as:

$$PMI_{tot} = PMI_W + PMI_{RM} + PMI_C$$

Where W= water, RM= raw materials, and C= consumables. Each input PMI is calculated as follows:

$$PMI_n = total\ material\ [n]\ input\ (kg)/total\ API\ produced\ (kg)$$

Overview
PMI Water

PMI_W

The PMI for water is defined in terms of municipal water for standardization. The multiplicative factor to convert PW and WFI water to municipal water is an average of member company's water purification systems (see table below). The equation for PMI_W is shown below where c_n is the conversion factor for each type of water.

$$PMI_W = (W_{mun} + c_{PR}W_{PR} + c_{PW}W_{PW} + c_{WFI}W_{WFI})/kg\ API$$

	From City Water to (Liter/Liter)		
Company	**Process Water**	**Purified Water**	**WFI**
Pfizer		1.35	1.45
DSM			1.65
JnJ		1.07	1.17
BMS			1.3
Genentech	50% recovery	1.46	1.61
Amgen		1.13	1.3
Overall Average		**1.25**	**1.41**

The conversion from PW and WFI to municipal water is performed automatically in the spreadsheet.

In scope: all process water including flush/rinse water and regeneration water
Out of scope: CIP/SIP

Overview
PMI Raw Materials

PMI_{RM}

Raw materials are defined to include, but are not limited to, media and cell culture feeds, bases, acids, salts, surfactants, and solvents.

$$PMI_{RM} = \frac{total\ kg\ raw\ materials\ used}{kg\ API\ produced}$$

*Pre-made solutions and liquid should be included in this tab.

*For solutions made in house, only include the raw materials used to make the solutions in this tab.

Overview
PMI Consumables

PMI_C

Consumables are defined as materials involved directly in processing or holding liquids or solids in the production process: wave bags, disposable bags, chromatography resins, filters, and membranes.

$$PMI_c = (U_f C_{bag} + U_f C_{resin} + U_f C_{filter} + U_f C_{membrane})/kg\ API$$

As some consumables are used for multiple runs in the production process, each type of consumable has an associated utilization factor (U_f) in the metric calculation.

$$U_f = (\#\ cycles\ used\ per\ batch)/(\#\ cycles\ in\ lifetime)$$

For example, if a chromatography resin has a lifetime of 100 cycles and is used for 4 cycles in a production batch, the U_f for each batch is 4/100 or 0.04.

*Do not include indirect materials such as vent filters.
*Average consumable weights are provided in the spreadsheet for convenience.

Example Calculations

PMI_W

PROCESS AREA	OPERATION	Type & Amount of Water Used (kg or L)				Process Liquid Volume	API Conc.	API	Total municipal water used	PMI_W
		Municipal Water	Process Water	Purified Water	WFI	L	g/L	kg	kg	kg water / kg API
USP	SEED TRAIN EXPANSION									
	N-3							0	100	NA
	N-2							0	350	NA
	N-1							0	450	NA
	FERMENTATION / CELL CULTURE		200	800		1000	4	4.0	1252.0	313.0

Entered from manufacturing process documents

Auto-calculated
API column is auto-populated in other tabs.

Repeat process for all steps in the production process. A step-wise PMI_W value will be calculated where API concentration is provided. Total PMI_W accounts for all water used even if a stepwise PMI_W can not be calculated.

PMI_W Continued

In the Water tab, you must provide the final total kg of API produced as this value is utilized by all other tabs.

PROCESS AREA	OPERATION	Type & Amount of Water Used (kg or L)				Process Liquid Volume	API Conc.	API	Total municipal water used	PMI_w
		Municipal Water	Process Water	Purified Water	WFI	L	g/L	kg	kg	kg water / kg API
PURIFIED DRUG SUBSTANCE	BULK FILL							0	0	NA
	FINAL FILL					400	7	2.8	0	0.0
							TOTAL	2.8	3404.5	1215.9

Total API (kg) entered in Final Fill row on Water tab will auto-populate all Total API cells in tool.

PMI_{RM}

PROCESS AREA	OPERATION	For each step, enter total amount of material used	Type & Amount of Raw Material Used (kg)						API	Total Raw Mats used	PMI_{RM}
		Total material (kg)	Media & other chemi-cals	Bases	Acids	Salts	Surfact-ants	Solvent	kg	kg	kg raw mat/ kg API
USP	SEED TRAIN EXPANSION										
	N-3	2.6	2.3		0.001	0.15	0.18		0	3.635	NA
	N-2	12.2	10		1	1	0.2		0	11.18	NA
	N-1	101.3	97		1	3.8	0.5		0	105.3	NA
	FERMENTATION / CELL CULTURE	1449.5	1445		2		2.5		4	1345.5	336.4

Either enter the total amount of raw material used per step or enter the amount for each component.

Auto-populated from Water PMI worksheet

Auto-calculated

PMI_C

PROCESS AREA	OPERATION	Type and amount of consumables used (kg)									Total API	Total Consumables Used [kg]	PMI_c
		Bags	Bio-reactor	Bio-reactor (U_f)	Resins	Resin (U_f)	Filters	Filter (U_f)	Membranes	Membrane (U_f)	kg	= Sum [U_f*kg consumable]	kg consumables / kg API
DSP	CHROMATOGRAPHY												
	Column 1				175	0.03	18.3	1			16	23.55	0.67
	Column 2				271	0.01	6	1			12	7.71	1.56
	Column 3				485	0.008	4.5	1			15	8.38	1.79
	Column 4										0	0	NA

Input utilization factor where applicable.
Cell value = #cycles used/total #cycles

Auto-populated

Auto-calculated

PMI_C Continued

Average consumable weights provided in separate tab. Use these values to streamline data entry. Examples shown below.

Key Consumable Items			
TYPE	**Item Description**	**SIZE with units**	**WEIGHT, kg**
Buffer Bags			
	Full assembly including filter & conectors	20 L	0.92
	Full assembly including filter & conectors	50 L	1.66
	Bag without filter	200 L	1.55
	Bag without filter	50 L	0.8
Single-Use Bioreactors			
	Wave bioreactor	10 L	0.5
	Wave bioreactor	25 L	0.76
	Wave bioreactor	50 L	1.12
Filters			
	filter cartridge	0.2 micron, 10"	0.4
	filter cartridge	0.2 micron, 20"	0.9
	filter cartridge	0.2 micron, 30"	1.3
	virus removal filters	1 m^2	0.9 kg/m^2
Ultrafiltration Membranes			
	membranes for buffer exchange, concentration etc.	1 m^2	0.9 kg/m^2
Chromatography Resins			
	packed resins for chromatographic column separation	1 L	1 kg/L

Total PMI Summary Tab

PROCESS AREA	OPERATION	PROCESS Contribution kg input		
		Water	Raw Materials	Consumables
USP	SEED TRAIN EXPANSION + PRODUCTION BIOREACTOR	2379.75	0	0
ISOLATION / RECOVERY	CENTRIFUGATION + DEPTH FILTRATION	417.5	0	0
DSP / PURIFICATION	CHROMATOGRAPHY- all	0	0	0
	VIRAL TREATMENT - Inactivation	0	0	0
	FILTRATION- all	0	0	0
	VIRAL TREATMENT - Filtration	0	0	0
	ULTRAFILTRATION/DIAFILTRATION	0	0	0
PURIFIED DRUG SUBSTANCE	FINAL FILL in FORMULATION BUFFER	0	0	0
	TOTAL INPUT	**2797.25**	**0**	**0**
	Total process API (kg)	2.8		
	Total PMI (kg/kg PMI)	**999.018**	**0**	**0**

Select from drop down menu for each UO as appropriate

Equipment type per UO	Cell Culture Mode	Product Identifier	Product Version

Choose batch or perfusion for cell culture mode.

Choose either “fixed” or “single-use” as the equipment type for each Unit Operation (UO). Fixed refers to multi-use equipment.

Total PMI is a separate worksheet in workbook.
These values are auto-populated from the other worksheets.

Long term tracking

Total PMI Summary tab includes 2 cells to help track process improvements over time.

- Product identifier- choose a generic identifier for each individual product submitted
  - Ex- P1, P2, P3, etc
  - This identifier will only be used by ACS GCI to match products if multiple versions are submitted
- Product version- identify the process version for each product
  - Ex- v1.0, v1.1, v1.2
  - Sharing data more multiple versions of a single product will allow us to show improvement over time