Understanding Sucrose:
Matching Sucrose Quality to Functional Need

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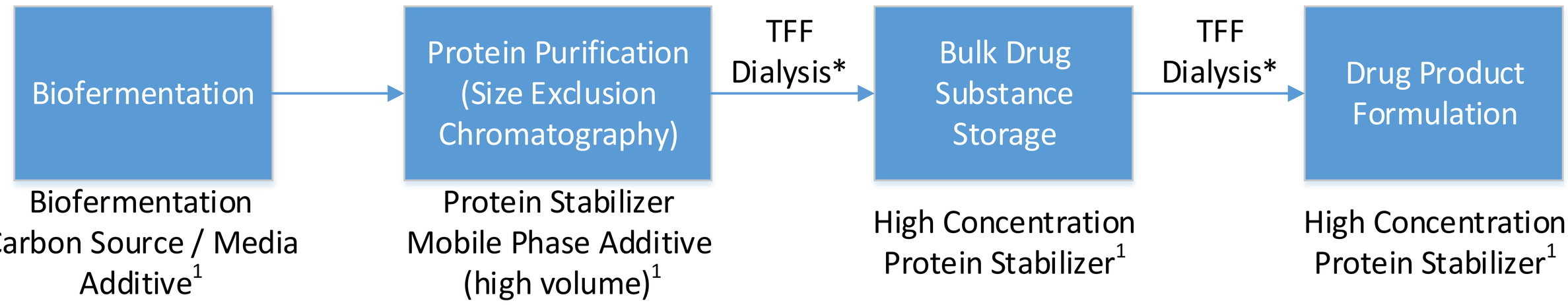
Section I: Uses of Parenteral Grade Sucrose in Biomolecule Development



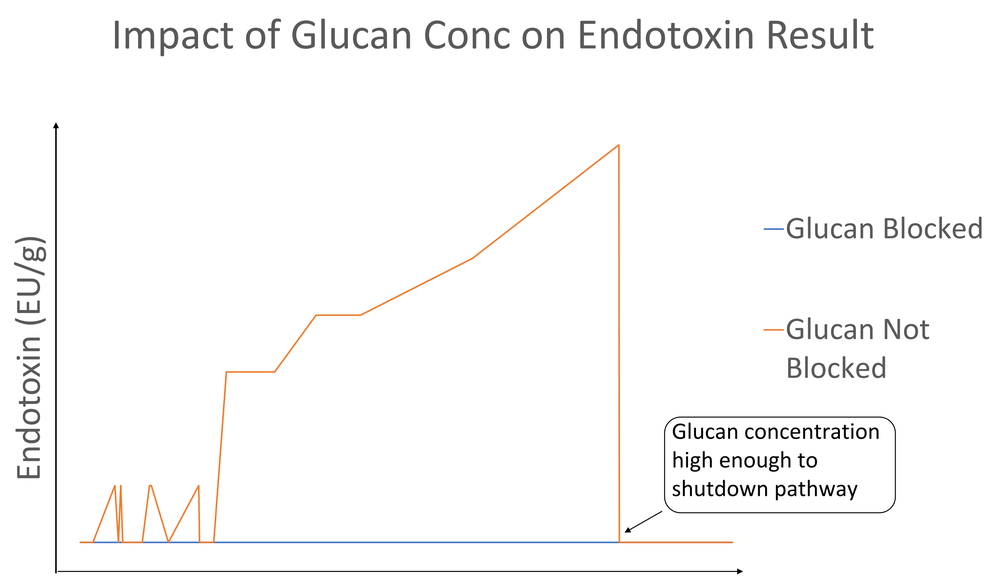
[1] Standard input points for Sucrose into large molecule manufacturing process
* Potential concentration point for endotoxin and β-glucans in a biologic manufacturing process

Section II: Why Sucrose Quality Matters / Implications

1) Compendial COA testing does not tell the whole story
2) Raw source (Cane vs Beet)-Cane derived generally has higher residual β-glucan load than beet derived sucrose which can carry over into final product
3) β-D-glucans could result in a potential immuno-stimulatory response at elevated levels (1)
4) Endotoxin and β-D-glucans can accumulate during drug substance / drug product processing. TFF purification membranes generally do not remove β-glucans when used as a buffer additive
5) Setting of more defined quality requirements for sucrose raw material may be necessary based upon point of insertion into the biomolecule drug substance / product process
6) Necessity to address potential future regulatory requirements to quantitate and set limits as low as 10 ng / mg for β-D-glucans in drug product (1)

Section III: β-D-Glucans and Accurate Endotoxin Results

1) The LAL test is currently the most sensitive and specific means to detect and measure bacterial endotoxin
2) β-D-Glucans can activate the LAL reaction through an alternate enzymatic pathway which interferes with the accurate detection of endotoxin
3) There is variability in the reactivity of LAL reagents to β-D-Glucans, which impacts the specificity of the test and interferes with inter-laboratory agreement
4) Though β-D-Glucans and endotoxin react synergistically in kinetic LAL tests, the Glucan pathway shuts down at higher concentrations of Glucans making product trending difficult
5) Use of a Glucan blocker for testing cane sucrose is essential for determining accurate endotoxin results due to the level of β-D-Glucans present
6) Providing an informational glucan level with each lot manufactured allows for end user to assess the risk of glucans in their finished products



KYPP Data: β-Glucans and Endotoxin for Cane and Beet Derived Sucrose				
Code	S-124-1-MC (cane)		S-124-2-MC (beet)	
Test	β-glucans	Endotoxin	β-glucans	Endotoxin
Number of Lots Analyzed	23	22	16	255
Maximum Result	3711 pg/g	0.4 EU/g	205 pg/g	0.3 EU/g
Average Result	1252 pg/g	<0.1 EU/g	<166 pg/g	< 0.2 EU/g

Specification Upgrade for all Pfanstiehl Sucrose Codes		
	Current Limit	New Limit
Color Value	≤ 45	≤ 10
Conductivity	≤ 35 µS/cm	≤ 5 µS/cm
Endotoxins	≤ 1.5 EU/g (cane) ≤ 0.6 EU/g (beet)	≤ 0.3 EU/g
β-Glucans		Report

(1) Barton, et. al. Beta-glucan contamination of pharmaceutical products: How much should we accept?, Cancer Immunother (2016), Vol 65, p 1289-1301.