The devil you know: look early, look hard and minimize the unexpected

Mark Krebs

MIBio, Cambridge

21 October 2015

Building bridges…

Candidate Selection	Pre-transition Activities	Development

CS

IND

How to bridge the gap?

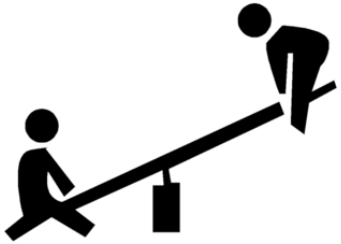
Biogen

Cambridge Mathematical Bridge: "The Mathematical Bridge" by Tanya Hart - the Mathematical Bridge. Licensed under CC BY-SA 2.0 via Commons
Oxford Bridge of Sighs: "1 oxford bridge of sighs 2012" by chensiyuan - chensiyuan. Licensed under GFDL via Commons
Millau Viaduct http://www.fosterandparents.com

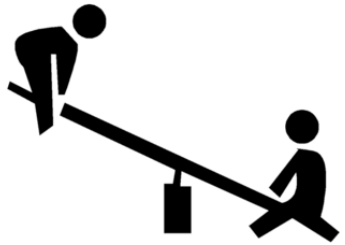
It’s all about risk

Candidate Selection	Pre-transition Activities	Development

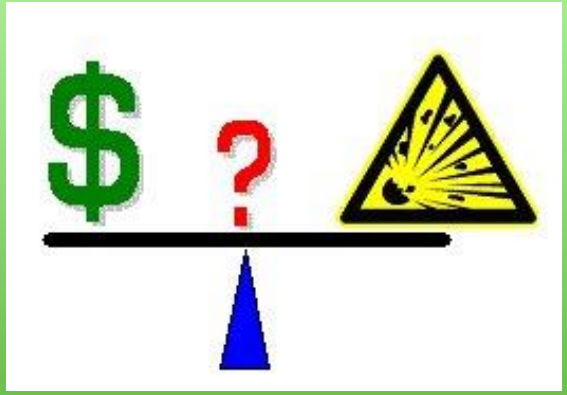
CS



IND



Biogen



Time is of the essence

- All mAbs behave the sa
- Use platform methods a formulation
- Optimise as you get confirm it “works” – costly bridgin studies?
- May not get optimal behaviour

Science

- Learn about each mAb
- Develop formulations
- Get the best behaviour
- No late(r) stage optimisation
- Takes time and resources

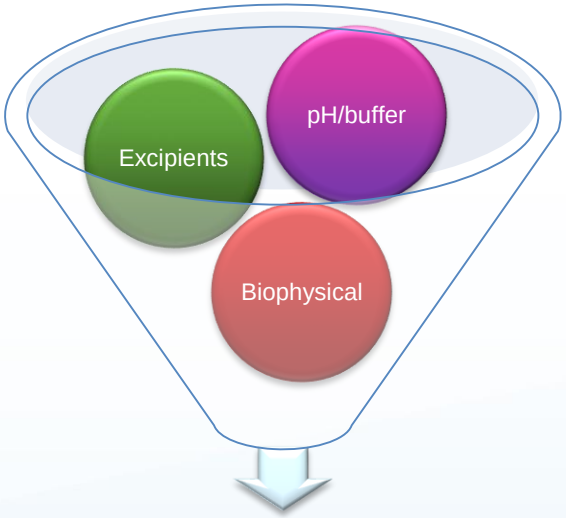
Biogen

Step 1: Candidate selection

- Determine main degradation pathways
- Begin mapping formulation design space

} Developability, deviceability

- Maximize information with minimal protein
- Rank candidates
- Potential impact on timelines
- Starting point for FIH formulation
- Assess the need for new method development



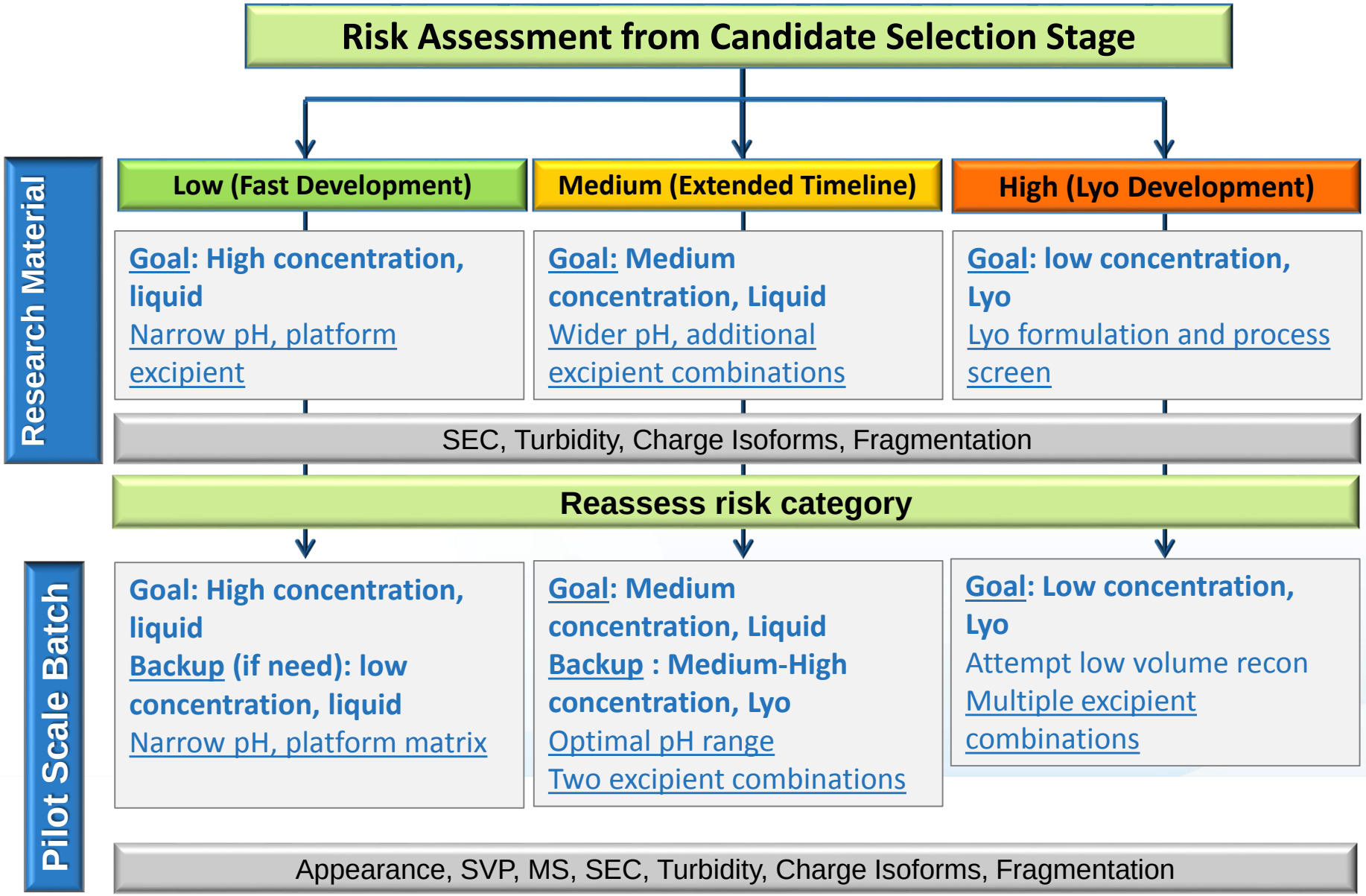
Risk assessment

Biogen

Step 2: Risk assessment

Properties	Measurement	mAb1	mAb2	mAb3
Sequence Analysis	Hypothetical Deamidation, oxidation, isomerization, and clipping sites	Met in CDR	Met, isomerization, deamidation sites in CDR	None
Biophysical profile	T_{m1} Onset (Rank)	1	3	2
	HIC (Rank)	1	3	2
	K_D	Positive	Negative	Negative
	pI	>8	<8	<8
High concentration properties	PEG Solubility (Rank)	1	3	2
	Viscosity at high concentration	Low	Medium	Low
Accelerated stability	ΔHMW after 4w 40 °C	< 3%	> 5 %	< 3%
	Δdegradation after 4w 40 °C	0%	0%	0%
Post-translational modification	ΔAcidic Species 4w °C	< 15%	> 40%	< 15%
Low pH Hold	Change in HMW and LMW after Neutralization	No Change	Increase HMW, Increase LMW, Monomer Loss	ND
Cumulative rating : Low- Medium-High		Low	Medium-High	Low

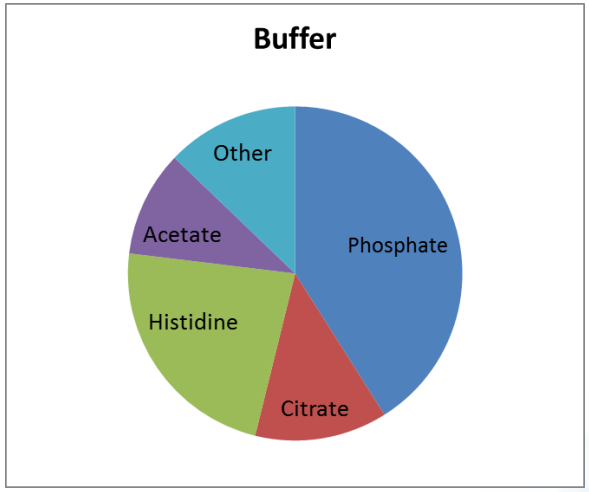
Step 3 and 4: Formulation studies

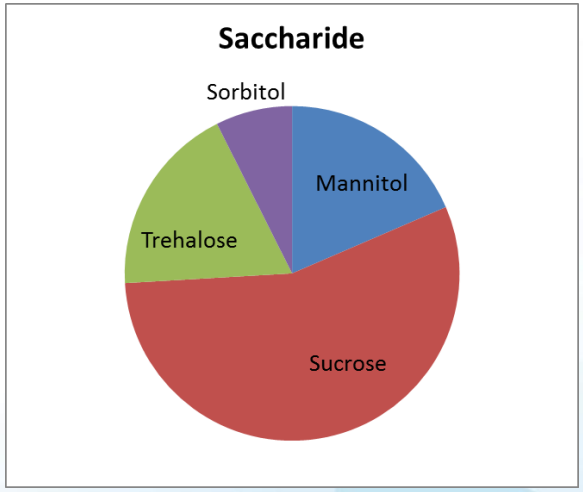


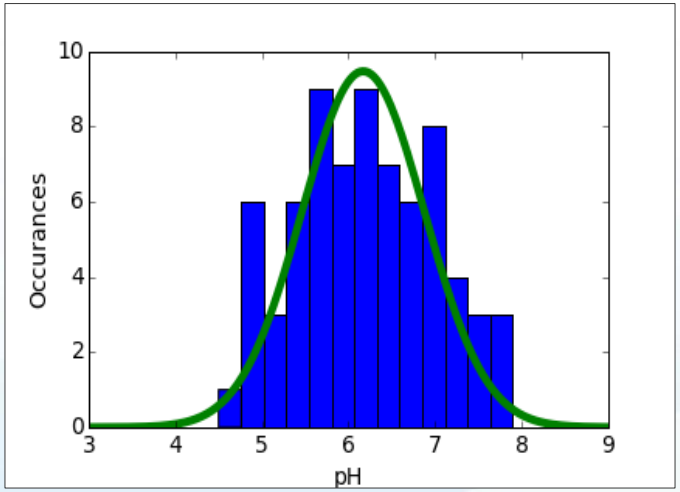
Platform approach, not platform formulation

- Goal: design a rational approach to screen likely formulations
- Use the risk assessment to guide extent
  - Candidate selection may also suggest types of excipients
- Based on an internal formulation analysis, restrict formulations at least initially

Formulation Composition of Marketed mAbs[1]



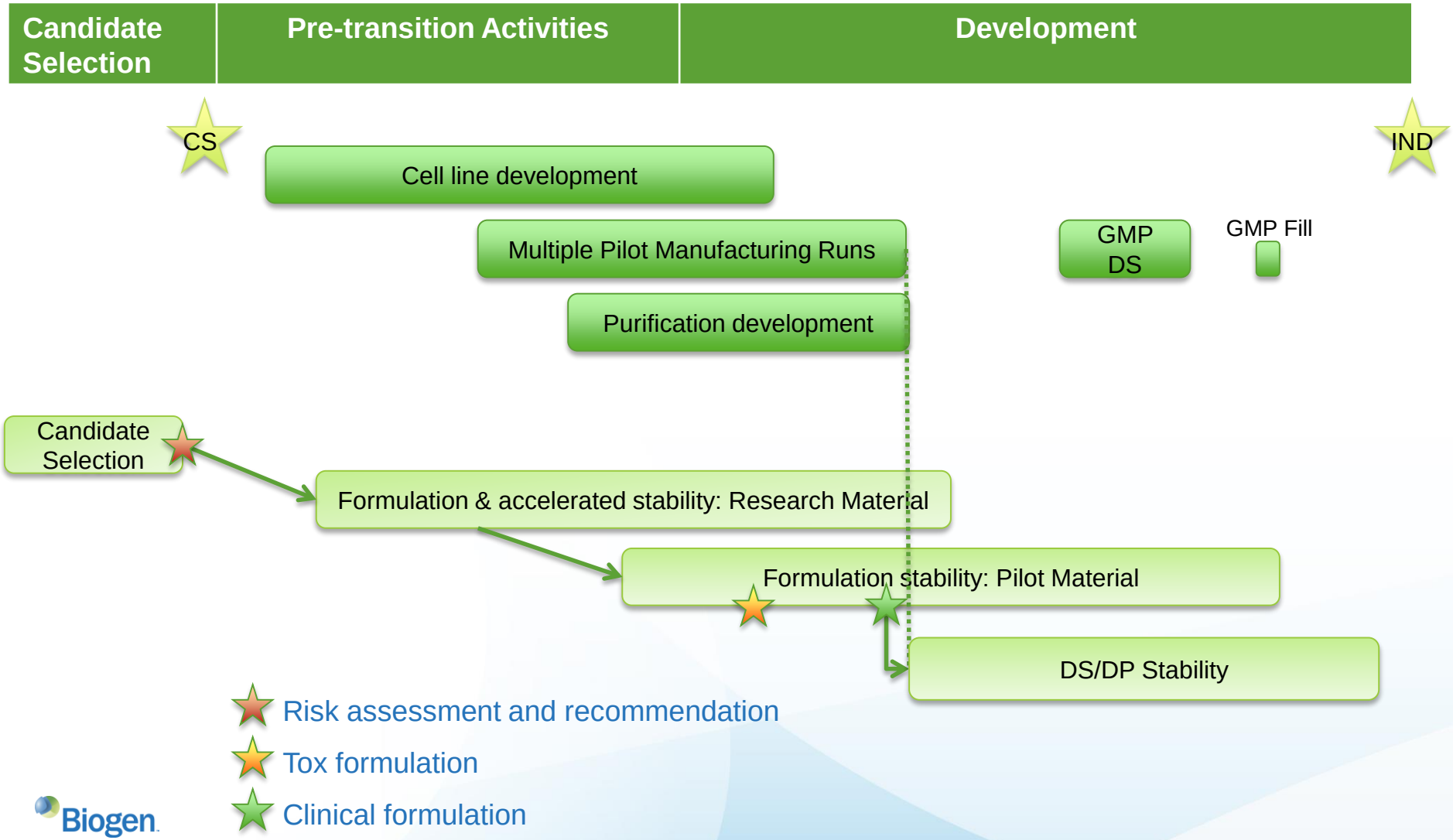




Biogen

1. Data from Uchiyama, S. (2014) Biochemica et Biophysica Acta 2041-2052

Overall timeline

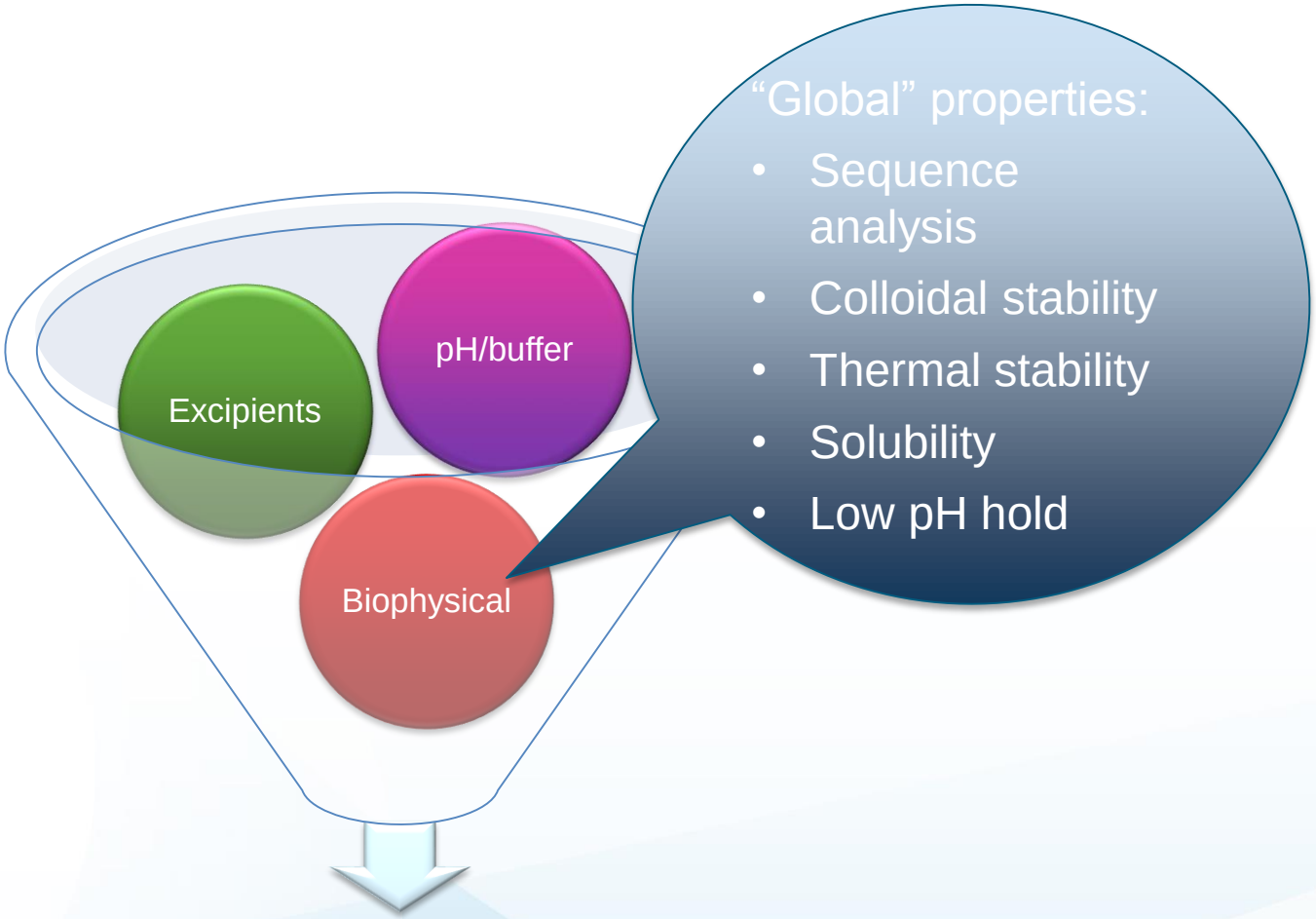


Case Study I

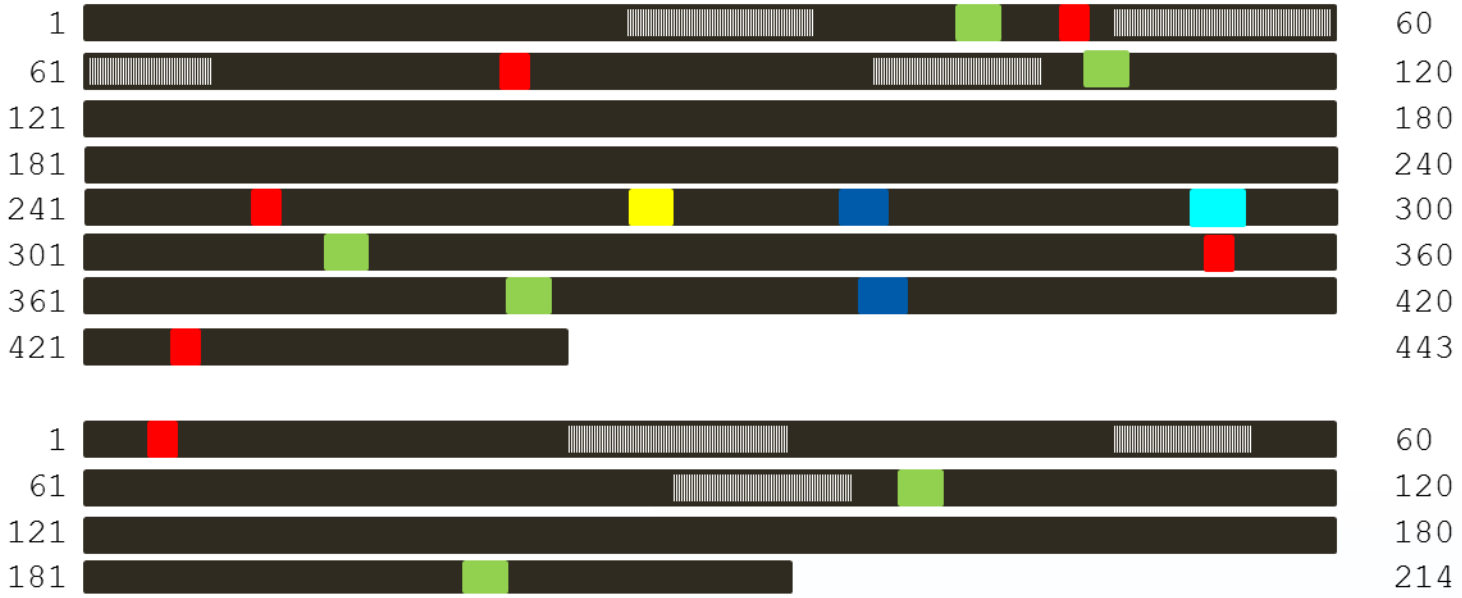
- Three candidates for one projects
- Likely product profile:
  - High concentration liquid
  - Self-administration
- Material available for candidate selection: 100-200 mg

Biogen

A comprehensive look



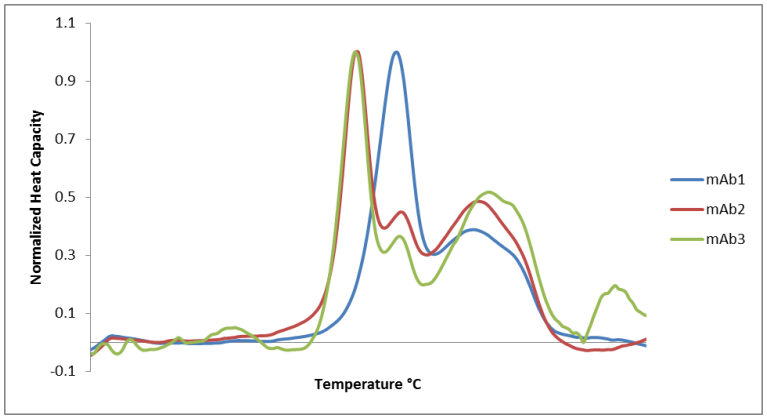
Sequence analysis



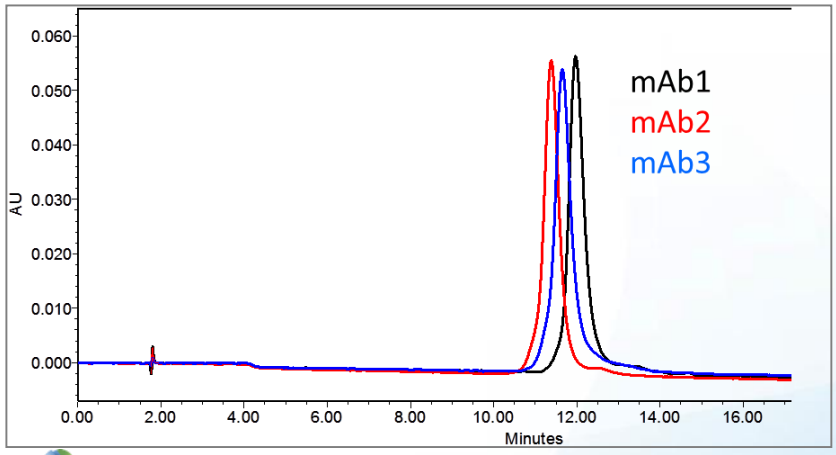
Key: Key: deamidation (green), oxidation (red), glycosylation (cyan), isomerisation (blue), clipping (yellow)
Kabat (except H1: Chothia) CDR (underlined)

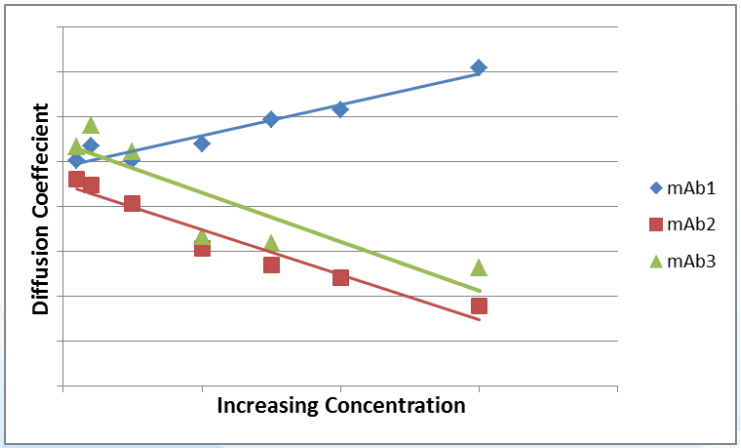
- Focus especially on the CDRs

Focus on solution properties



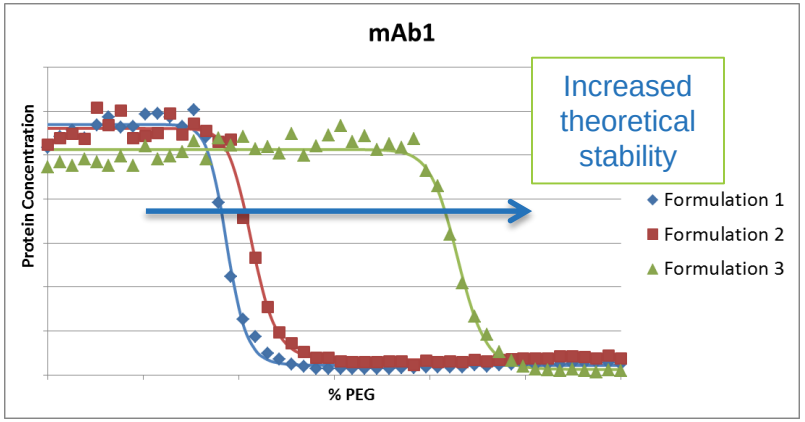
- Sequence analysis shows “hot-spots” in the CDR’s of mAb 2 and 3
- Reasonable thermal stability
- mAb1 least hydrophobic
- Colloidal stability by K_D suggests attractive intermolecular interactions with mAb 2 and 3

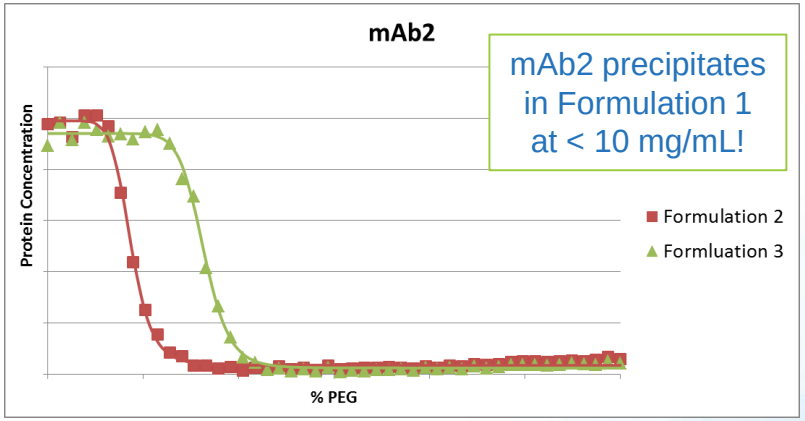




Biogen

PEG Solubility





- Use PEG solubility to predict high concentration properties
- Early on, we were able to flag mAb2 as having unfavorable properties

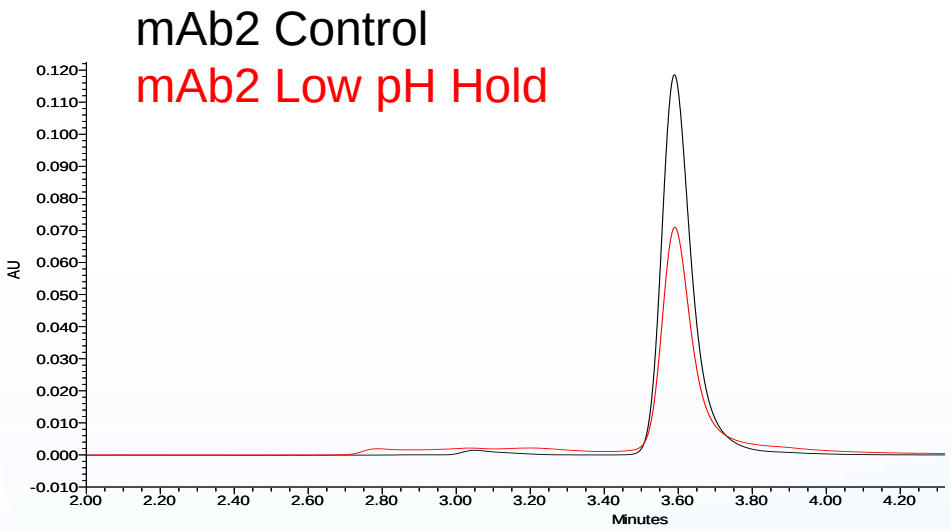
Biogen

Assessing manufacturability

Can we flag issues that will arise in other development groups?

Simulated viral clearance

- Low pH holds are routinely used for viral clearance
- May result in aggregation and low yields



Results

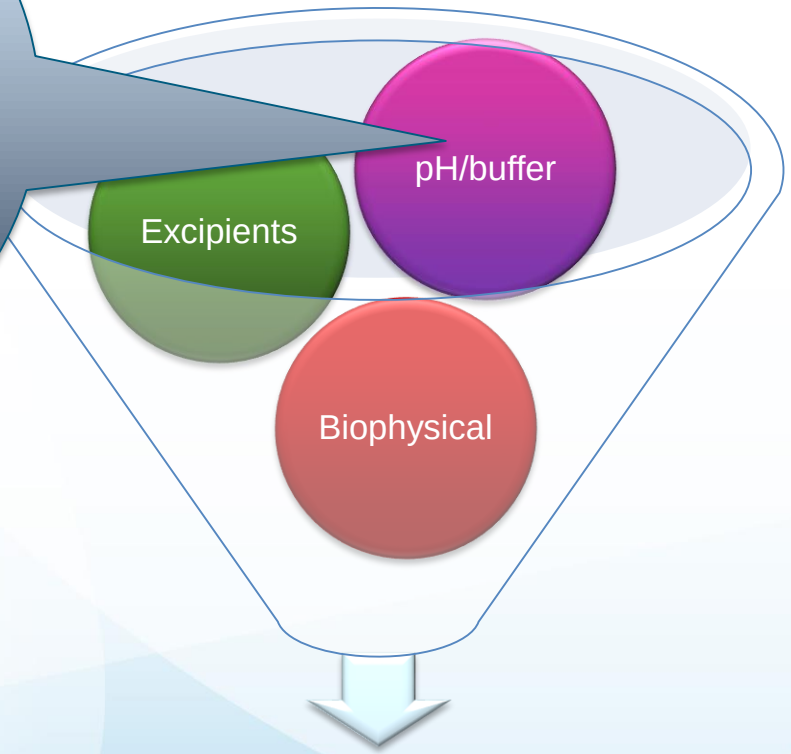
- mAb1 and 3 show no change as a result of exposure to low pH
- mAb2 may require a different method of viral inactivation

Biogen

A comprehensive look: pH

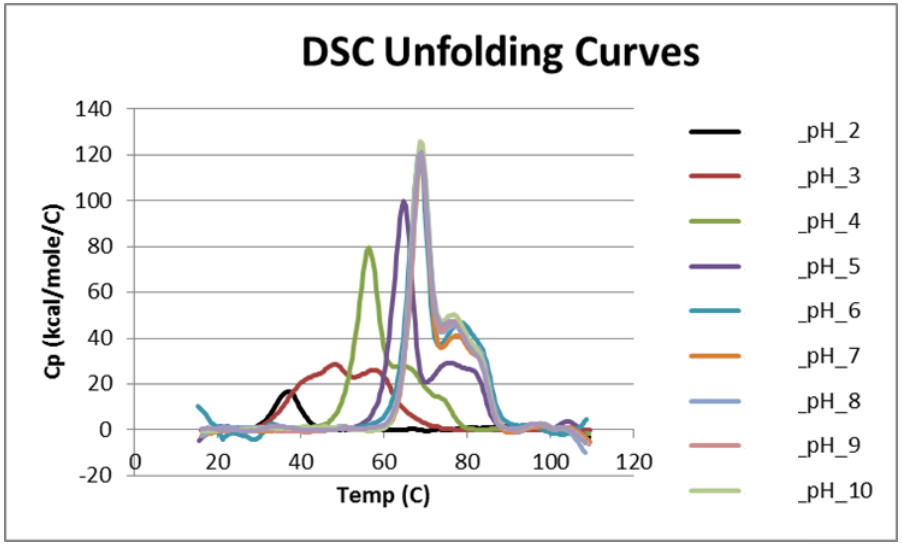
Explore mAb pH range:

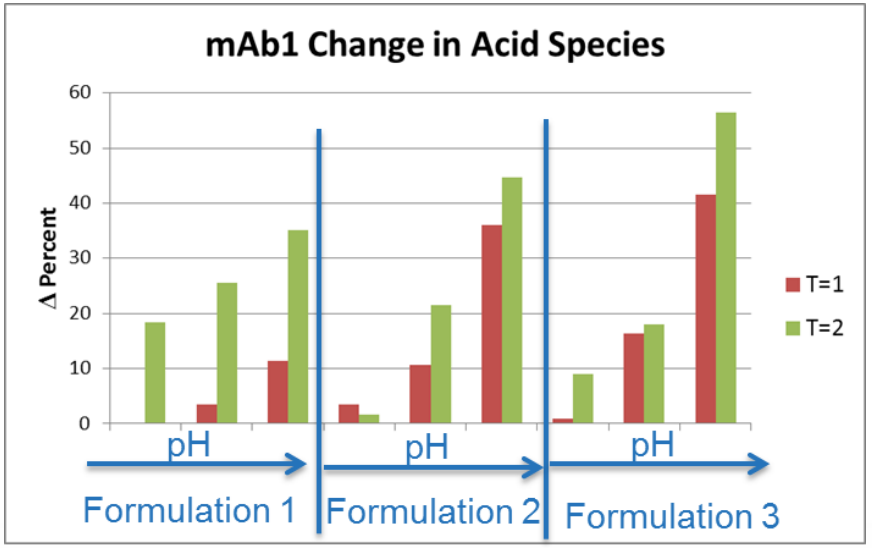
- Low concentration
- Buffer ~ pH
- Accelerated stability
- Aggregation
- Integrity, clipping
- Charge states



Risk assessment

Mapping the formulation space: pH





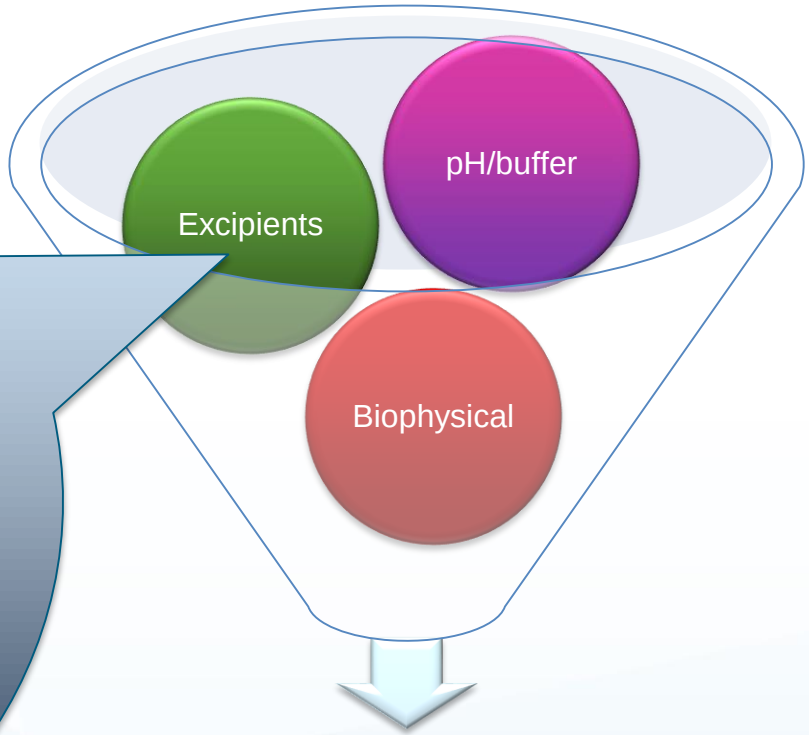
- Decrease in thermal stability at low pH
- Little aggregation and clipping were observed on stability
- Main form of degradation: increase in acidic species
  - Might not be a concern
  - Deamidation sites in CDR of mAb 2 – Potential functional impact!

Biogen

A comprehensive look: excipients

Explore high concentration:

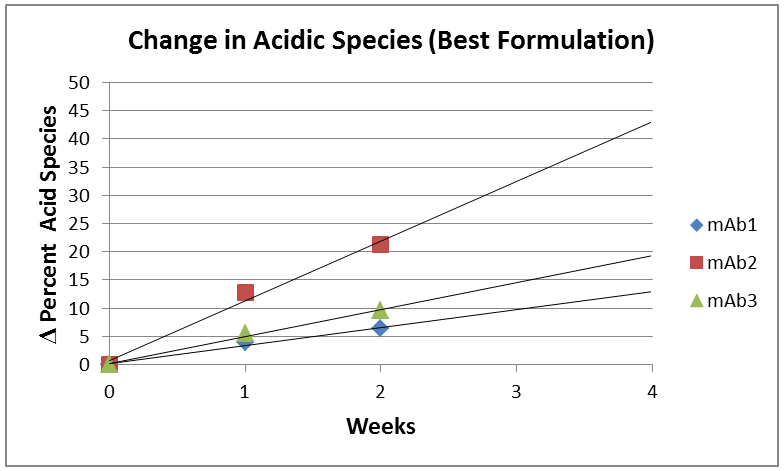
- “as high as possible”
- pH, buffer from before
- Salts, sugars, amino acids
- Accelerated stability
- Aggregation
- Integrity, clipping
- Charge states

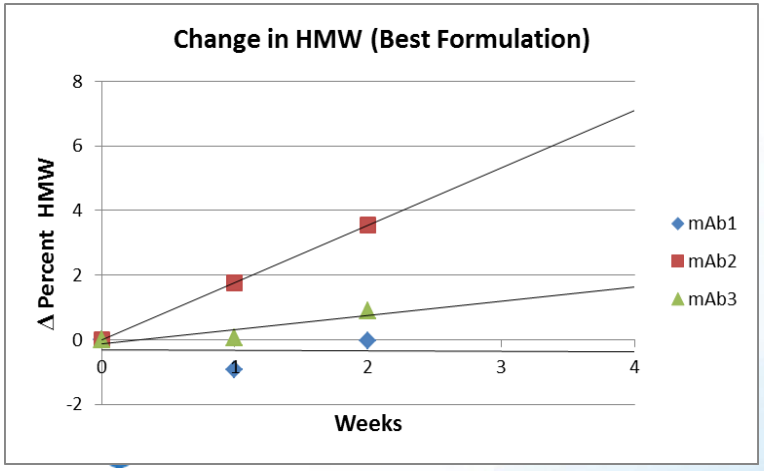


Risk assessment

Biogen

High concentration excipient screen



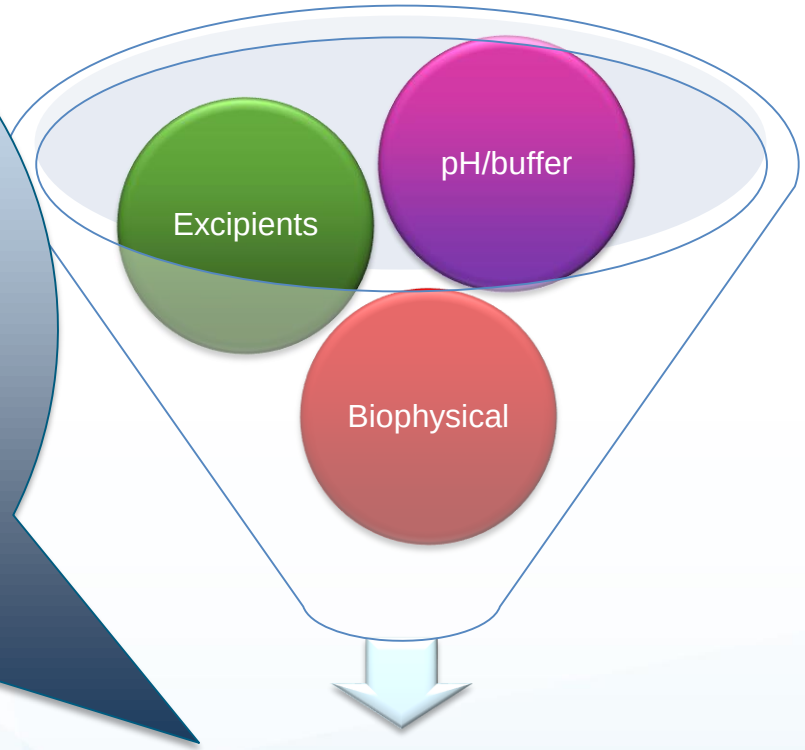


- High levels of aggregation and formation of acidic isoforms in mAb 2
- mAb 1 and 3 perform best under accelerated conditions
- mAb1 behaved well in all formulations

A comprehensive look: risk assessment

Tying it all together:

- Have rules of thumb, criteria
- Look at all of the data
- Ranking
- Identify weaknesses
- Start to see formulation space



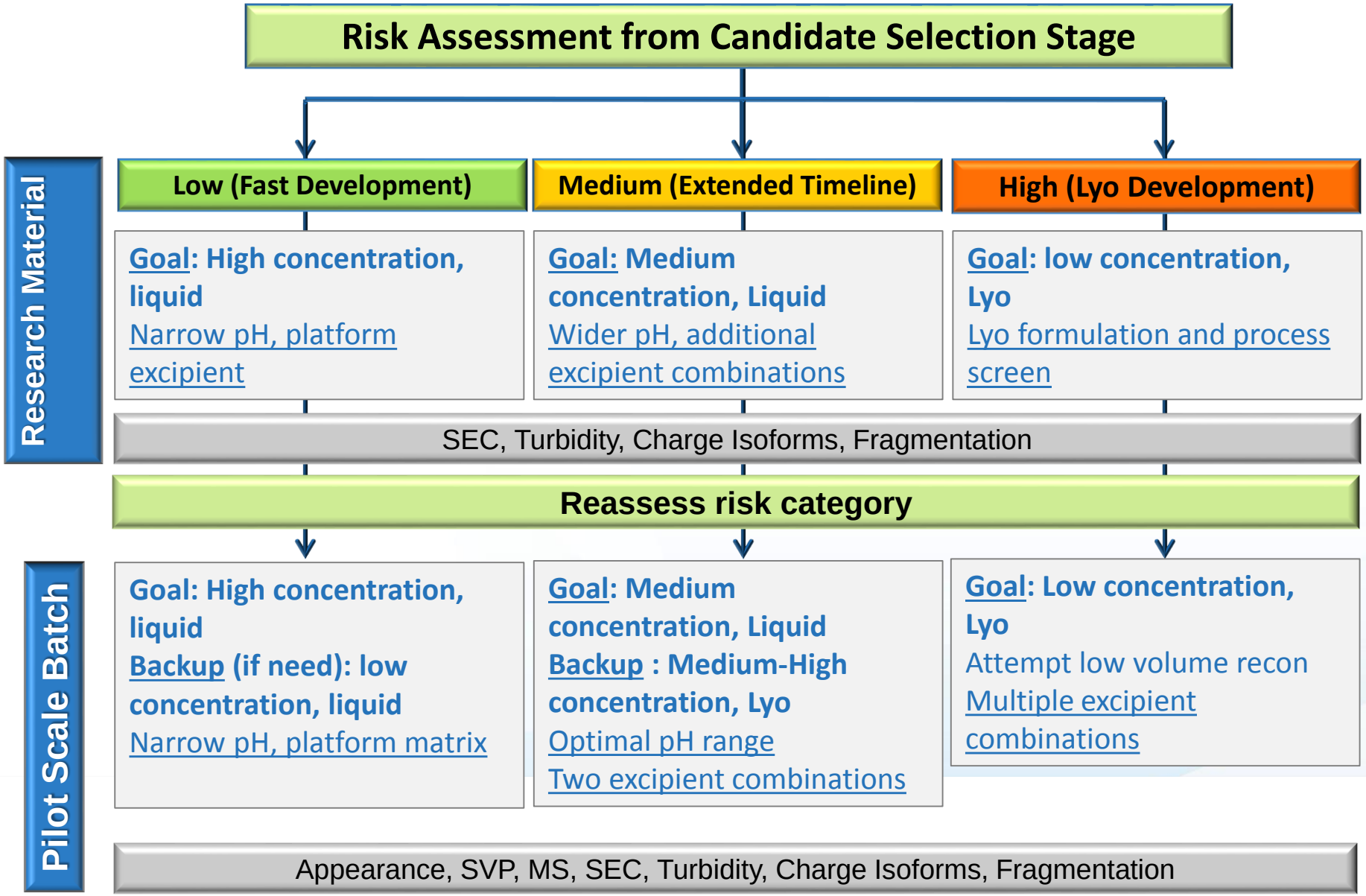
Risk assessment

Biogen

Risk assessment

Properties	Measurement	mAb1	mAb2	mAb3
Sequence Analysis	Hypothetical Deamidation, oxidation, isomerization, and clipping sites	Met in CDR	Met, isomerization, deamidation sites in CDR	None
Biophysical profile	T_{m1} Onset (Rank)	1	3	2
	HIC (Rank)	1	3	2
	K_D	Positive	Negative	Negative
	pI	>8	<8	<8
High concentration properties	PEG Solubility (Rank)	1	3	2
	Viscosity at high concentration	Low	Medium	Low
Accelerated stability	ΔHMW after 4w 40 °C	< 3%	> 5 %	< 3%
	Δdegradation after 4w 40 °C	0%	0%	0%
Post-translational modification	ΔAcidic Species 4w °C	< 15%	> 40%	< 15%
Low pH Hold	Change in HMW and LMW after Neutralization	No Change	Increase HMW, Increase LMW, Monomer Loss	ND
Cumulative rating : Low- Medium-High		Low	Medium-High	Low

Risk assessment informs formulation



Case Study II: From CS to FIH

mAb A was one of four screened candidates

- All showed high propensity to aggregate – assessed as medium risk

Initial stability study (research material) showed high aggregation *across the board:*

- High and low concentration
- Stressed and accelerated conditions,
- Intended storage in some formulations

The usual questions:

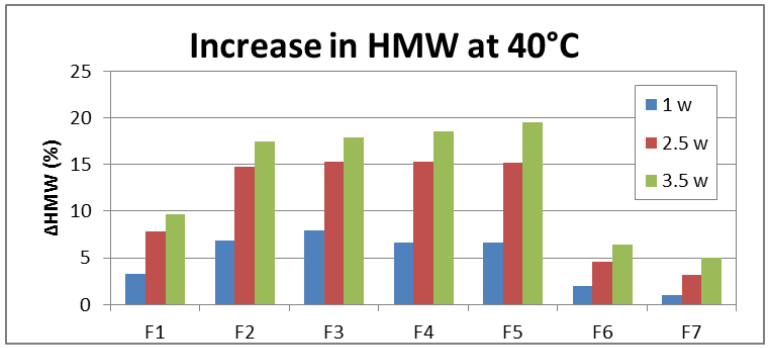
- Is this representative material?
- Are stressed/accelerated conditions predictive?
- Will the rate flatten out after ~3 months?

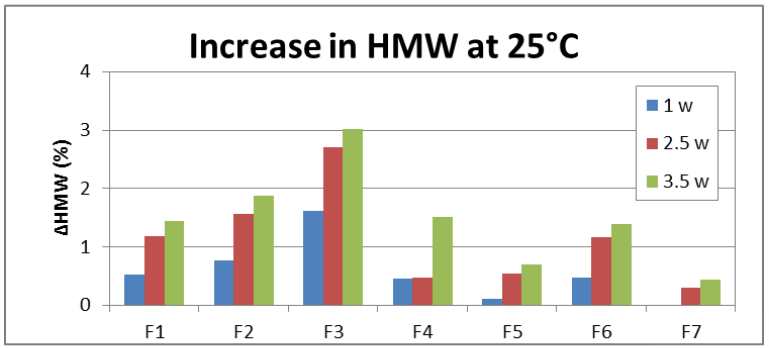
The usual problem:

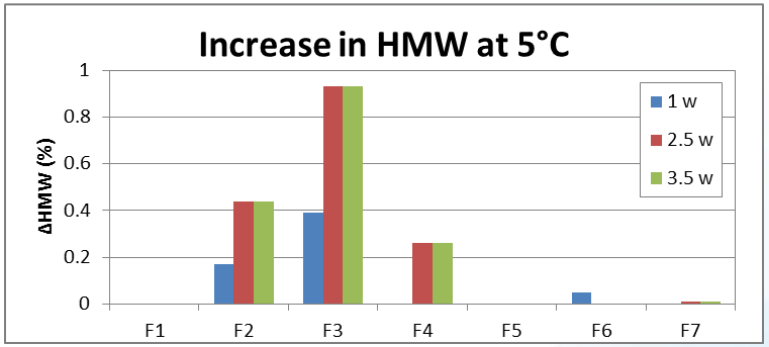
- You're holding up the program and timeline…

Biogen

New material, new formulations





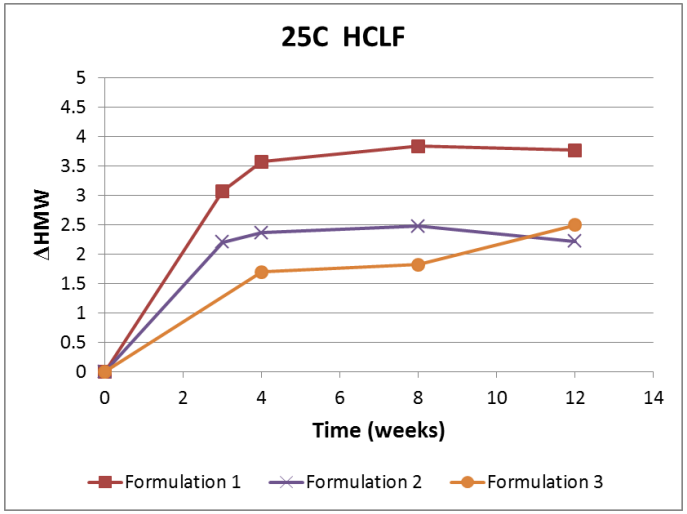


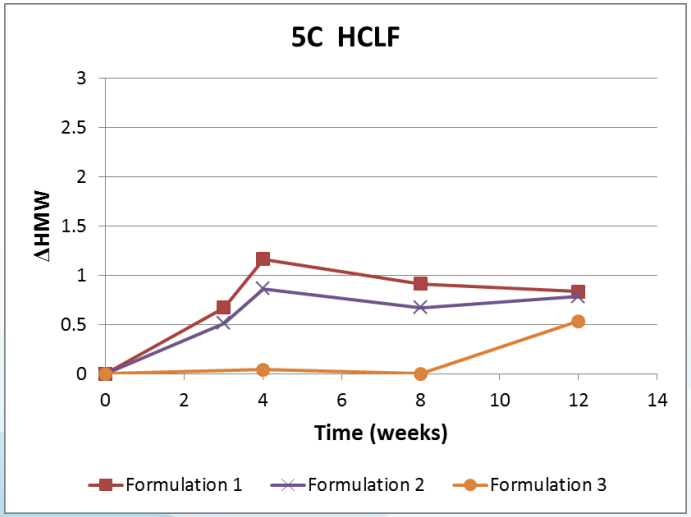
- Using pilot material
- Showing high concentration data
- Old formulations
  - Similar aggregation behaviour: research batch was representative?
- New formulations show promise
  - Especially 6 and 7
- Set up further variants for new study

Biogen

Positive results

- Results allowed for a high concentration liquid formulation for tox and FIH
- Suggests that for this protein 40°C may not predictive





Summary

- Can combine speed and being thorough
- Layer information:
  - Candidate selection (accelerated conditions)
  - Initial formulation (research material, 3 temperatures)
  - Pilot material formulation study
- Use one study to inform the next
- Combined with overlap in studies and the different batches, can be confident in nomination

Biogen

Conclusions

- LOOK EARLY: engaging with research at candidate selection stage, looking to get insights earlier
- LOOK HARD: with minimal protein can still map the major degradation pathways and get some early stability

RIGOROUS

- THE DEVIL YOU KNOW: a rigorous risk assessment, which allows appropriate resources allocation

ALLOWS FOR SPEED

- MINIMIZE THE UNEXPECTED: better understanding early on and layering of stability studies allows a de-risking of the use of different materials and short-term studies to predict long-term behavior

NOT ALL-ENCOMPASSING

Biogen