AstraZeneca

Regulatory strategy to enable enterprise-wide replacement of LAL with recombinant Cascade Reagent (rCR) technology

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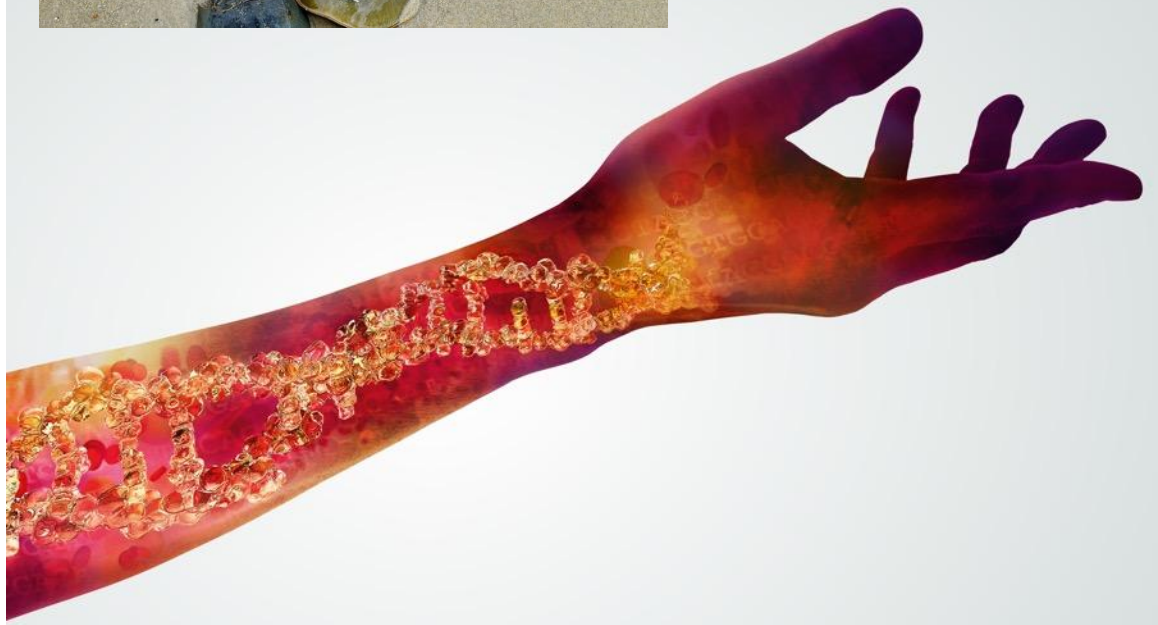

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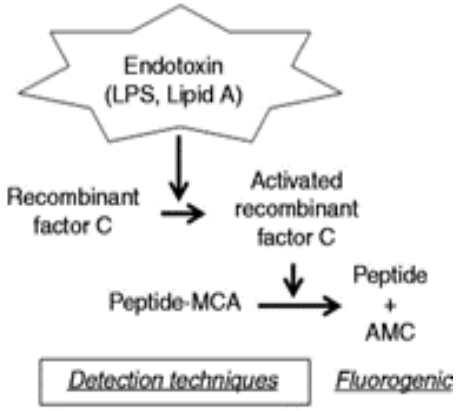
Amanda Jacobs is an employee of AstraZeneca and has stock ownership and /or stock options or interests in the company

Aim

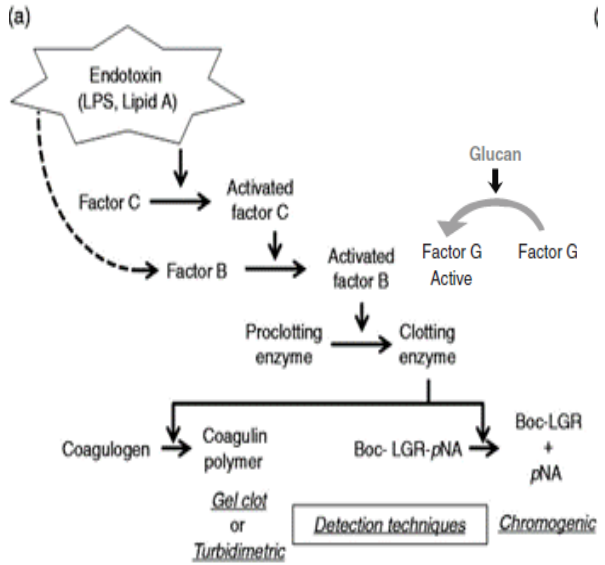
Meeting AstraZeneca and Health Authority ambitions for sustainability and reduction of the use of animal materials

Replace the use of Limulus Amebocyte Lysate (LAL) in endotoxin testing with recombinant reagents (rCR or rFC) for all of AstraZeneca's portfolio, for Drug Substance, Drug Product and in-process testing, by 2030 in all markets.

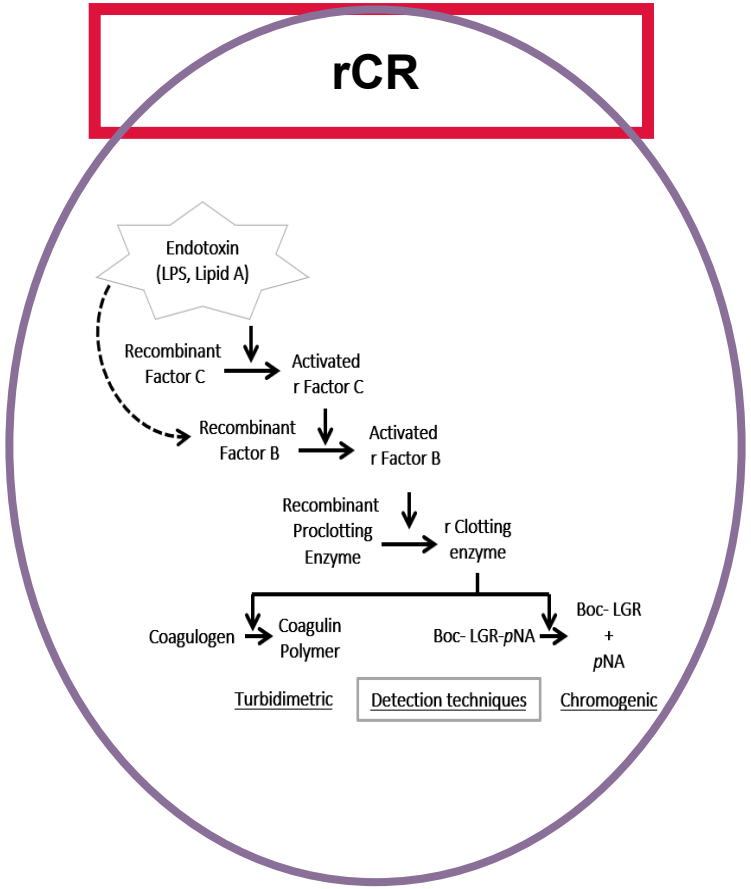
rFC



Horseshoe crab derived LAL reagent



rCR



The Challenge

Differing Regulatory Positions Globally

- **rFc:** compendial in some markets (e.g. EU) and a pharmacopeia recognised alternative in others (e.g. USA)
- **rCR:** pharmacopeia recognised alternative in some markets (e.g. USA) and a non-pharmacopeial method in others (e.g. EU)

Differing Submission Categories Globally

- **rFc:** ranges from notification low to notification major
- **rCR:** ranges from notification moderate to notification major

How do we enable a portfolio wide global change to enable site implementation and influence our contract manufacturers?

Total Scope (parenteral, vaccine and sterile)

Early clinical products	Late clinical products	Commercial products
• Pre-IND • Phase 1/2	• Registrational studies • Phase 3 • Pre-PPQ	• Commercialised • Post PPQ, MAA in-progress

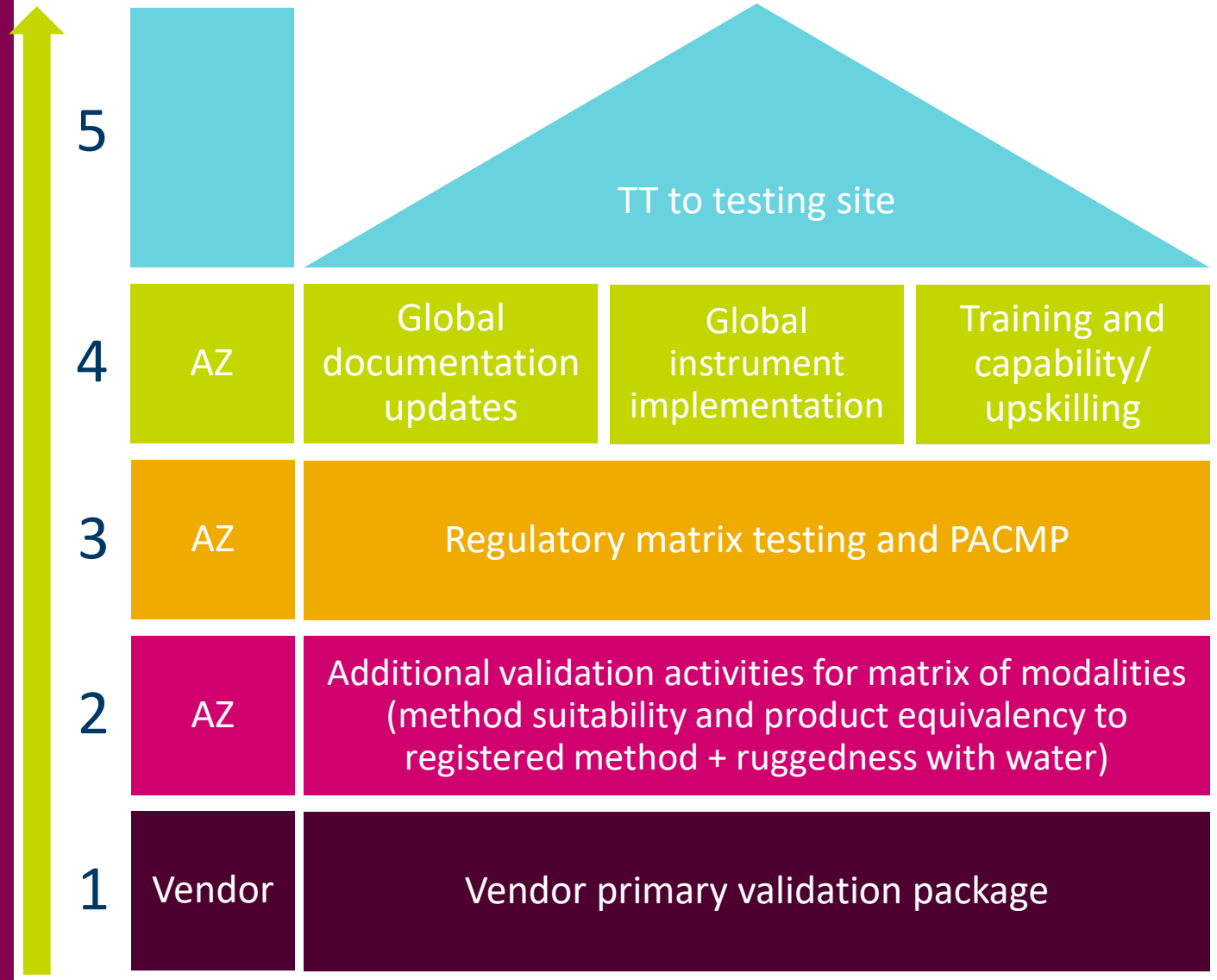
- The regulatory strategy is dependent on the stage of the product
- Focus: commercial products

The regulatory strategies to overcome the complex challenges

AZ is adopting an accelerated multi-product regulatory strategy to expedite timelines and facilitate portfolio-wide implementation leveraging:

- PACMP and product agnostic data.
  - PACMP under ICMRA pilot review
  - Data from synthetic and biological products to prove technical capability of the rCR method
  - Product specific method validation
  - Change implemented after notification moderate submission
- Reliance (implementation phase)
  - Requires a consistent validation approach
  - PACMP approval used for market consultations
  - Approval reliance (international markets) for products related to PACMP
  - Potential for cross referral to approved PACMP, without resubmission of the PACMP to a new product, and reduced submission category

House of recombinant endotoxin testing



Assessment of products

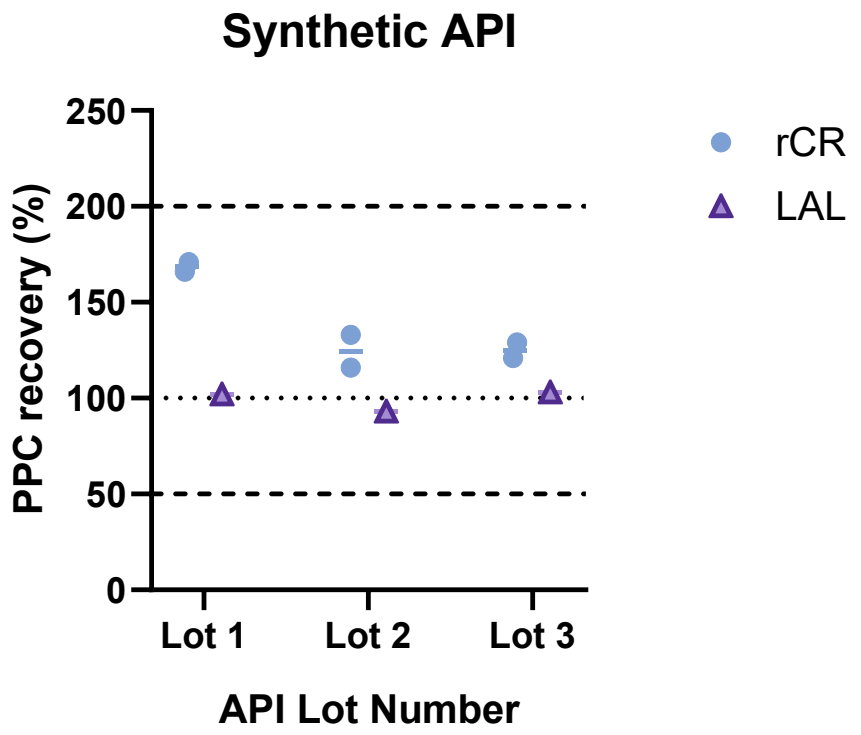
Matrix approach

- Synthetic product
- Monoclonal antibody
- Peptide
- Vaccine
- Oligonucleotide

Synthetic API

- Legacy product with registered LAL method
- Inhibition/enhancement testing performed for both reagent types.
  - Optimum dilution = **1:10,000** for both rCR and LAL.

- Endotoxin value for testing on LAL during feasibility assessment all <LOD as well.

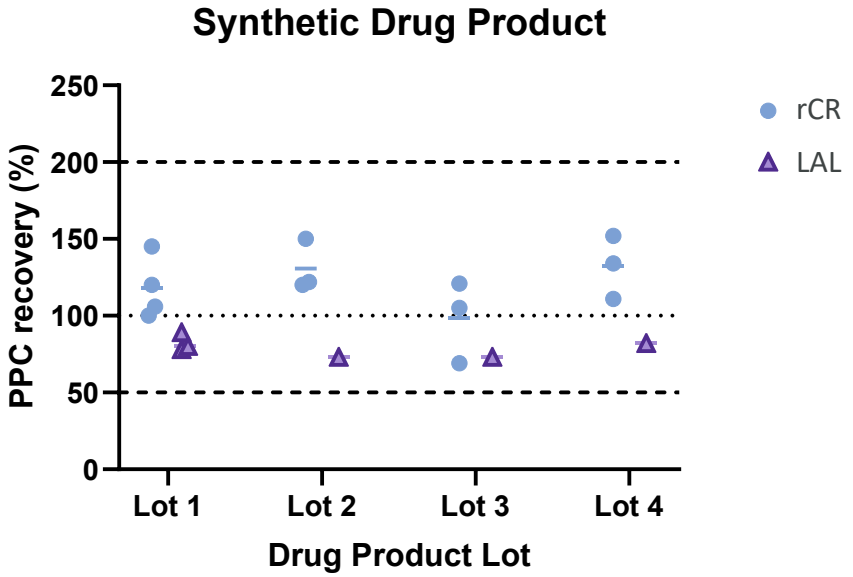


Lot	Release result	
	rCR	LAL
Lot 1	<LOD, <LOD	<LOD
Lot 2	<LOD, <LOD	<LOD
Lot 3	<LOD, <LOD	<LOD
LOD <5.00 EU/mL for both test methods		

Synthetic Drug Product

- Legacy product with registered LAL method.
- Inhibition/enhancement testing performed for both reagent types.
  - Optimum dilution = **1:300** for both rCR and LAL.

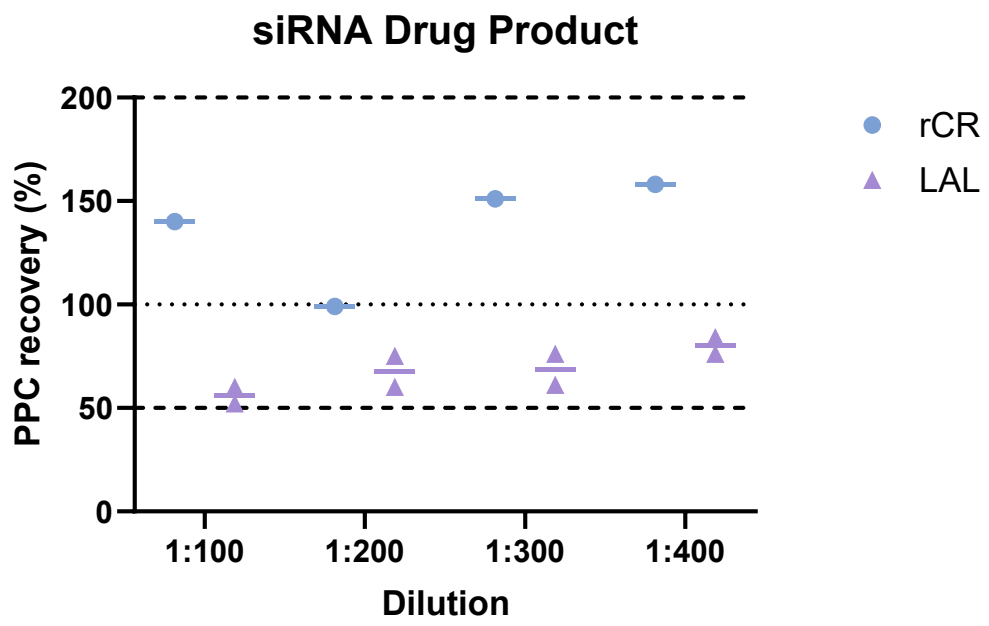
- Endotoxin value for testing on LAL during feasibility assessment all <LOD as well.

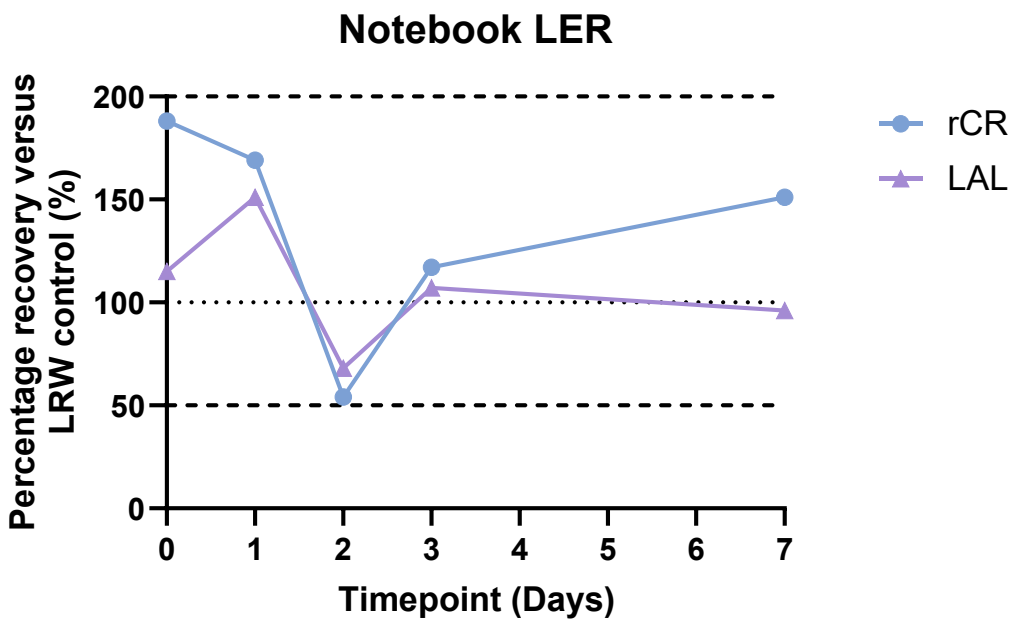


Lot	Original release result	
	rCR	LAL
Lot 1	<LOD, <LOD, <LOD, <LOD	<LOD
Lot 2	<LOD, <LOD, <LOD	<LOD
Lot 3	<LOD, <LOD, <LOD	<LOD
Lot 4	<LOD, <LOD, <LOD	<LOD
LOD different for rCR/LAL test methods (<15/<5)		

siRNA Drug Product

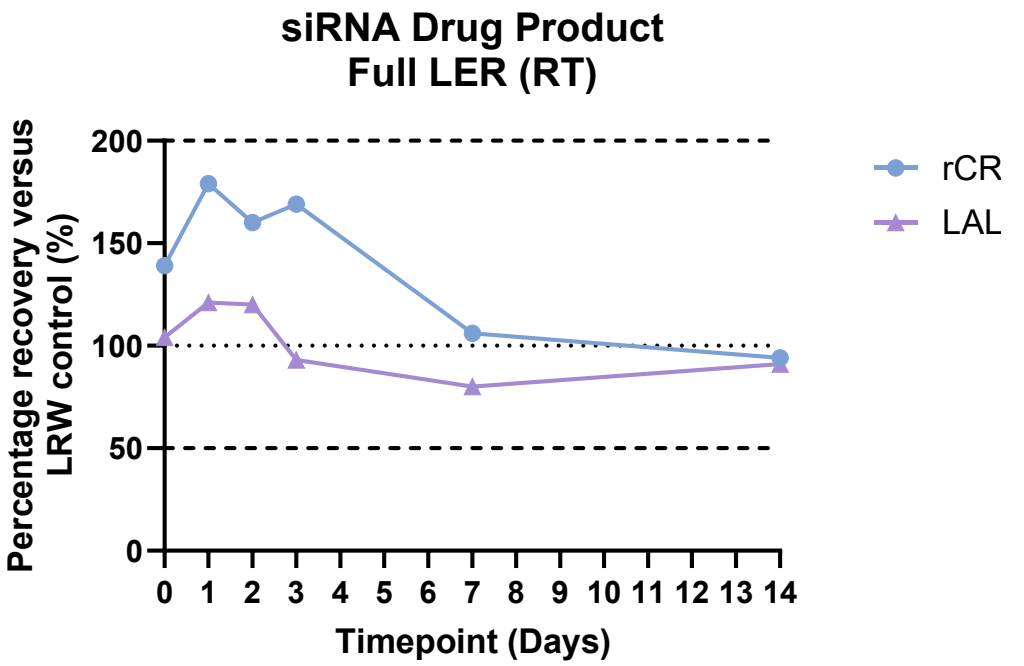
- Development project, not yet registered.
- MVD is 1:500.
  - 1:400 selected for LAL, 1:200 selected for rCR.
- Notebook LER performed at room temperature.

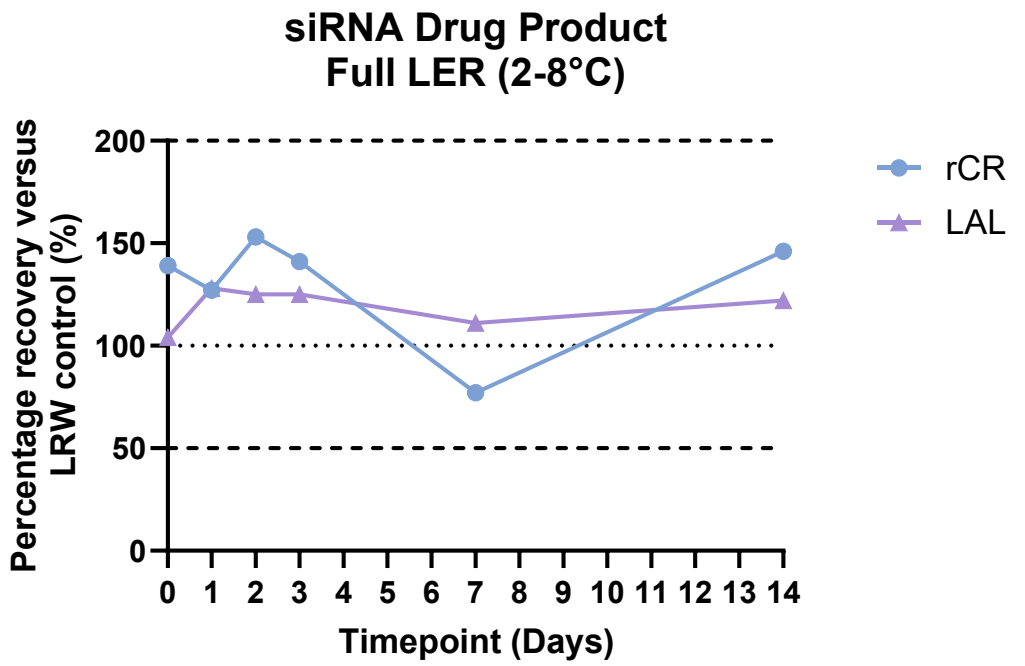




siRNA Drug Product

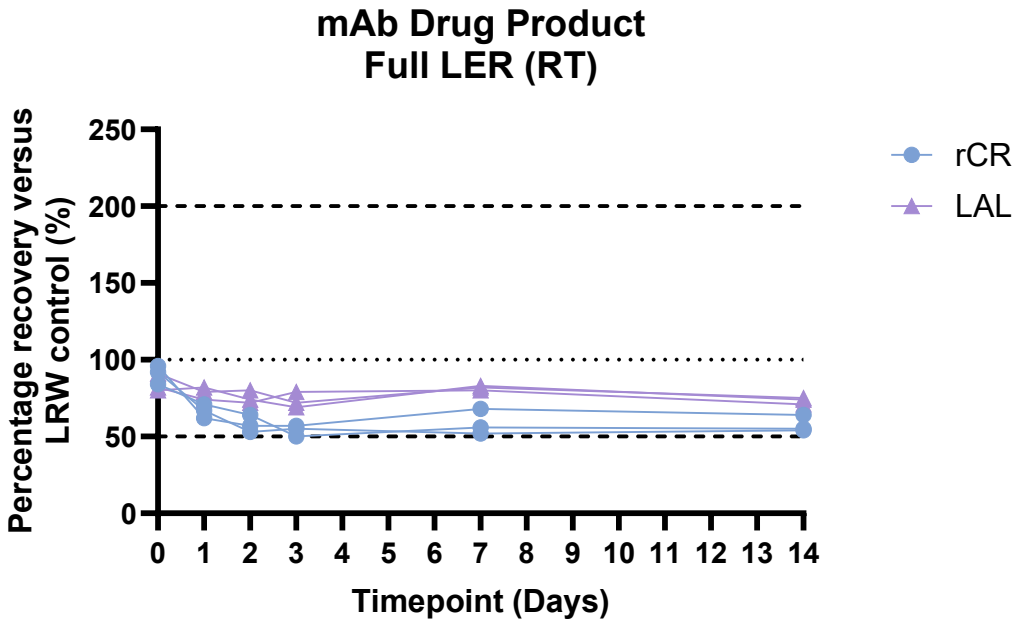
- 1:400 selected for LAL, 1:200 selected for rCR.
- Full LER performed at room temperature and 2-8°C.

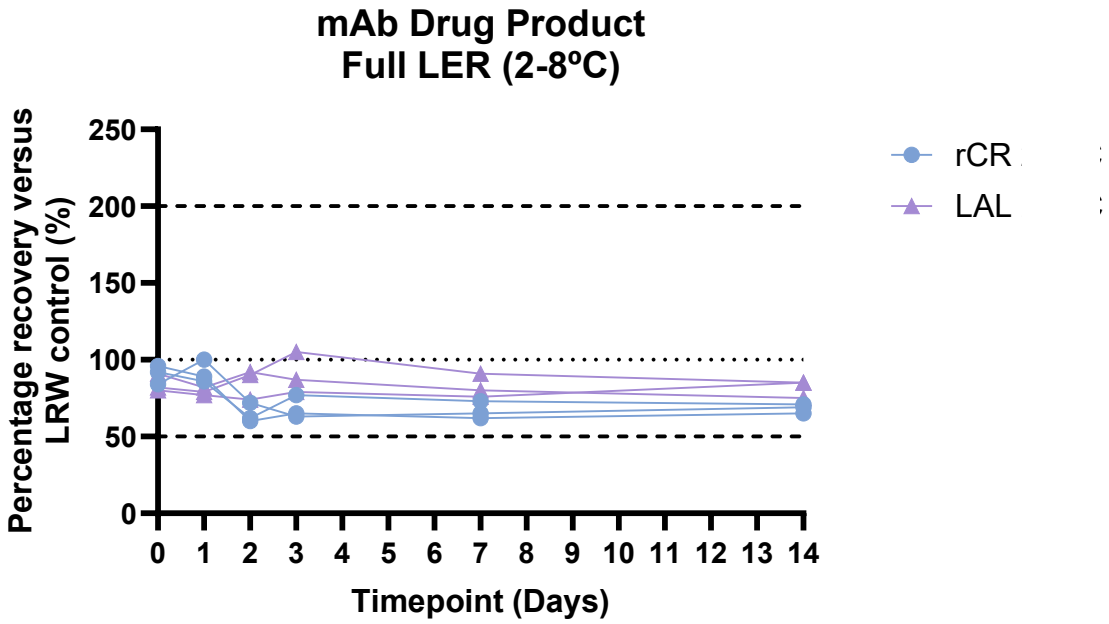




Monoclonal Antibody Drug Product

- Development project, not yet registered.
- MVD = 1:380.
  - 1:100 dilution chosen based on method suit work (data not shown).
- Full LER performed at room temperature and 2-8°C.
- Three batches included per condition.





Discussion and next steps

- Transition the entire commercial portfolio to rCR in a single, coordinated exercise
- Using a matrix of products to demonstrate suitability of synthetic reagents for endotoxin testing
- Use vendor primary validation work to support product testing
- Demonstrated suitability of rCR for endotoxin testing of synthetic API, synthetic drug product, siRNA drug product and mAb drug product
- Higher PPC recovery seen with rCR than LAL
  - Difference between statistical and practical significance

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