Recombinant methods for endotoxin testing in India

Cost and market analysis

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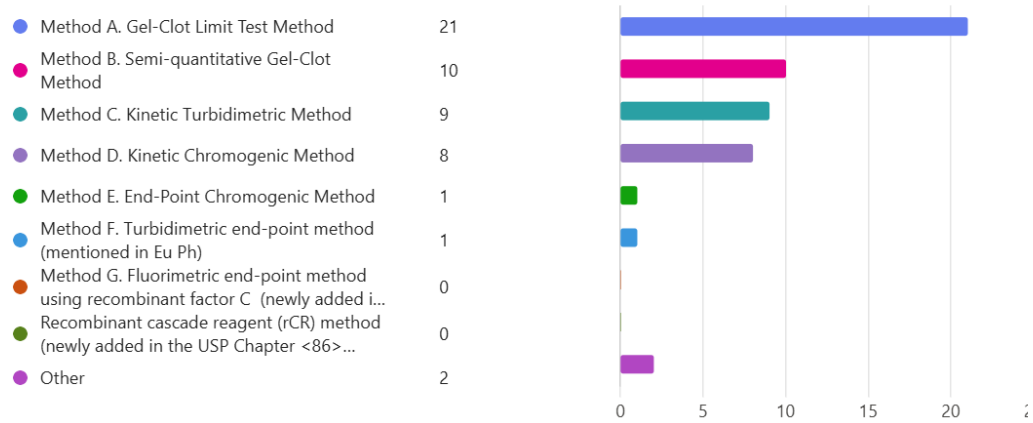
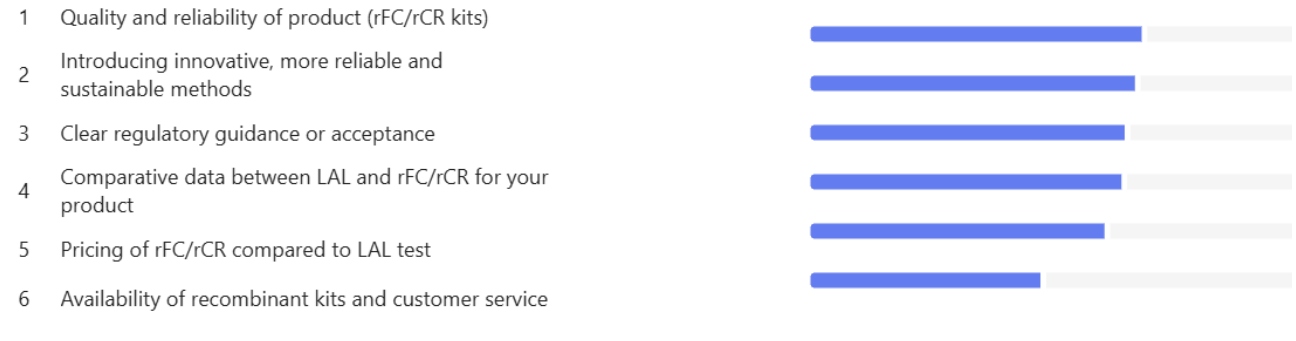
Use and awareness of recombinant endotoxin testing methods in India

We performed a survey on the use and awareness of recombinant endotoxin testing methods in India.

5. What method do you/your company use for performing BET?

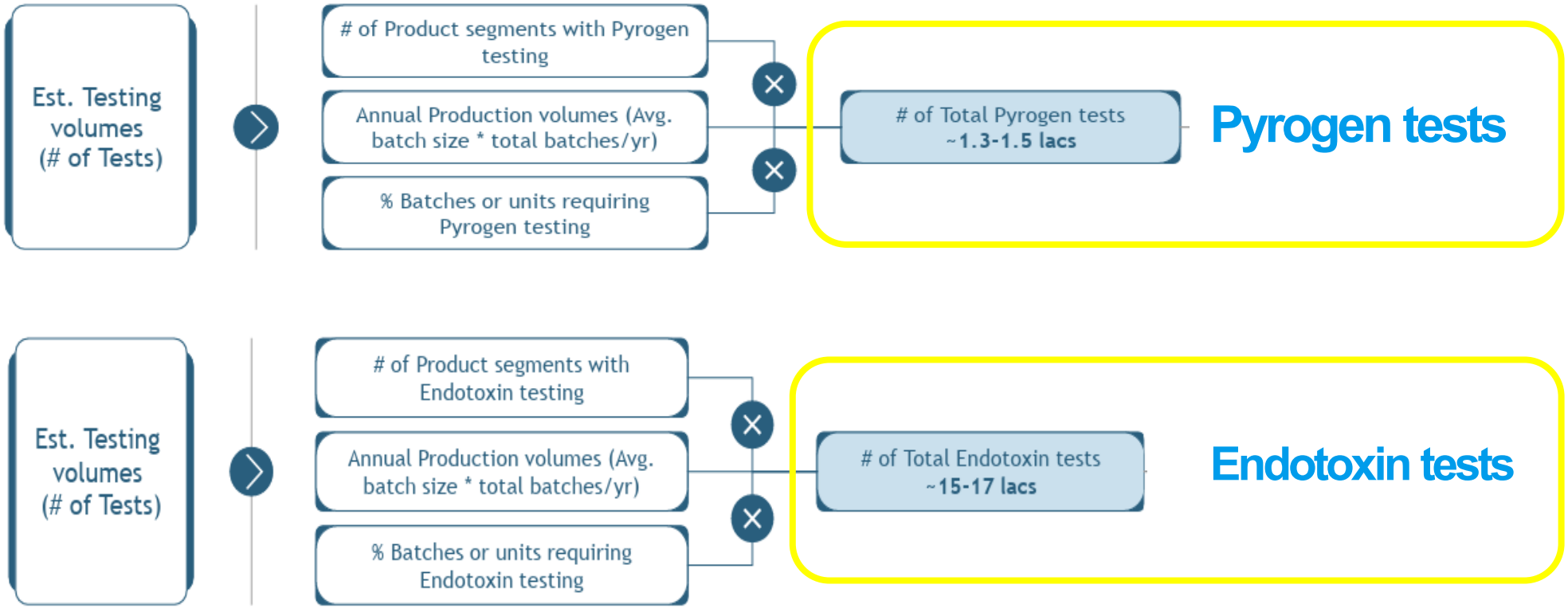


Please rate these in the order of importance for you/your company while considering a shift from LAL to recombinant reagents



Market size analysis – pyrogen and endotoxin tests in India

(Humane World, Boston Consulting Group and Dr. Reddy's)



Cost analysis – LAL vs rFC/rCR

Analysis by : BCG and Dr. Reddy's

List	LAL (in INR)		rFC (in INR)	rCR (in INR)
Cost for each sample test	500-1K		1.5K	6-7K
Cost for sample validation (one trial)	85-90K /year		~1.5 lakhs	~1.5 lakhs
Personnel cost	1K test		3-4K/test	

List	LAL (gel clot) (in INR)	LAL (kinetic method) (in INR)	rFC (in INR)	rCR (in INR)
Cost for each sample test	2-3K	6-7K	18-20K	11-13K
Cost for sample validation (one trial)	8-10K	20-25K	50-55K	20-22K

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Why did we decide to explore rFC/rCR !!!

Ethical & Sustainable Considerations:

Replacement of animal use with biotechnological production

Reproducible outcomes, Lower risk:

Consistency, Reproducibility and Reduced Risk of False Positives

Simplified Testing Procedures:

As requires fewer steps compared to LAL test

Stability and Shelf Life:

rFC tends to be more stable and has a longer shelf life compared to LAL reagents

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Factors	rFC	rCR	LAL
❑ Simple molecules	• High efficient	• High efficient	• High efficient
❑ Low endotoxin recovery (LER)	• High efficient • High recovery %	• High efficient • Achieving recovery % within acceptance criteria	• Not suitable
❑ Turbid and colored samples	• High efficient	• High efficient	• Moderately suitable
❑ **β -** glucan molecules	• High efficient • Highly specific only to endotoxin	• High efficient • Highly specific only to endotoxin	• Suitable with employment of **β -** glucan blockers
❑ Complex molecules with different functional group such as Thiol, alcohol molecules	• High efficient	• High efficient	• Not suitable
❑ Protein molecules	• High efficient	• High efficient	• Suitability is less
❑ Chelating ion molecules	• Efficient	• Efficient	• Not suitable
❑ Best case of use	• Suitable for excipients and final product release	• Suitable for excipients and Final product release	• More suitable for final release product
❑ Does it require dedicated set up?	• Yes, for uninterrupted results	• Yes, for uninterrupted results	• No
❑ Lysate sensitivity	• High	• High	• Moderate

Comparison of Impact on Cost of rFC/rCR VS LAL

	Impact	LAL	rFC/rCR
DIRECT COST	**Reagent Cost**	✓ Moderate	× Slightly higher (Kits)
	Instrument Cost	✓ Low (heating blocks)	× High (Compatible readers)
	Validation Cost	✓ Minimal (well-established)	× High (comparability & bridging studies)
	Regulatory Filing	✓ Low (widely accepted)	× Higher (additional documentation)
INDIRECT COSTS	**Risks & Sustainability Concerns**	× Dependency on horseshoe crab harvesting leads to sustainability concerns × Potential future cost escalation × **Risk of supply chain disruption** due to ecological regulations	✓ **One-time transition cost** (training, SOP updates) ✓ **Reduced long-term risk (synthetic source, no animal dependency)**
LONG-TERM ECONOMIC IMPACT	**Regulatory associated cost challenges**	× Increasing regulatory pressure for animal free alternatives × **Unsustainability may lead to cost ineffectiveness**	✓ **Lower variability and reduced batch failures -> Cost savings over time** ✓ Future-proof investment aligned with global sustainability goals

Cost Factors on Implementation of rFC/rCR VS LAL

Factors	LAL	rFC/rCR
Method Validation costs	❑ **LAL is well-established**; validation costs are lower due to standardized protocols. ❑ LAL **infrastructure is already in place**, hence, does not require any extra efforts. ❑ In the current scenario, **LAL holds a cost advantage for method validation**. However, **from a future sustainability perspective, overall costs are expected to rise as reagent production declines.** ❑ **Susceptible to false positives**: **Interference from β-glucans** may necessitate additional mitigation controls, **increasing validation workload**.	❑ **Dual Validation Burden:** Requires **comparability studies with LAL** for legacy products, doubling validation efforts. ❑ **Matrix Interference Studies**: May require additional robustness checks for product-specific interference compared to LAL. ❑ **Equipment & Consumables**: rFC/rCR kits and specialized readers can increase initial investment. ❑ **Time & Labor**: rFC/rCR validation timelines are longer due to regulatory scrutiny and lack of historical data.
Regulatory Acceptance costs	❑ **Established compendial method**: **But environmental concerns are intensifying regulatory scrutiny.** ❑ **Not a part of 21 CFR as it's a qualitative test only**.	❑ **Growing compendial acceptance**: • **Europe**: Included in European Pharmacopoeia monograph. • **China**: Recognized in Chinese Pharmacopoeia. • **USA**: USP Chapter <86> (official as of May 2025) transitions rFC from "alternative" to compendial. • **FDA**: Officially allows rFC as acceptable endotoxin test. ❑ **Reduced regulatory burden**: With compendial status, regulatory filings rely on present validation data rather than submitting alternative justification—sparing time and overhead. ❑ **21 CFR compliant**

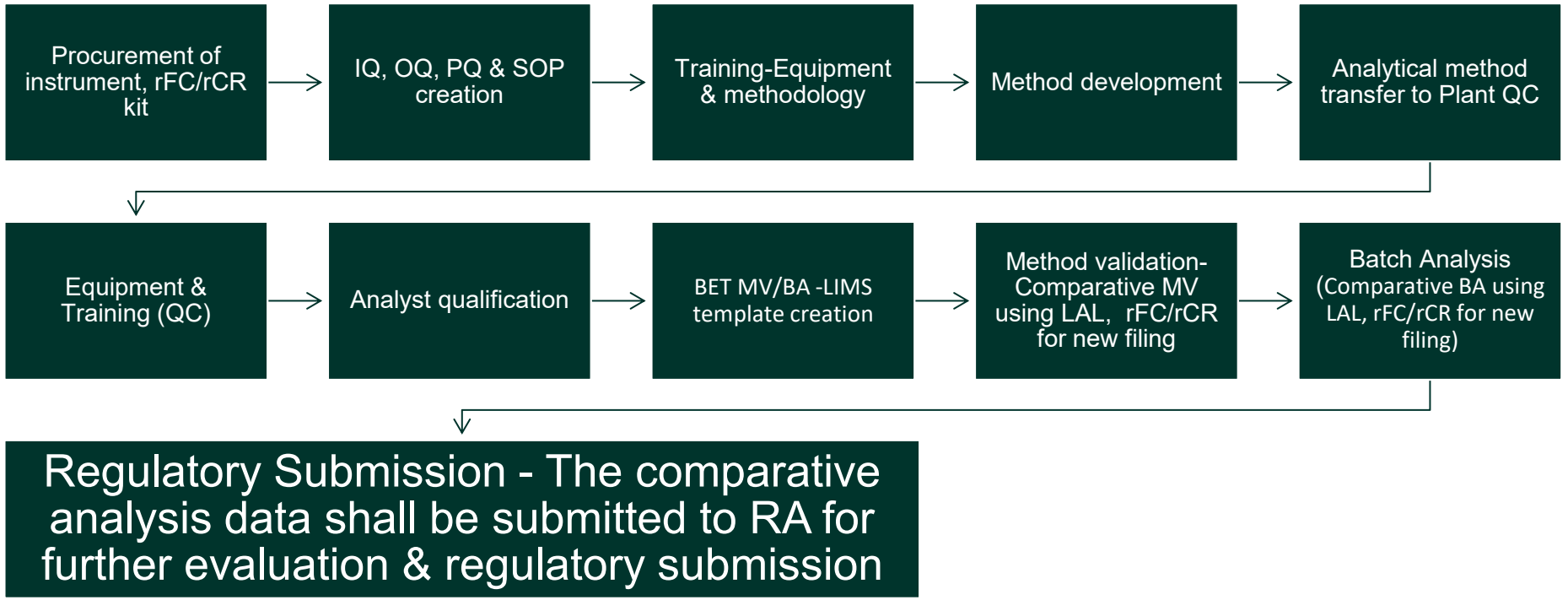
PROS and CONS w.r.t Training

LAL	rFC
❑ **PROS** • **Established method:** Most QC staff already familiar; minimal retraining for experienced teams. • **Regulatory comfort:** Long-standing acceptance reduces need for extra compliance training. ❑ **CONS** • **Higher troubleshooting burden:** Variability in reagent lots and environmental sensitivity means more advanced skills needed. • **Frequent refreshers:** Staff must stay updated on mitigation strategies for false positives and sustainability concerns.	❑ PROS • **Simpler workflow**: Single-enzyme reaction reduces complexity, making training faster and easier. • **Shorter training time**: Operators can become proficient quickly due to fewer steps and less troubleshooting. • **Consistency**: High batch-to-batch reagent uniformity minimizes variability, reducing the need for advanced troubleshooting skills. • **Eco-friendly narrative**: Training includes sustainability benefits, which can align with corporate CSR goals. ❑ CONS • **New technology adoption**: Staff may need mindset shift from traditional LAL methods. • **Limited historical familiarity**: Trainers and auditors may require additional orientation on regulatory acceptance and compendial status. • **Initial learning curve for data interpretation**: Slight differences in assay readouts compared to LAL may require extra explanation.

Economic Implications of Adopting rFC

Short-Term (Set-up & Transition)	Long-Term (Sustainability & Scalability)
❑ **Initial Capital Investment**: Higher upfront costs for infrastructure, validation, and regulatory compliance. ❑ **Training & Workforce Development**: Expenses for skill upgradation and process adaptation. ❑ **Supply Chain Adjustment**: Transition from horseshoe crab-derived reagents to recombinant systems requires vendor realignment. ❑ **Regulatory Approval Costs**: Additional expenditure for documentation and global harmonization.	❑ **Cost Efficiency**: Reduced dependency on natural resources lowers procurement and conservation costs. ❑ **Predictable Supply Chain**: Eliminates seasonal and ecological variability, ensuring stable pricing. ❑ **Scalability**: Recombinant production supports high-volume manufacturing without ecological constraints. ❑ **Sustainability Advantage**: Aligns with global biodiversity conservation goals, reducing long-term compliance risks. ❑ **Market Competitiveness**: Early adoption positions companies as leaders in sustainable biopharma practices.

Roadmap for transitioning from LAL to recombinant methods (DRL strategy)



Technology transfer from development Labs to QC Labs

Conclusion

- ✓ Based on our experience, rFC/rCR technology demonstrates superior effectiveness and sensitivity compared LAL for endotoxin recovery.
- ✓ Although the current cost is relatively high due to limited production and consumption, it is expected to decrease as demand and manufacturing scale increase.
- ✓ Considering the quality and reliability of endotoxin testing, as well as its status as an animal-free, sustainable, and regulatory-compliant solution for modern QC needs, we strongly recommend the further adoption of rFC/rCR technology.

Economic Implications of Adopting rFC/rCR