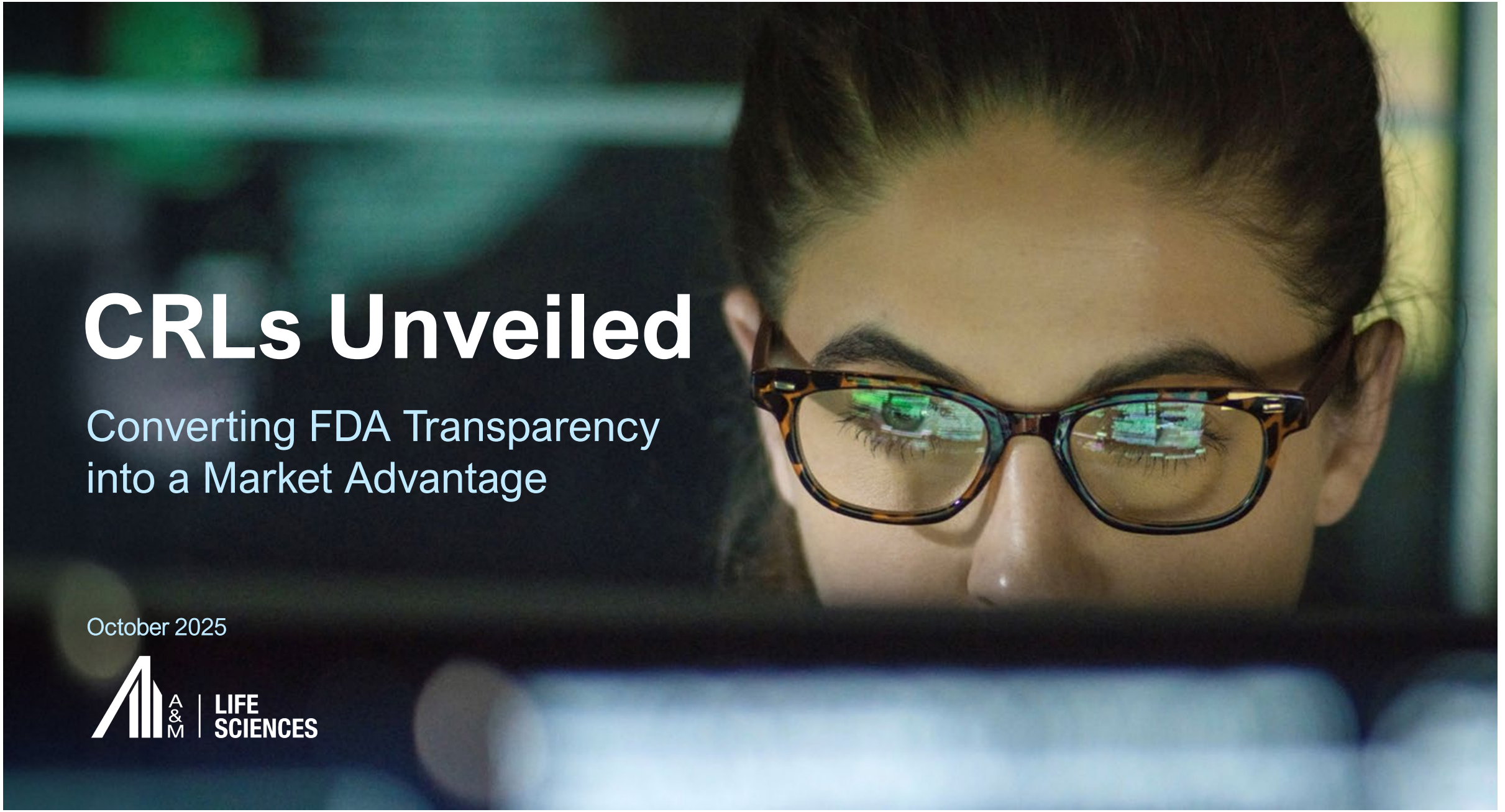


CRLs Unveiled

Converting FDA Transparency into a Market Advantage

October 2025

A&M | LIFE SCIENCES

FDA’s recent disclosure offers a glimpse into the regulatory black box

The Food Drug Administration (FDA) recently gave the industry a rare peek behind the curtain by releasing 200 Complete Response Letters (CRLs). While it's a small and specific sample, these letters offer an unprecedented look at the regulatory "why" behind the "no”. For the first time, leadership teams have a rare view of the patterns and trends that shape the FDA's decisions.

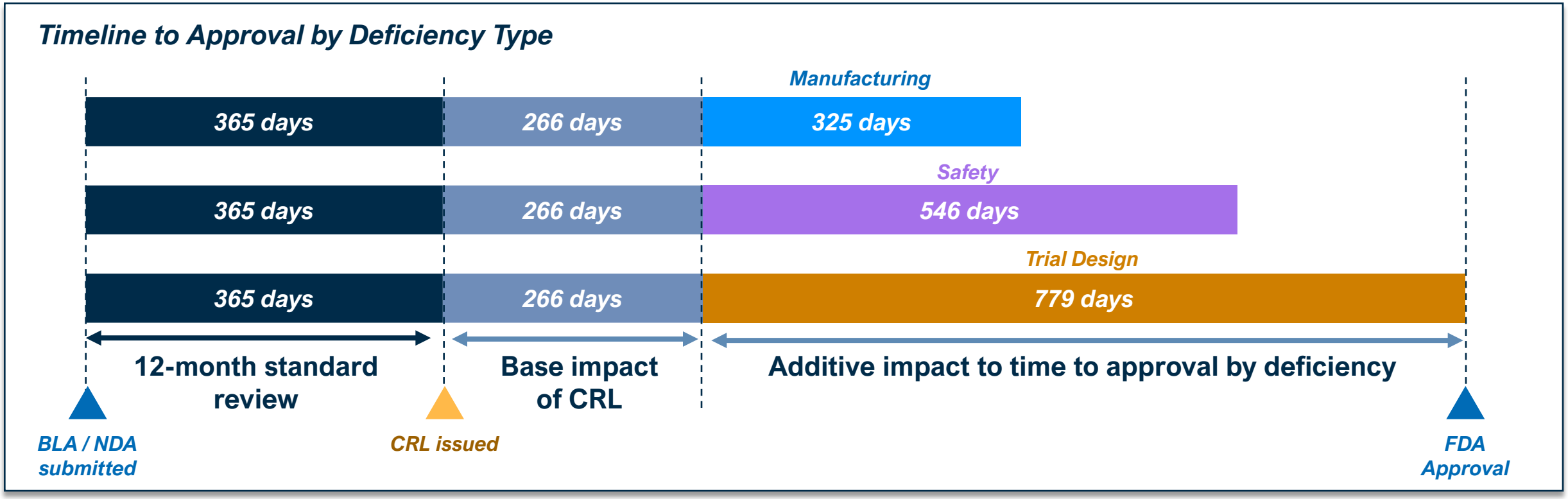
This information is no longer locked away; it’s a new opportunity for executives to challenge assumptions, strengthen governance, and anticipate preventable setbacks. At a time when regulatory risk directly impacts valuation, capital access, and leadership credibility, these insights are invaluable for smarter boardroom decisions.

FDA’s release of 200 CRLs moves regulatory risk from the back room to the boardroom. Every leadership team is now on display

CRLs significantly delay approval timelines

CRL trends – timeline to approval

Products with a CRL typically face approval timelines **approximately twice** the standard 12-month review, and **certain deficiency types can prolong the process even more**



*If a CRL is issued, a product will average 631 days from submission to approval ($p < 0.001$). Certain deficiencies can extend approval timelines even further: manufacturing ≈325 days ($p = 0.022$), safety ≈546 days ($p < 0.001$), and trial design ≈779 days ($p = 0.001$); Source: FDA CRL data, A&M analysis

Calculated risk is unavoidable in drug development, but avoidable risks are leadership choice

Calculated risks

- Unavoidable risks are the cost of innovation
- Only approximately 10% of drugs in clinical development receive FDA approval; some failure is inherent to the business model and quantifiable in Probability of Technical and Regulatory Success (PTRS) analysis
- Calculated risks such as missed endpoints, biomarker challenges, or requests for additional data can be anticipated and incorporated into strategic plans and financial models

Example

Submitting without all secondary endpoints met represents a deliberate, quantified risk trade-off

Avoidable risks

- Most CRLs are triggered by avoidable failures, not scientific uncertainty. These include manufacturing, CMC, and safety failures.
- These failures often stem from incomplete CMC data, limited engagement with the FDA, misinterpreted guidance, or unaddressed safety signals.
- PTRS analysis does not account for avoidable risks, and resulting CRLs can create unforeseen impact on SMIDs

Example

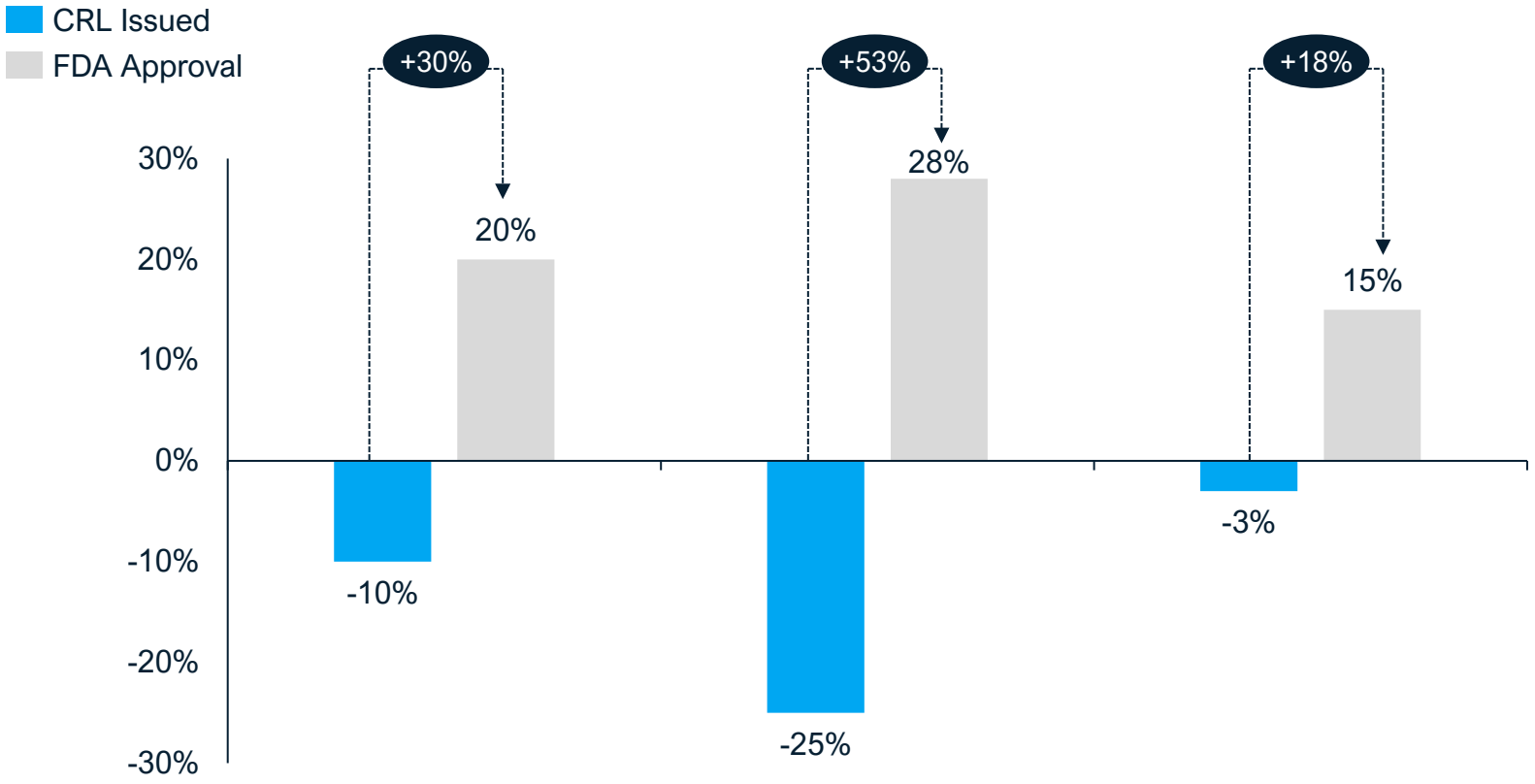
Choosing a lower-tier CRO to conserve cash can lead to a CRL, delays, and new capital needs

While capital trade-offs are inevitable, closing avoidable risk gaps improves approval odds and limits exposure to valuation and cash pressures

Sources: Patent PC

The value at risk from a CRL is substantial

CRL impact on market-cap among public companies (N=70)



Overall

Strong market rebound is possible if corrective measures are implemented properly

SMIDs

Highlights the substantial impact CRLs have on investor confidence in SMIDs

Big Pharma

Underscores how large portfolios can help cushion the CRL impact or ease investor concerns

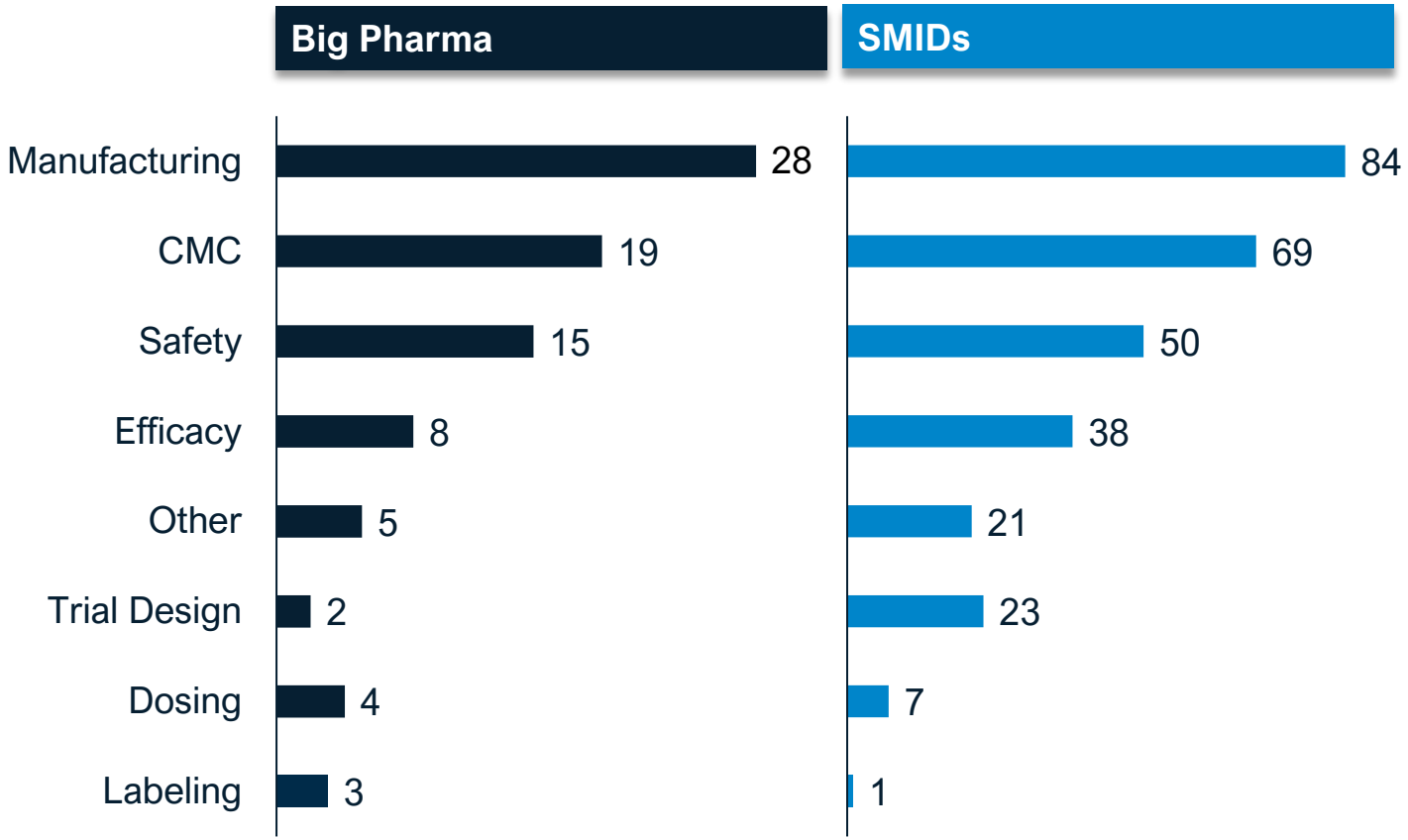
Analysis was completed with publicly available market cap data; market data as of 31-Jul-2025 extrapolated from Yahoo Finance; Large pharma N = 42, SMIDs = 28; SMIDs market cap <$10B, Big Pharma market cap >$10B

CRLs pose a greater risk to SMIDs…

- **For SMIDs, a single CRL triggers an average 25% drop in market cap**, meaning ability to raise capital becomes more challenging
- **Even for Big Pharma, a CRL erodes value**, but SMIDs face exponentially bigger swings
- **Market recovery for SMIDs is possible**, but only after re-approval and successful remediation, with a typical delay of over 1.7 years per CRL
- Approval delays aren't theoretical. **CRLs can double time-to-market and increase total costs and the risk** of strategic derailment
- The **price of a CRL is paid in enterprise value, pipeline momentum, and leadership reputation**

The anatomy of failure and what triggers a CRL

Top reasons for CRL issued, no. of CRLs issued 194*



Most often these CRLs are avoidable…

- **Manufacturing, CMC, and safety failures dominate CRLs**. Most could be prevented with stronger quality systems and up-front investment
- **Recurring pain points**: inadequate site controls, data integrity breakdowns, missed GMP standards, lack of REMS or post-marketing plans
- **SMIDs are the most vulnerable: 77%** of reviewed CRLs were issued to small or private companies, often due to outsourced operations or lack of in-house expertise
- **Most failures are not technical surprises but operational lapses:** each flagged area is a call for direct C-suite supervision

**Total CRLs evaluated N = 194, FDA released 200 CRLs, analysis excluded 5 medical device and 1 duplication; SMIDs market cap <$10B, Big Pharma market cap >$10B*

Disclosure creates board and shareholder implications

The impact of a CRL extends far beyond delays

- FDA's release of CRLs gives boards and shareholders an unprecedented window into common, costly failure points and remediation pathways
- Investors, partners, and analysts gain sharper tools to scrutinize a company's controls, quality, and risk posture to ask: "How do we stack up against avoidable delay and value loss?"
- Leadership teams should now institutionalize learning from CRL patterns, using those benchmarks to guide oversight, capital deployment, and scenario planning
- The true governance risk now lies not in public embarrassment, but in the opportunity cost of failing to adapt

The triple threat to SMIDs and why leadership matters most here

Leadership is critical as the company declines in value, needs more money, and its time to market is severely delayed.

Threat 1
Value

A CRL drives an immediate approximately 25% drop in market cap for SMIDs. This undermines investor confidence and limits access to quality capital

Threat 2
Money

The dual burden of new remediation costs and a weakened valuation means recapitalizations or capital raises occur at a disadvantage, often diluting shareholders or forcing pipeline cuts

Threat 3
Time

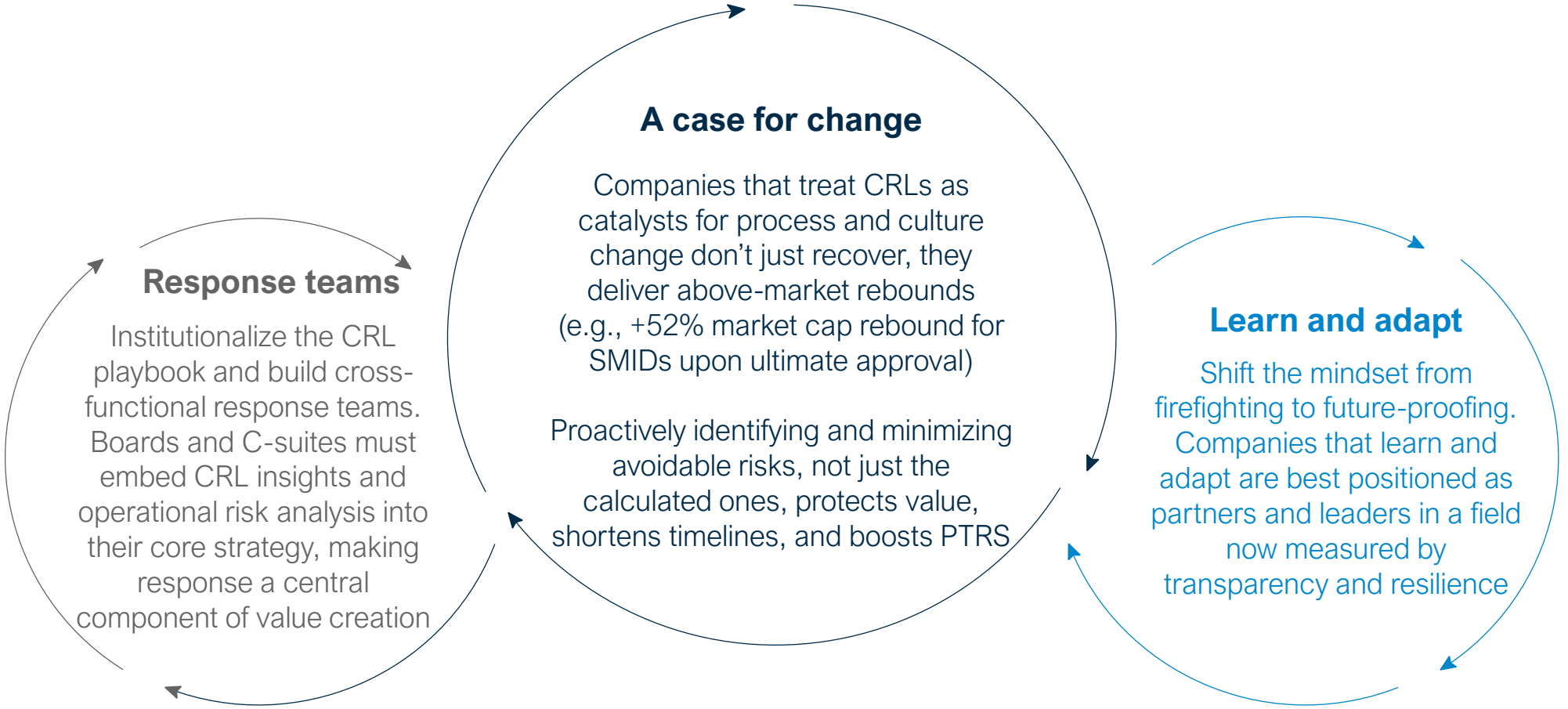
Each CRL delays approval by approximately 510 days (1.4 years), inflating cash needs and risking operational slowdowns or non-core asset sales just to survive

Leadership teams that fail to proactively manage these risks are exposed at every level

Source: FDA CRL data, A&M analysis

The opportunity to turn regulatory adversity into outperformance

The difference isn't whether a setback happens, but how leadership responds. Prepared organizations convert risk into lasting competitive advantage



The FDA's commitment to real-time release of CRLs underscores its focus on transparency
For industry leaders, embedding these learnings into organizational culture is now the imperative

What leadership teams must do now

Institutionalize CRL risk

Make CRL analysis and scenario planning a standing board agenda item for SMIDs. Treat it as a core enterprise risk, not just an operational worry

Integrate functions for a rapid response

Build playbooks and teams that combine regulatory, quality, finance, investor relations, and legal; ready to act the moment a trigger is hit

Recalibrate capital allocation

Invest preemptively in critical CMC/ manufacturing and trial design elements to avoid the high multiple of downstream remediation costs

Upgrade vendor and quality oversight

Audit partners continuously, enforce accountability, and reward quality and compliance, but do not delegate risk outside the enterprise

Leverage regulatory intelligence

Use CRL data for pipeline reviews, deal negotiations, and ongoing risk assessments, such as PTRS analysis

Boards and C-suites set the tone.

Those who act now will define industry standards, build stakeholder trust, and be positioned to outperform.

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