Workshop on Technical and Regulatory Barriers to Innovations in Pharmaceutical Manufacturing

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Regulatory Challenges to Pharmaceutical Innovation

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ABSTRACT

Pharmaceutical manufacturing innovations are ostensibly developed to improve manufacturing capabilities, i.e., increase process control, reduce costs, expedite manufacturing time, introduce flexibility and improve product quality assurance.

Decisions to pursue and implement innovations are frequently based on regulatory receptivity

> *What are the regulatory hurdles vs. incentives to introduce, adopt and continually improve innovative technology to ensure sustainability and ROI*?

To date, two significant regulatory challenges have emerged as hurdles, and in some instances, obstacles to manufacturing innovation:

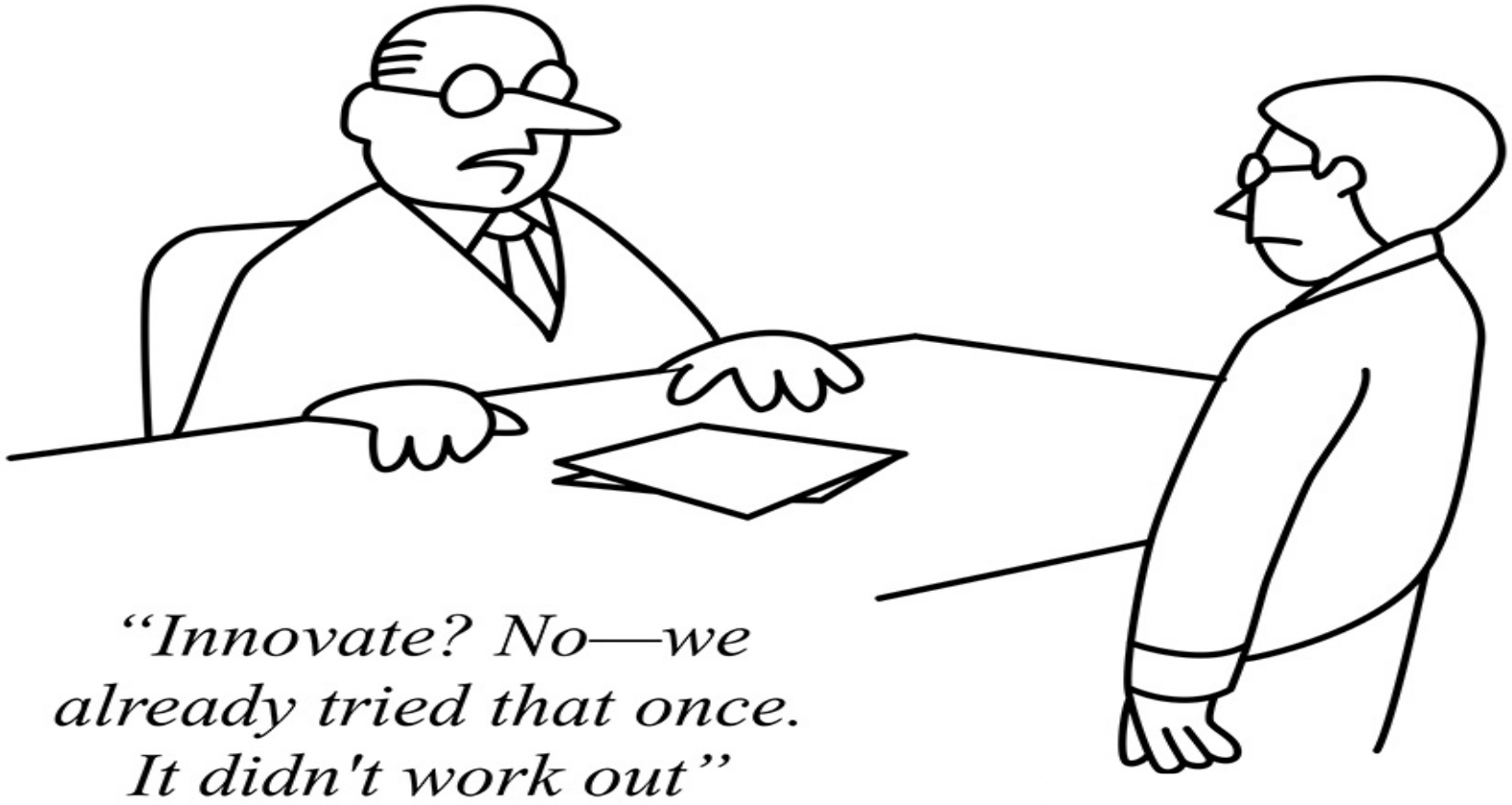
- Expanding application expectations & standards
- Global regulatory divergence

This presentation will focus on examples of each of these challenges and the specific hurdles that had to be reconciled to obtain regulatory approvals.

PHARMACEUTICAL MANUFACTURING HAS BEEN CHARACTERIZED AS . . .

- "Largely based on 1950's technology"
- Large volume of old products & non-contemporized, '*fit for purpose*' mfg. processes
- Susceptible to generating a vulnerable drug supply
- Reliant on complex supply chains – span multiple suppliers & countries
- Limited & fixed capacity that is not reliable or readily adaptable to surges in demand or supply disruptions
- Over-regulated - inflexible, inconsistent & divergent regulatory requirements & oversight

HAS INDUSTRY BEEN CONDITIONED TO REMAIN ENTRENCHED?



ANTAGONISTIC FACTORS TO INNOVATION

Desire to pursue innovation does not translate to actually achieving it*

Pharmaceutical Industry

- Unrealized ROI
- Impact to product acceleration
- Incompatibility w/corporate goals
- Global regulatory divergence
- Universality i.e., applicability to diverse portfolio
- Depreciation of existing mfg. footprint
- Risk Aversion

Regulatory Authorities

- Lack of incentives
- Punitive regulatory actions
- Increased regulatory expectations – need for mfg. experience
- Emphasis on standardization
- Risk Aversion

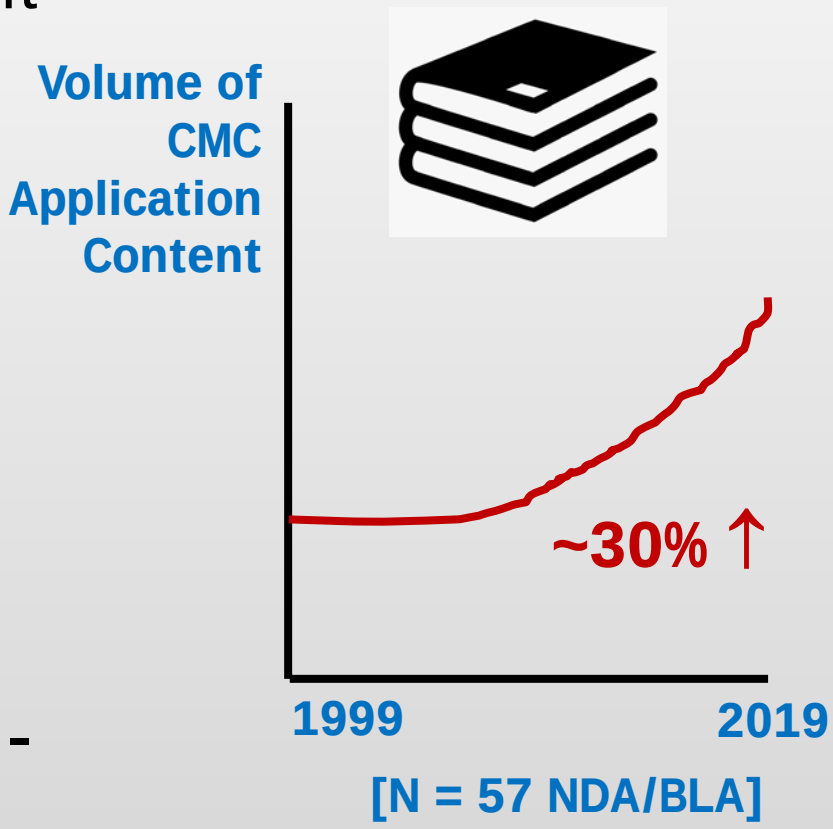
*Pistoia Alliance inaugural conference, Boston, MA, in April 2011

EXPANDING APPLICATION EXPECTATIONS & STANDARDS

Innovation or quality assurance.
It's not one or the other.
It's Both.

EXPANDING APPLICATION EXPECTATIONS & STANDARDS

- Regulatory Commitments - Detail
  - Tightened specification criteria - clinically relevant
  - Microbial controls
  - Mfg. Equipment
- *Confirmatory Content* managed in PQS under cGMP
  - Facility, utility & systems validation
  - Equipment qualification IQ/OQ/PQ
- Comparability, i.e., stability, additional tests - dissolution



WHERE TO INNOVATE?

Janet Woodcock, CDER

Frame of Reference

"Most shortages are driven by the marketplace. It really pisses me off when critics blame FDA for shortages since the FDA staff are 'saints' for their efforts to mitigate shortages. Single source products, complex supply chains, and a lack of contingency plans are the primary reasons for production disruptions.

The health and consolidation of the generic drug industry is in a "silent crisis" where consumers pay less for a life-saving drug than they would for a cup of coffee. We don't typically see shortages in the innovator drug market since they make more substantial investments in quality."

ASPIRATIONS FOR INNOVATIONS IN PHARMACEUTICAL MANUFACTURING

Pharmaceutical Industry

- Improve productivity & reduce costs
- Reduce quality issues
- Global regulatory convergence, i.e., Mutual Reliance/ Recognition
- Improve quality assurance
- Increase flexibility to accelerate
- Improve regulatory collaboration & reduce punitive oversight
- Introduce incentives to innovate old & Gx products
- Automate

Regulatory Authorities

- Resolve quality issues
- Improve quality assurance
- Establish quality mfg. maturity
- Focus on product reliability & sustainability
- Create agile & flexible mfg.
- Provide regional adaptable technology
- Integrate mfg. redundancy
- Leverage ICH

Patients

- Provide consistent product quality
- Reduce costs
- Improve quality assurance
- Improve convenience for administration compliance

AMENDING MISCONCEPTIONS OF QUALITY

- Expanded CMC application content does not increase product quality. It only increases the volume of regulatory maintenance.
- Specifications do not control product quality. They confirm quality. Product quality is controlled by mfg. processes (Process Parameters) & material & component quality (Material Attributes) – *Quality by Design*.
- The focus on improving *Quality* should be redirected to emphasize *Quality Assurance*.
- One size does not fit all……Innovative vs. Generic Products have different business profiles.

RTRt EXAMPLE

Abandoned RTRt for use in 7 product approvals due to maintenance costs & regulatory lifecycle burden

- Adjustments to probe sensitivity or model algorithm modifications require post approval regulatory submissions
  - Specification regulatory commitment includes both RTR & traditional methods & validation
  - Detailed description of NIR model
  - Significant level of detail, e.g., sample size, calibration, could not be managed w/in PQS under cGMP

GLOBAL REGULATORY CHALLENGES

Assessors & inspectors are not trained to see the big picture.
They are trained to be critical & find inconsistencies.
Who assesses benefit/risk?

- Experience since with innovation since 2005 suggests . . .
  - Agreements in principle do not reflect practice
    - ✓ Inconsistent adoption & implementation of ICH, i.e., Q1, Q5, Q6, Q8, Q9, Q11, Q12, M7 . .
    - ✓ Default to prescriptive rather than flexible standards, i.e., impurity limits, viral clearance, dissolution, etc.
  - Inconsistent Regulatory Expectations
    - ✓ Inspection vs. review criteria
    - ✓ Model optimization e.g., NIR
    - ✓ Mfg. scale adjustments

WHAT REGULATORS HAVE SAID . . .

"If the technology does not improve predictability of product variability it is not an innovation."

"How can I be sure the quality of the product will be the same in 15 years?"

"With new technology we have to default to the most conservative approach until you have mfg. experience"

"We can't approve a product specification that is not verified by clinical experience."

"We don't have enough experience to reduce the regulatory requirements for this innovation."

"Tighten specification limits until there is sufficient batch experience to justify the proposed ranges."

"Why can't the industry achieve 6 sigma?"

"Process modeling must be validated by manufacturing experience at scale."

GLOBAL REGULATORY BARRIERS TO INNOVATION

- Inadequate technical training, time constraints &/or lack of capacity
- Adherence to regulatory norms rather than scientific principles
- Different & conservative perceptions of risk
- Confusion between business vs. regulatory risks – Focus on how vs. what industry should do to reconcile innovation challenges*

*FDA Critical Path Initiative: 'Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products', March 2004. 'The European Medicines Agency Road Map to 2010 – Preparing the Ground for the Future', (promised "to stimulate innovation, research and development in the European Union (EU). WHO's 'Priority Medicines for Europe and the World' which references "innovation" and "barriers to innovation" a multiplicity of times. Also in 2004, EFPIA and the EU created the Innovative Medicines Initiative, to which the European Commission's Seventh Framework Programme will contribute €1 billion and member companies of the EFPIA will provide at least another €1 billion in matching, in-kind contributions.

PCMM EXAMPLE

Regulatory Criteria

- Definition of a Batch
  - ❑ Required to file a “batch size”
  - ❑ Characterize run time (hrs) vs. volume (# kgs)
  - ❑ Justify max run time w/data
- Lot Traceability
  - ❑ Trace raw material pedigree
- Batch Uniformity
  - ❑ On-line analytics critical to demonstrate batch consistency
- Process Upsets
  - ❑ Demonstrate process perturbations are managed*

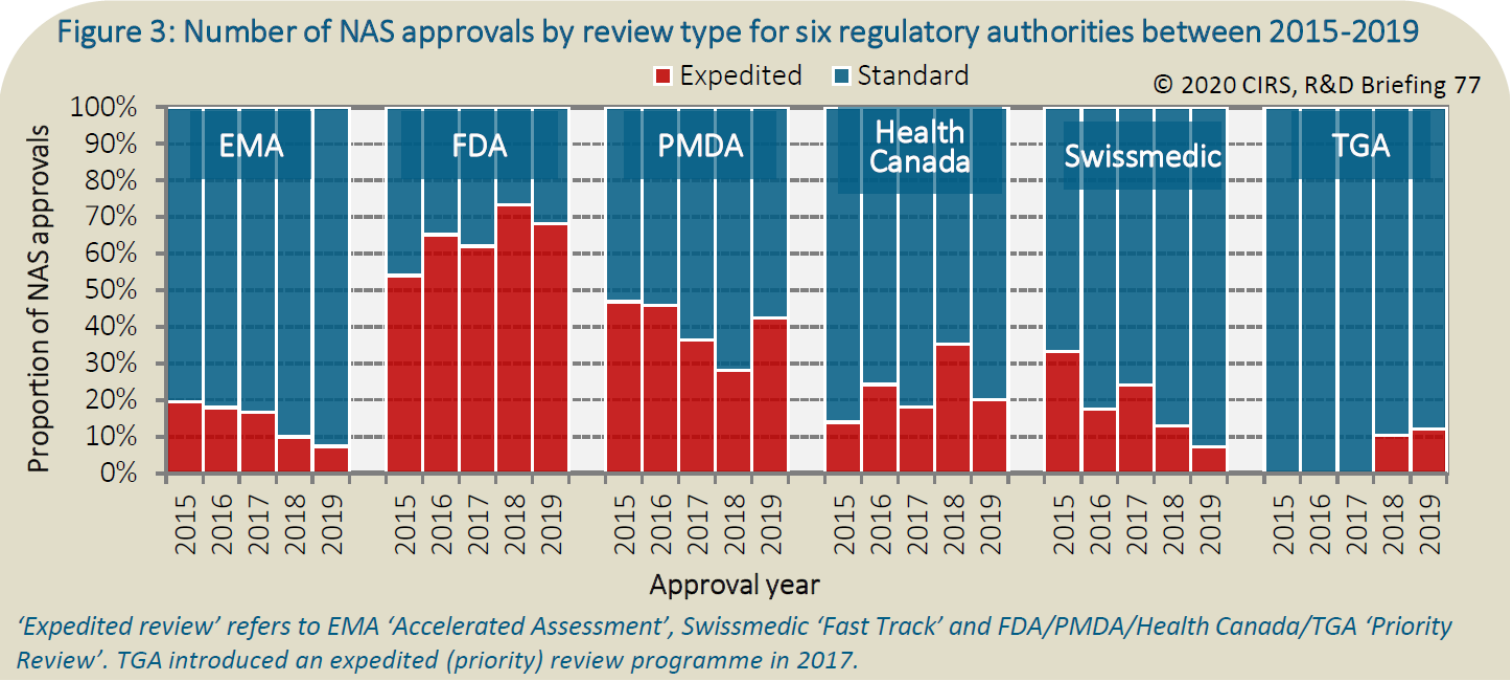
Global Challenges

- Ability to change batch size?
- APC vs. PAT Monitoring
  - ❑ NIR – # of batch & scale to qualify model
  - ❑ Model Updates?
- Lifecycle Raw Material Control
- Site Transfers
- Inspections
- Compendial Criteria
- Volume of Submission Data

*Includes disposition of material already produced, investigation steps, process restart procedures, etc.

IMPACT OF ACCELERATED & SIMULTANEOUS GLOBAL REGULATORY APPLICATIONS ON INNOVATIONS

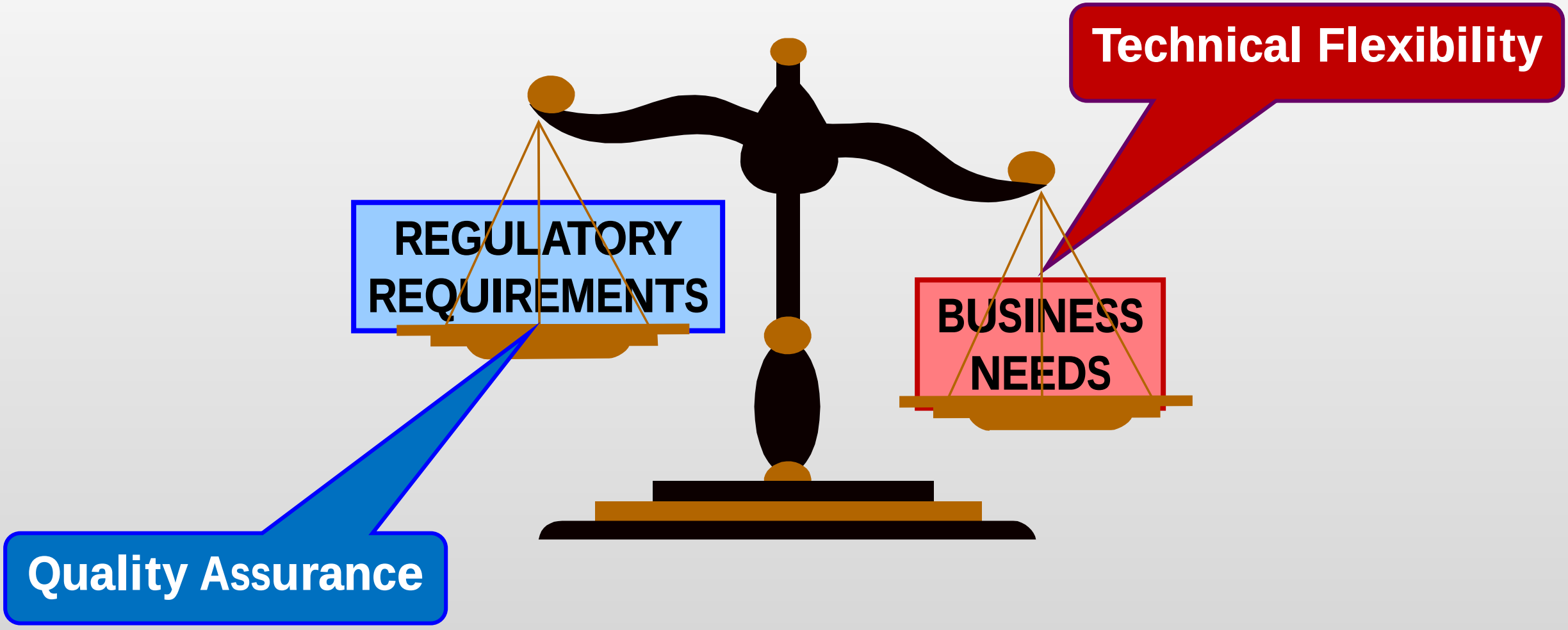
>80% of new products will proceed through accelerated regulatory pathways.



CIRS R & D Briefing 77, May 2020

Effective, expeditious regulatory approval relies on quality & relevance <u>not</u> on quantity of information in the application

AN INCENTIVE FOR INNOVATION IS REGULATORY FLEXIBILITY



SUMMARY

- Establish a new normal
  - Refocus regulatory applications on relevant scientific justifications vs. regulatory norms
  - Create incentives for industry to invest in & replace antiquated processes w/innovative technology particularly for branded & generic products
  - Accommodate innovations that improve quality assurance but permit managing business adjustments
  - Introduce a new paradigm for transparency – Cloud-based applications
- Improve global regulatory authority & industry collaboration
  - Leverage & continue to invest in ICH
  - Expand mutual reliance & recognition programs

Thank You


Change is hard. Let's just do what we always do and call it a "tradition"