U.S. FOOD & DRUG ADMINISTRATION

24th Annual GMP by the Sea

Update from FDA CDER

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Outline

- Focus on Patients
- Focus on Quality
- Leveraging Capabilities
- Opportunities at the Intersection

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Focus on Patients

Patient-Centered Approach to Product Quality

- Ensuring patients have timely access to safe and effective medicines--
  - Seeing beyond the product being manufactured—to the patient—who needs the product
    - Availability of already-approved medicines addressing vital needs
    - Development of new medicines to treat unmet needs

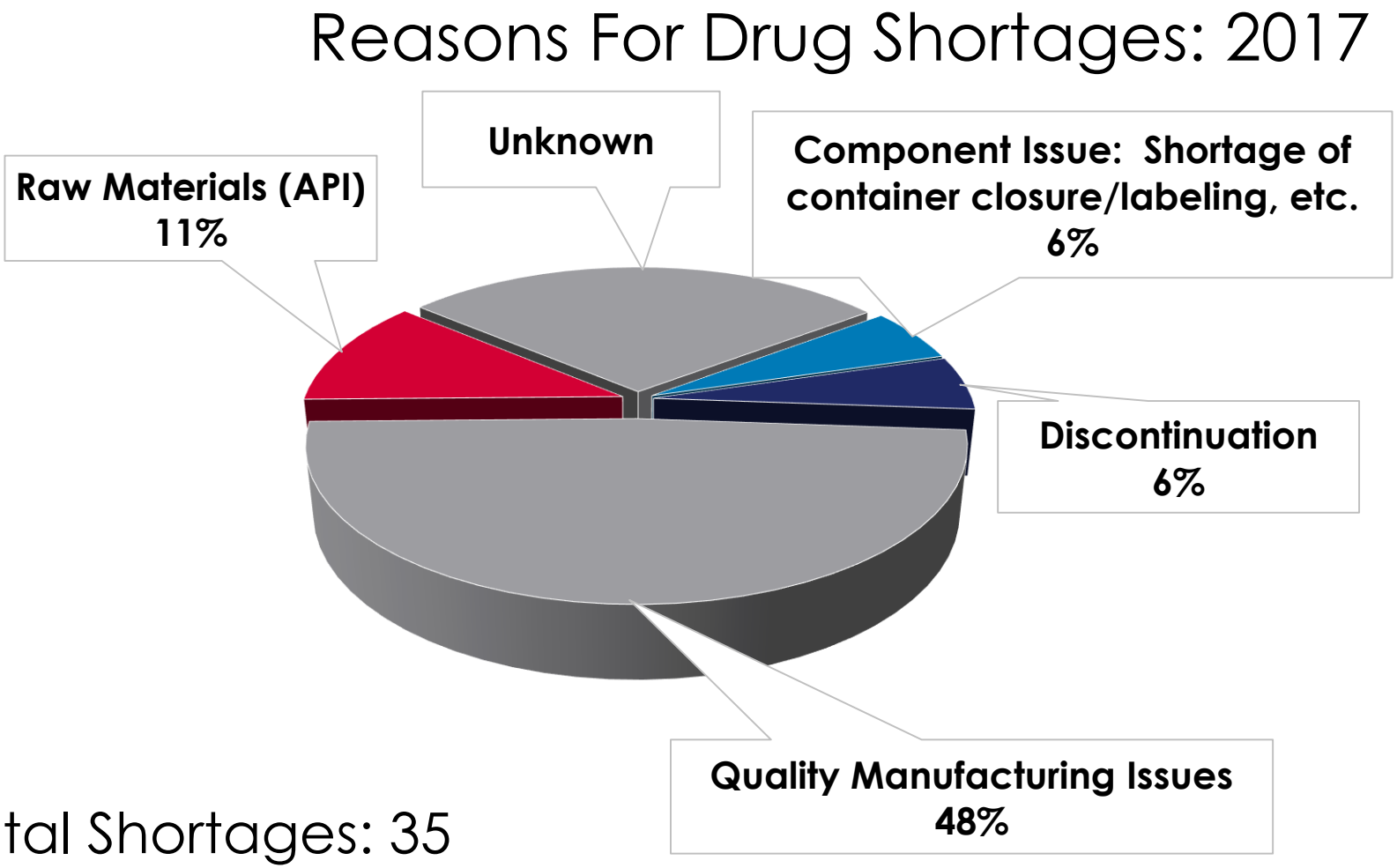
Patient-Centered Approach to Product Quality

- **Ensure availability of already-approved medicines**
  - Promote behavior that can help prevent shortages
    - Effective quality management and continuous improvement (PACs needed as facilities age; technologies evolve; suppliers change; operations need updating, etc.)
      - E.g., ICH Q12 tools and enablers can support continued improvement and modernization of manufacturing throughout the life cycle
      - Currently PACs often require prior approval from the regulatory authority of each country where product is marketed
    - Explicit regulatory attention to and recognition of effective quality management, e.g. during inspection

Learning from Drug Shortages

- A drug inspection paradigm..
  - focused only on compliance with current Good Manufacturing Practice (cGMP) regulatory requirements
  - Is not likely to succeed in shifting the drug industry's focus as needed to achieve and maintain a state of acceptable product quality to ensure clinical effectiveness and patient access to protect public health.

Most drug shortages are due to quality/manufacturing problems



Total Shortages: 35

Erwinase: a case study

- Approved to treat patients with acute lymphoblastic leukemia (ALL) in patients with allergies to E.coli-derived chemotherapy drugs
- Once a death sentence, this form of leukemia is now considered extremely treatable
- 3,100 children in the US are diagnosed each year and more than 85% go on to live a normal life
- 1 in 3 patients are allergic to the more commonly used drug, PEG-L-asparaginase

Erwinase Shortage

“Manufacturing problems leave Jazz with 'extremely limited' Erwinaze supply”

BIOPHARMDIVE Aug. 9, 2018

Dive Brief:

- *Jazz Pharmaceuticals continues to grapple with manufacturing complications that have crimped the supply and sales of its blood cancer drug, Erwinaze.*
- *Though second quarter Erwinaze revenue rose 20% year over year, Jazz leadership noted inventory is "extremely limited" due to issues at the drug's single-source provider, Porton Biopharma Limited. In March 2016, the Food and Drug Administration hit PBL with a Form 483 detailing significant violations in the way the company was manufacturing finished pharmaceuticals and active pharmaceutical ingredients.*
- *Since then, PBL has received a warning letter, another Form 483 and ruffled feathers with U.K. regulators. While the production problems have made Erwinaze vulnerable to supply disruptions, Jazz reiterated guidance this month that net 2018 sales of the drug will be between $190 million to $220 million.*

What About the Impact on Patients?

- Ava – 2 year only diagnosed with ALL in Jan 2016
- Last dose of Erwinase was given to another 7-year old boy who suffered an unexpected relapse of his leukemia
- Ava's mother called over 100 hospital pharmacies in every US state, plus a few in Canada; contacted FDA once a day; spoke with CEO of Jazz 2-4 times per day looking for a dose for Ava
- Ava missed four doses of Erwinase and was ultimately able to obtain access to the tainted batches

https://www.statnews.com/2016/10/31/cancer-drug-shortage/

Patient-Centered Approach to Product Quality

- **Facilitating development of new drugs to treat unmet needs**
  - Enable firms to innovate
    - Apply knowledge gained during commercial operations to continually improve process and product
    - Operationalize ICH Q10 expectations
    - Implement ICH Q12 tools and enablers

ICH Q10 Annex 1: Opportunities to Enhance Science & Risk-Based Approaches

Scenario	Potential Opportunity
1. Comply with GMPs	Compliance – status quo
2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g., ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk based approaches for regulatory inspections.
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).	Opportunity to: • facilitate science based pharmaceutical quality assessment; • enable innovative approaches to process validation; • establish real-time release mechanisms.
4. Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk based approaches for regulatory inspections; • facilitate science based pharmaceutical quality assessment; • optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement; • enable innovative approaches to process validation; • establish real-time release mechanisms.

Enabling Innovation and Continual Improvement

ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*

Provides framework to facilitate the management of post-approval changes in a more predictable, efficient manner.

How increased product and process knowledge can help reduce the number of regulatory submissions, using these tools and enablers:

1. Categorization of Post-Approval CMC Changes
2. Established Conditions (ECs)
3. Post-Approval Change Management Protocol (PACMP)
4. Product Lifecycle Management (PLCM)
5. Pharmaceutical Quality System (PQS) and Change Management
6. Relationship Between Regulatory Assessment and Inspection
7. Post-Approval Changes for Marketed Products

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Focus on Quality

Focus on Quality

1) Added attention to quality maturity in facility inspections
   - St. Gallen University findings on quality maturity
   - Inspecting for regulatory compliance complemented by consideration of quality maturity

2) Building quality into regulatory decision making
   - Public expects FDA to be consistent and transparent
   - FDA decision making is based on science and law; our decisions can set precedents

1) Quality Maturity in Manufacturing Facilities

St. Gallen top 10 quality maturity attributes*

1. Optimized set-up and cleaning procedures are documented as best practice process and rolled out throughout the whole plant.
2. A large percentage of equipment on the shop floor is currently under statistical process control.
3. For root cause analysis, the firm has standardized tools to get a deeper understanding of the influencing factors for problems.
4. Goals and objectives of the manufacturing unit are closely linked and consistent with corporate objectives and the site has a clear focus.
5. Manufacturers have joint improvement programs with suppliers to increase performance.
6. All potential bottleneck machines are identified and supplied with additional spare parts.
7. For product and process transfers between different units or sites, standardized procedures exist that ensure a fast, stable and complied knowledge transfer.
8. Charts showing the current performance status such as current scrap rates and current up times are posted on the shop floor and visible for everyone.
9. The firm regularly surveys customers' requirements.
10. The firm ranks its suppliers and conducts supplier qualifications and audits.

*FDA Lauds St. Gallen's Findings On 10 Metrics For Ensuring Drug Quality, *Pink Sheet*, June 15, 2018

2) Quality in Regulatory Decision Making

- Elements of knowledge management (for consistency)*
  - Capturing decisions in structured manner
  - Performing analysis of precedents
  - Engaging in public dialogue over policy
  - Use of precedents and policy in decision making
  - Use of all of the above in training

- Elements of clear decision making (for transparency)*
  - Structured inputs (data sets, flows, forms)
  - Structured assessment process
  - Formal problem identification
  - Structured decision process
  - Documentation of the above

* Janet Woodcock, MD, *The Case for Knowledge Management,* CIRS workshop, June 2019

2) Building Quality into Decision Making

- Example: Quality Assessment*
  - Aiming for an integrated team-based assessment (by ORA field investigators and CDER compliance staff) with single document
  - Have created a rigorously maintained database (*inventory*) of all facilities making drugs for the US market, where they are, what they make, their compliance record (and other factors) that input to risk-based inspection program
  - ARB/nitrosamine crisis has demonstrated the importance of this knowledge

* Janet Woodcock, MD, *The Case for Knowledge Management,* CIRS workshop, June 2019

2) Building Quality into Decision Making

- Example: Quality Assessment (cont.)*
  - Facility inventory allows CDER OPQ Office of Surveillance to prepare a "dossier" on facility prior to inspection
  - Inspection reports that focus only on deficiencies do not provide sufficient information to gauge overall state of quality /quality management in a facility
  - We need better tools, particularly as we engage in mutual reliance with other inspectorates and continue to apply a risk-based approach to oversight

* Janet Woodcock, MD, *The Case for Knowledge Management,* CIRS workshop, June 2019

New Inspection Protocol Project (NIPP)

- General principles
  - Inspections should gather analyzable data where possible--to inform on-going assessment of facility state of quality (effectiveness of quality management)
  - Develop standards to more consistently gauge state of quality maturity observed during inspection, e.g., across the 6 systems+
  - Develop a data-rich abbreviated inspection format and more structured, standardized inspection report.
    - More readily accessible, interpretable, and analyzable post-inspection, to maximize downstream use to inform FDA (and potentially other regulators)

+ Quality; materials; production; facilities and equipment; packaging and labeling; and laboratory control

New Inspection Protocol Project (NIPP)

- FDA (ORA and CDER) are working to develop this new inspection and reporting paradigm to better assess and record the state of quality and compliance in manufacturing facilities.
- NIPP uses standardized electronic inspection protocols and templated semi-automated inspection reports.
- Protocol development, IT implementation, piloting and refinement, training, and operational implementation will include:

• Sterile dosage form • Solid oral (non-sterile) dosage form • Transdermal products • Creams, ointments, and solutions	• Metered dose inhalers • Terminally sterilized products • Active Pharmaceutical Ingredients (API)

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Leveraging Capabilities

US-EU Mutual Reliance: GMP Inspections for Human Drugs

- Mutual Recognition Agreement (MRA) between FDA and European Union allows drug inspectors to rely upon information from drug inspections conducted within each other's borders.
  - Agreement signed in November 2017
  - US assessment of comparability of capabilities of EU Member States inspectorates –focusing on GMP inspections--completed by July 2019

https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra

FDA Metrics Captured

(from November 2017—as of March 2019)

Metrics captured	Value
Number of inspection the FDA has requested of the EU	173 • 34 requested, agreed • 128 requested, declined • 11 requested, no response (UK)
Number of inspections the EU has requested of the US FDA	6
Number of EU inspections deferred	61
Number of EU inspection reports reviewed	69
Number of FDA inspection reports provided to EU capable countries	28 - biologics 68 - pharmaceuticals

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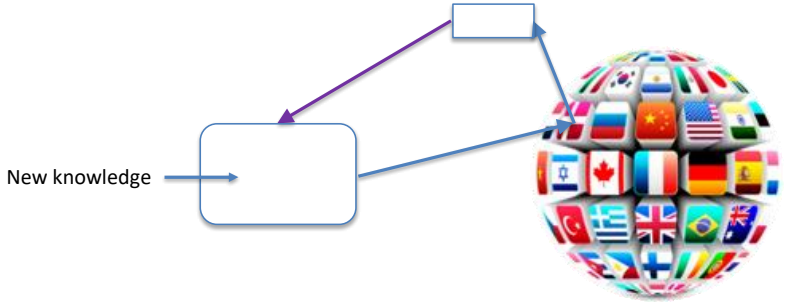
Opportunities at the Intersection

Work to Date Provides a Foundation

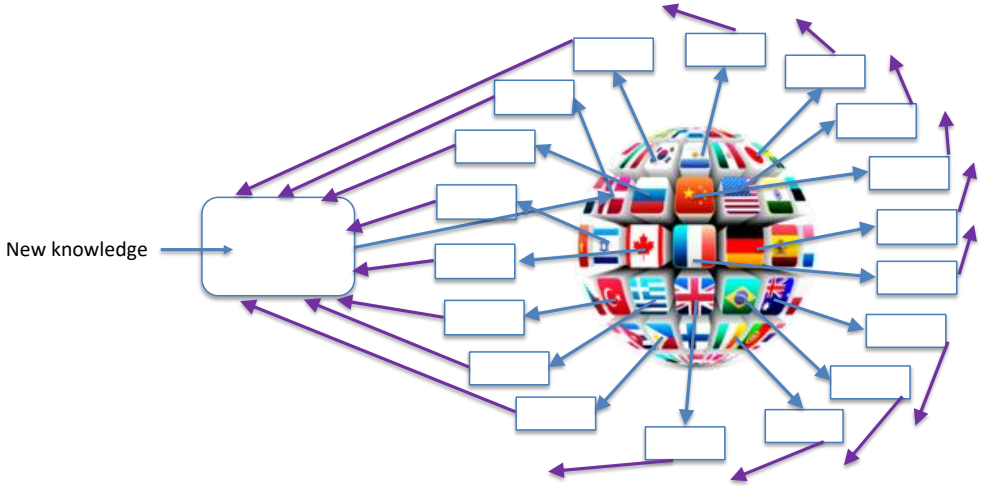
- Reliance approach to date substitutes traditional compliance-focused GMP inspection by one inspectorate for that conducted by another inspectorate
  - Traditional FDA inspection finding of NAI and EU GMP Certificate, provide little information to assess the state of quality management beyond "pass"

- If capable medicines regulatory authorities are going to be successful in implementing policy in ICH Q12—to encourage and enable firms to proactively manage, innovate, and continually improve quality—further steps (and collective KM strategy) will be needed

Regulatory Complexity –
Seen From Different Angles



"PAC visibility"
for a
Regulatory Agency



"PAC visibility"
for a
Pharma Company

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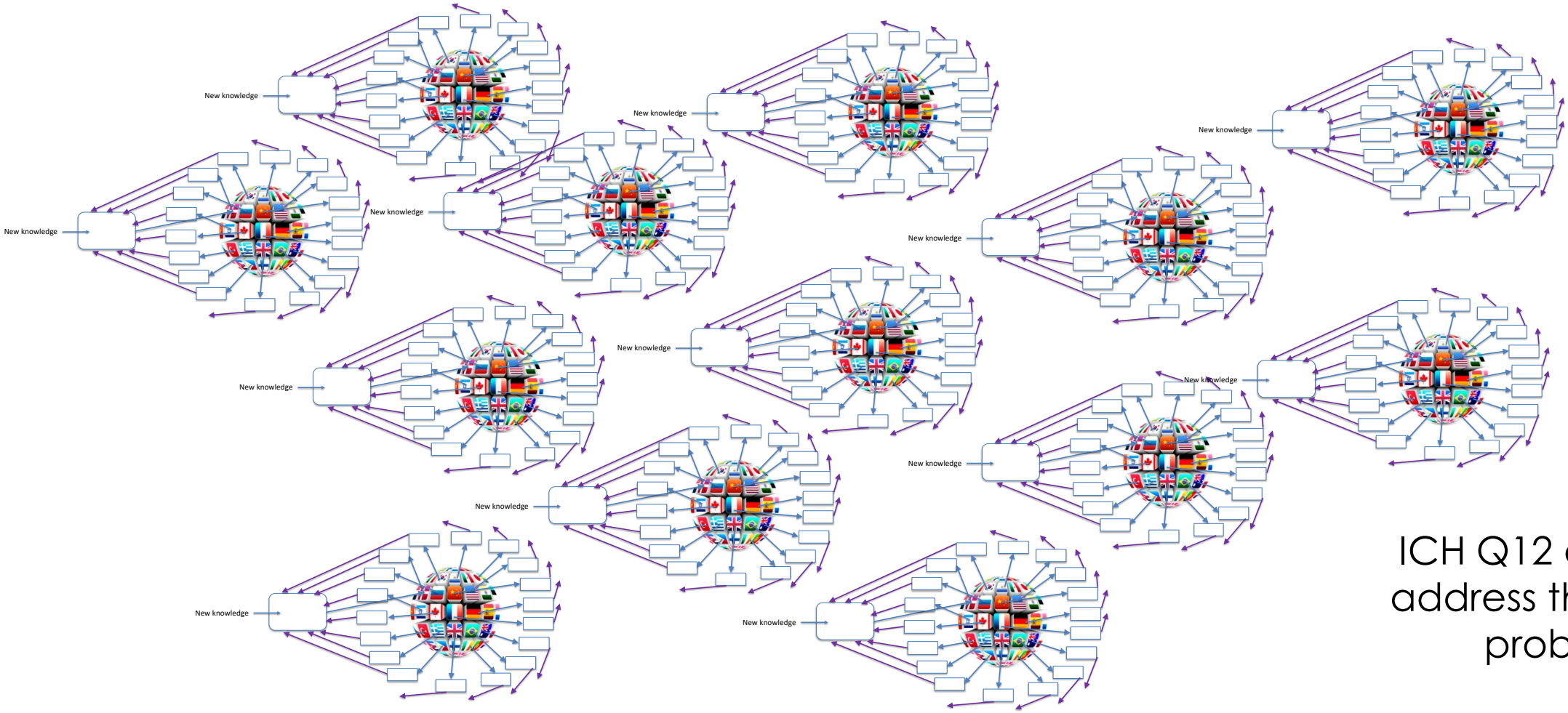
In reality many PACs at the same time



ICH Q12 does not address this global problem

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Thank you