ICH Q12: Experience from PLCM submissions

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What are ICH Q12 tools?

Established Conditions (ECs)

Post-Approval Change Management Protocols (PACMPs)

Product Lifecycle Management (PLCM) document

Categorisation of CMC PAC

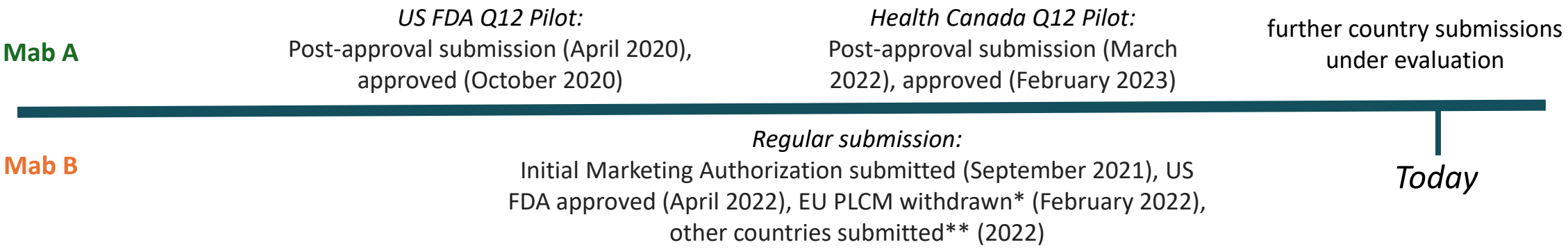
PQS and Risk-Based Change Management

Relationship Regulatory Assessment and Inspection

Structured Approaches for Frequent CMC PAC

Stability Data Approaches to Support Evaluation of CMC Changes

Two Product Experiences with ECs and PLCMs



	Mab A	Mab B
Development Type / Control Strategy	Enhanced process development Leveraging prior knowledge Platform process	Enhanced process development Leveraging prior knowledge Platform process
EC/Non-EC Identification Scope	Process parameters, in-process controls, reference standards, stability	All CMC, including materials and analytical procedures
Reporting Categories	Defined for all ECs: Prior Approval, Notification Moderate and Notification Low	Defined only Notification Low ECs (other ECs default to “Per Regulations”)

* PLCM not allowed within the legal framework, **Submitted but final acceptance is TBD.

General Principles of ECs in PLCM

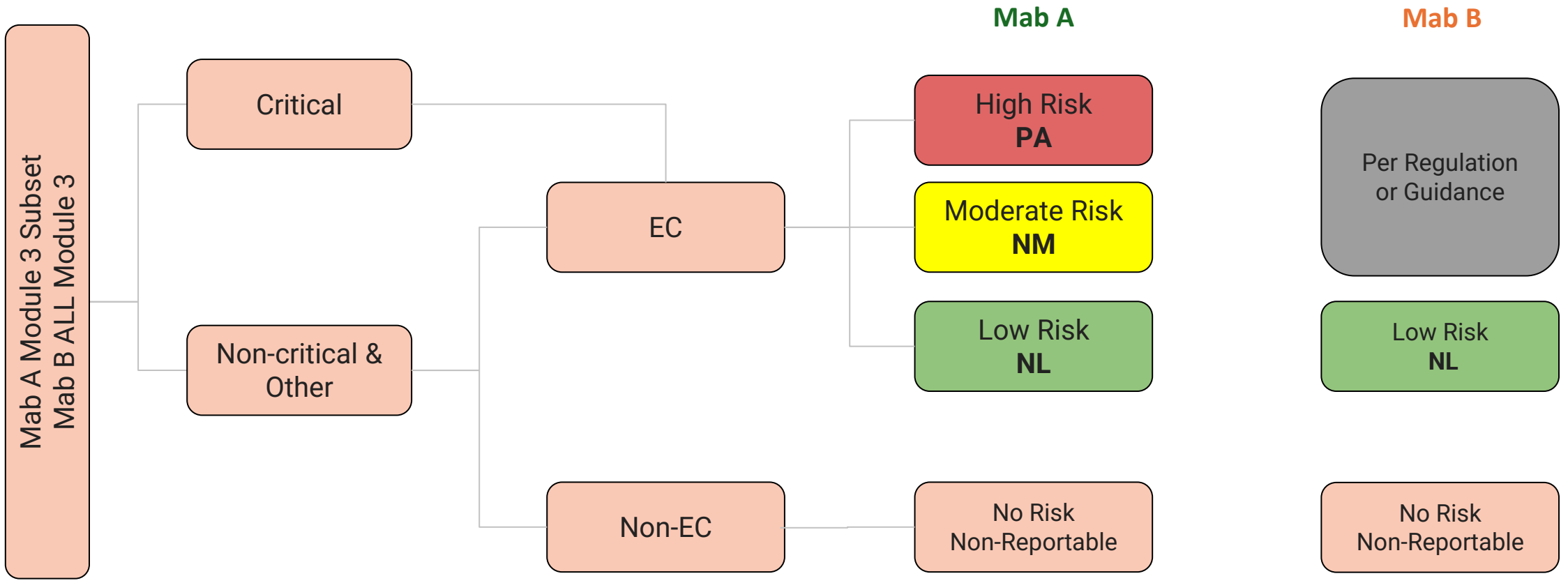
- During **process development**, **formal criticality assessment** of process parameters based on established tools were done leading to **critical process parameters (CPPs) and non-CPPs**
- **ECs** were defined at a **later stage** by an **informal risk assessment** using the CPP and non-CPP definition as basis

  → **Process parameters were assessed for their potential risk to impact critical quality attributes**
- **Critical process parameters** (manufacturing process) were considered **ECs**
- Several other **process parameters** have been identified as **ECs or non-ECs**
- **Differentiation between ECs and non-ECs** can be based on impact on product quality within and beyond approved range

General Principles of ECs in PLCM (continued)

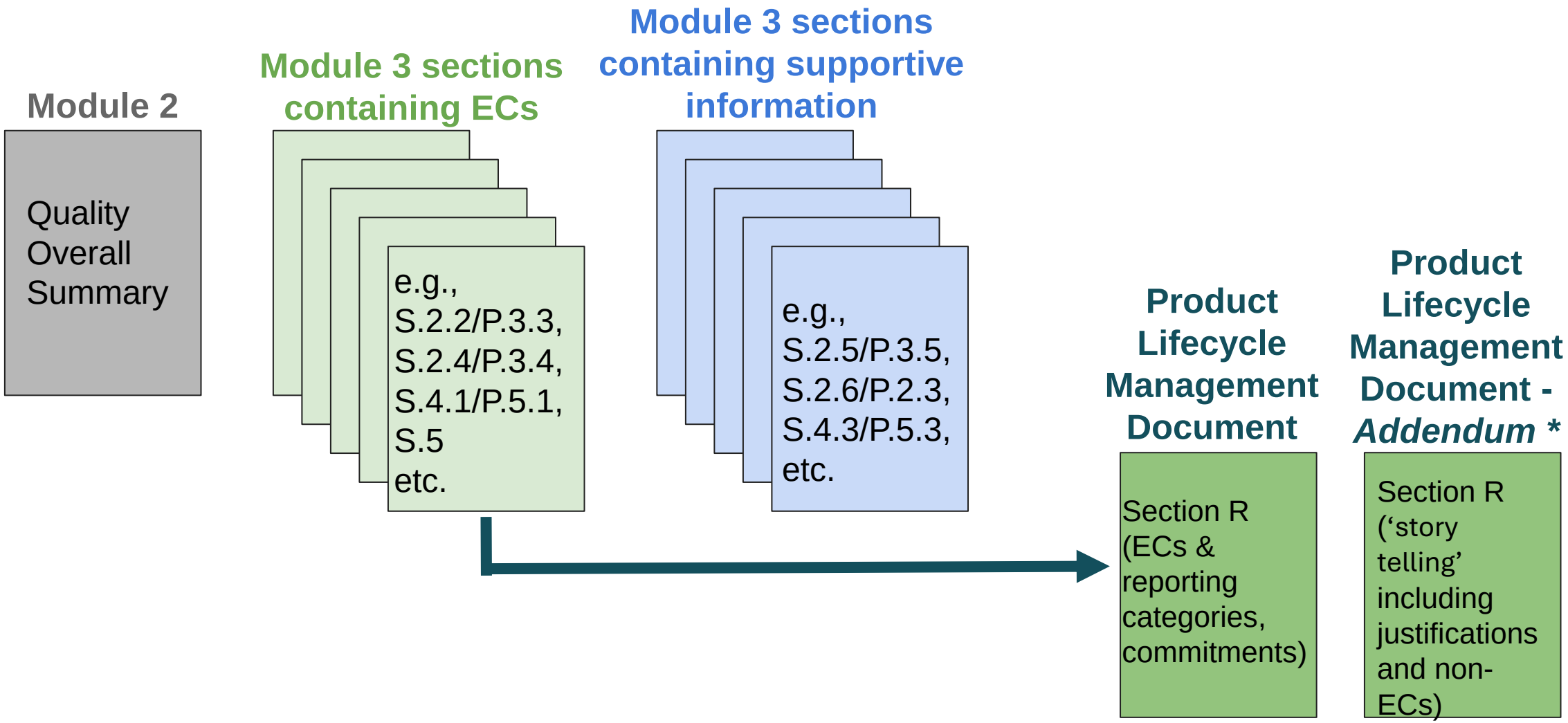
- All **technical changes** are **evaluated** per **pharmaceutical quality system** (ICH Q10), regardless of EC/non-EC status
- All **changes** that impact **ECs** will be reported according to the risk-levels and reporting categories **as defined in the PLCM**
- Applicant may choose to **operate within tighter ranges** than approved limits; this can be **managed within pharmaceutical quality system** provided this is not being done to address a product quality issue
- **Reporting categories** in the PLCM are intended as **default reporting categories** (at the time of change if the risk is assessed to be higher, the change will be reported in a high submission category)
- **Changes** to supportive information (**non-EC**) will be managed within the Applicant's **pharmaceutical quality system** and not reported to the Health Authority

Established Conditions Definition & Reporting Categories Approach



MabA: Subset of M3 assessed. Reporting categories and justification provided for all ECs identified.
MabB: All of M3 assessed. Reporting categories only identified for low risk changes (i.e AR). All M3 sections assessed.

CMC documentation and the EC definition



** Addendum was used in the first iteration to share detailed insight into the EC assessment and to collect feedback to this (submission of such an addendum may change in future submissions).*

Harmonized Approach Still Requires Regional Customization

- **Goal: use ICH Q12 terms** as much as possible and avoid Health Authority-specific terms so that the same PLCM can be used **globally**
- **Mapping of Q12 terms** to **multiple categories** makes this **challenging**: Health Authorities may still require country-specific designations and designations might not map directly to the Q12 terms

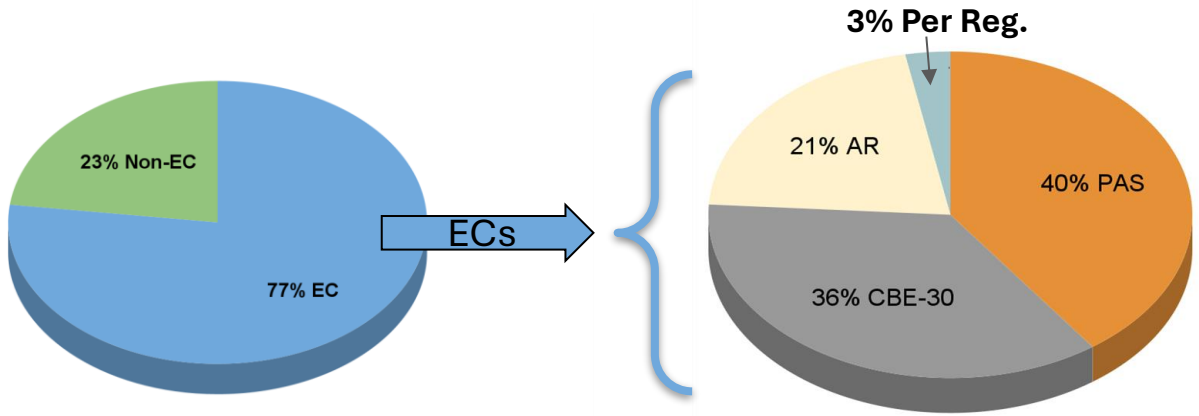
ICH Q12 Term	Canada	US
Prior Approval	Level 1, Level 2	PAS (prior approval supplement)
Notification Moderate	Level 2 (default)	CBE-30 (changes being effective within 30 days)
	Level 3 Immediate (under negotiation)	
Notification Low	Level 3 Immediate	CBE-0 (changes being effective within 0 days)
	Level 3 Annual	AR (annual report; default)

- There are also still “PLCM-like” documents like M1 (Japan) and CPID (Canada)

More ECs, More ‘low-risk ECs’

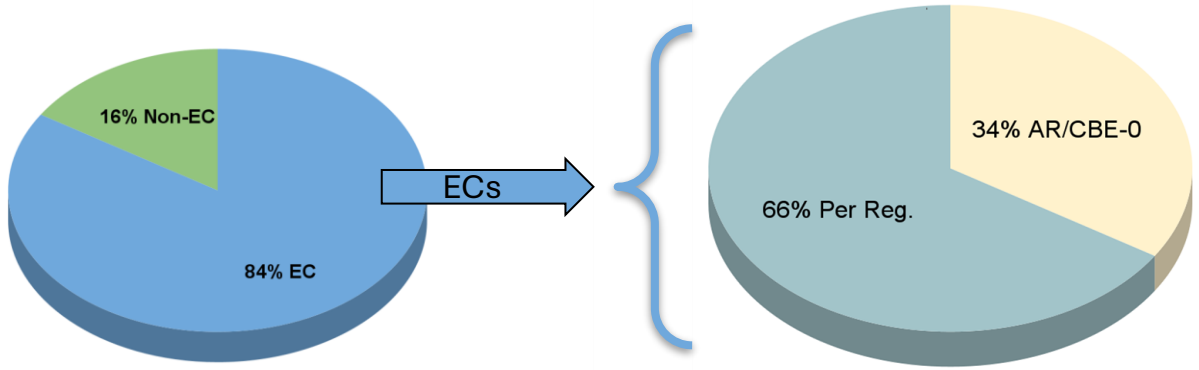
Mab A (Post-approval, FDA pilot)

- PLCM = 37 pages
- PLCM addendum = 84 pages
- # FDA questions = 26
- % are for the sections in scope, not all sections were in scope



Mab B (Initial Marketing application)

- PLCM = 53 pages
- PLCM addendum = 106 pages
- # FDA questions = 52



AR = annual report; CBE-0/30 = Changes being effective within 0/30 days; PAS = prior approval supplement; per reg. per regulation

Key learnings & challenges of these EC approaches

- **Overall positive experience:**
  - EU rapporteur was encouraging to further think about defining more non-ECs (risk based approach)
  - U.S. FDA was engaged and willing to gain understanding (verbal interactions helpful)
  - General strategy and documentation to define ECs accepted by U.S. FDA and Health Canada; no questions concerning non-ECs

- Information Requests by U.S. FDA and Health Canada focused mainly on **reporting categories** (rather than ECs vs. non-ECs) and link to local post-approval variation categories

- **Modulating reporting** in accordance with **magnitude of potential impact** was challenging

Key learnings & challenges of these EC approaches (continued)

- **Justifications** for **lower reporting categories** became **part of main PLCM** (these turned into "Conditions to be met" and/or "mini-protocols" before a NL reporting category could be applied)

- **Consistency is still a challenge**
  - Within agency
  - Across all agencies (harmonization)
  - Across product types

- **Lifecycle of documentation is challenging** (e.g., PLCM addendum, simultaneous changes, multiple versions)

- **Maintaining AND demonstrating** a robust **pharmaceutical quality systems** is crucial

- Confusion between EC and PLCM

Outlook

- **Quality by Design (QbD)** is **not mandatory to define ECs** but can be an **enabler** for a more systematic EC definition
- **Strategy to define ECs** and **how ECs are documented** is expected to **further evolve** with increasing experience
- Further leverage **prior knowledge** and **control strategy elements** in risk assessments may facilitate EC definition
- **Global implementation** of ICH Q12 takes time
- Further work ongoing on **analytical methods** and ICH Q2/14 implementation

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Minh Luu

Bahareh Barzegar

Shirley Chan

Sarah Kennett

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Sharon Ong

Ainy Huynh

Saurav Aneja

Dulce Aldana Sanchez

… and so many others …

Doing now what patients need next