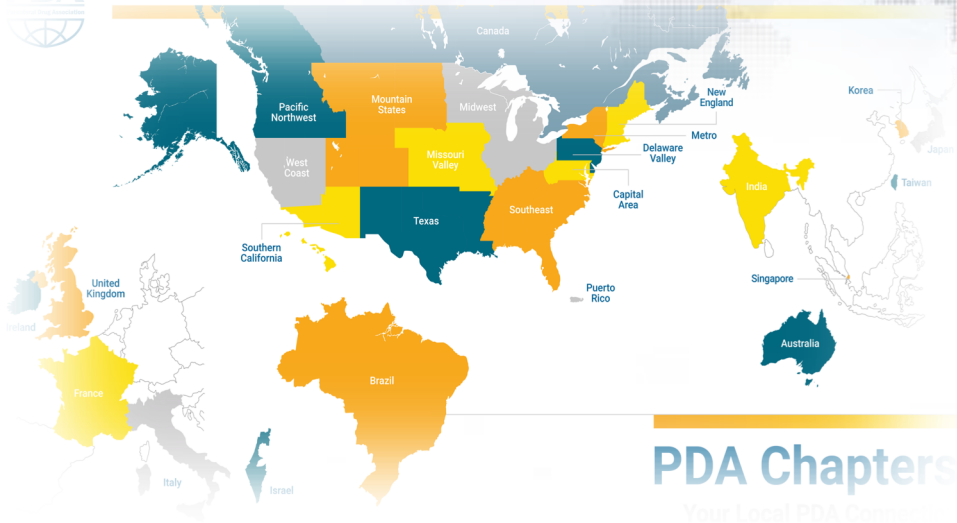
Media Fill- Current Trends

In Isolators

Ivy Louis
Member, SAB, PDA Inc.

PDA - The Global Leader

Connecting People, Science and Regulation®



25 Chapters Around the Globe

&

almost

10,000 Members

PDA
Parenteral Drug Association

Connecting People, Science and Regulation®

About PDA

The Parenteral Drug Association (PDA) is the leading global provider of science, technology, and regulatory information. PDA creates awareness and understanding of important issues facing the bio/pharmaceutical community and delivers high-quality, relevant education to the industry. Since its founding in 1946 as a nonprofit organization, PDA has been committed to developing scientifically sound, practical technical information and expertise to advance bio/pharmaceutical manufacturing science and regulation, so members can better serve patients.

PDA Vision

To maximize product quality, availability, and value by connecting people, science, and regulation within the bio/pharmaceutical community so that PDA is:

- The preferred choice for professionals who seek specialized, innovative skills and knowledge enhancing their professional development
- The premier educational partner for professionals in academia, industry, and government for the advancement of manufacturing, quality, and regulatory science
- An organization that aligns its practices and resources in support of its **core values** of a basis in **science (science based), integrity,** and **inclusion**

PDA Mission

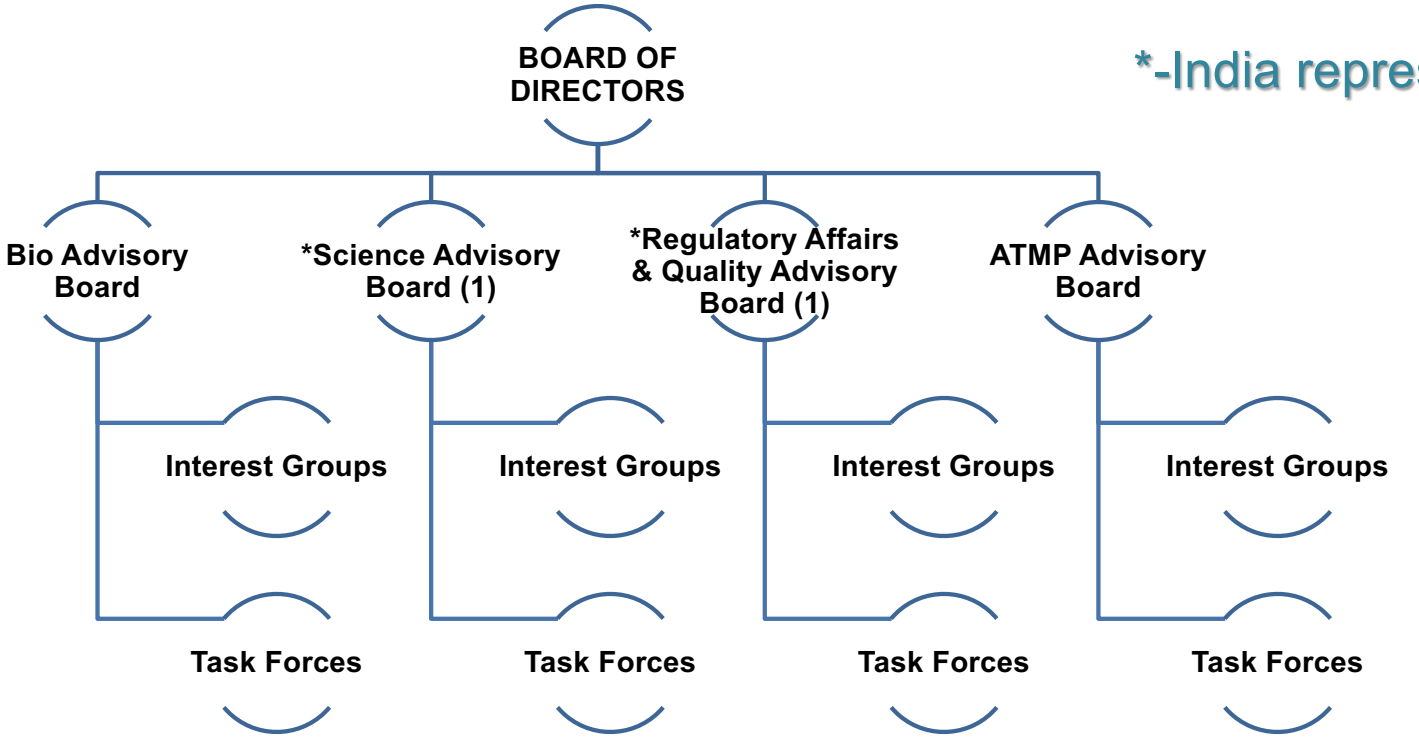
To advance pharmaceutical/biopharmaceutical manufacturing science and regulation so members can better serve patients.

Learn more at *pda.org*

PDA Technical Report Portal

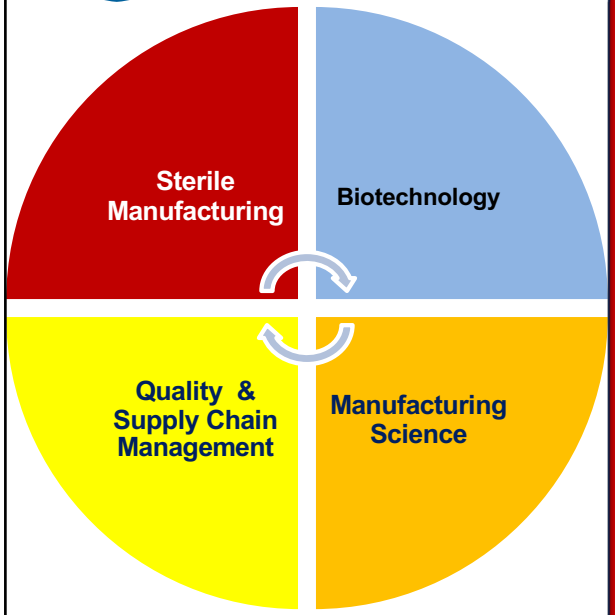
PDA Members have 24/7 access to more than 70 active technical resources in the PDA TR Portal.

Advisory Boards of PDA Inc.



*-India representation

PDA's Science-Based Activities



Sterile Manufacturing

- QRM for Aseptic (Std.)
- PUPSIT Research
- Zero Defects for Visible Particles (TR)
- PFS Design Control Annex (TR)
- Isolator Technology (TR)

Quality & Supply Chain Management

- Purchasing Controls (Std)
- Data Integrity (multiple TRs)
- QRM for Excipients (TR)
- Post Approval Change Management Plans (TR)
- Phase-Appropriate GMPs -- Technology Controls for Pilot Plants (TR)

Biotechnology

- Cryopreservation (Std)
- Cell & Gene Therapy
- Phage Retention Nomenclature Rating for Small and Large Virus Retentive Filters Std)
- Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness and Response (TR)
- Process Validation for Protein Manufacturing (TR)

Manufacturing Science

- Big Data in Mfg. (TR)
- Operational Metrics (TR)
- Cleaning Validation (TR)
- Tech Transfer (TR)

Volunteer Opportunities at PDA

Volunteering is a powerful way to connect with the global PDA community, advance professionally, and contribute to the industry.

PROJECT-BASED VOLUNTEERING

WRITING OPPORTUNITIES:
- Author/Contributor to the *PDA Letter*
- Post to PDA Connect
- Author/Contributor to the *PDA Journal*

DOCUMENT REVIEWER:
- Technical Report Peer Reviewer

SPEAKING/PRESENTING OPPORTUNITIES:
- Speaker
- Education Instructor
- Poster Presenter

LONG TERM PROJECTS:
- Task Force Member
- PDA Connect Community Coordinator
- Program Planning Committee Member

LEADERSHIP LEVEL VOLUNTEERING

STANDING COMMITTEES:
- Audit Committee Member
- Exhibits Committee Member
- Membership Advisory Committee Member
- *PDA Letter* Editorial Committee Member

ADVISORY BOARDS (AB):
- Biotechnology AB Member
- Regulatory Affairs & Quality AB Member
- Science AB Member
- Education AB Member
- Marketing AB Member

LEADERSHIP ROLES:
- Interest Group Leader
- Chapter Officer
- Committee or AB Leader

EXECUTIVE COMMITTEE MEMBER

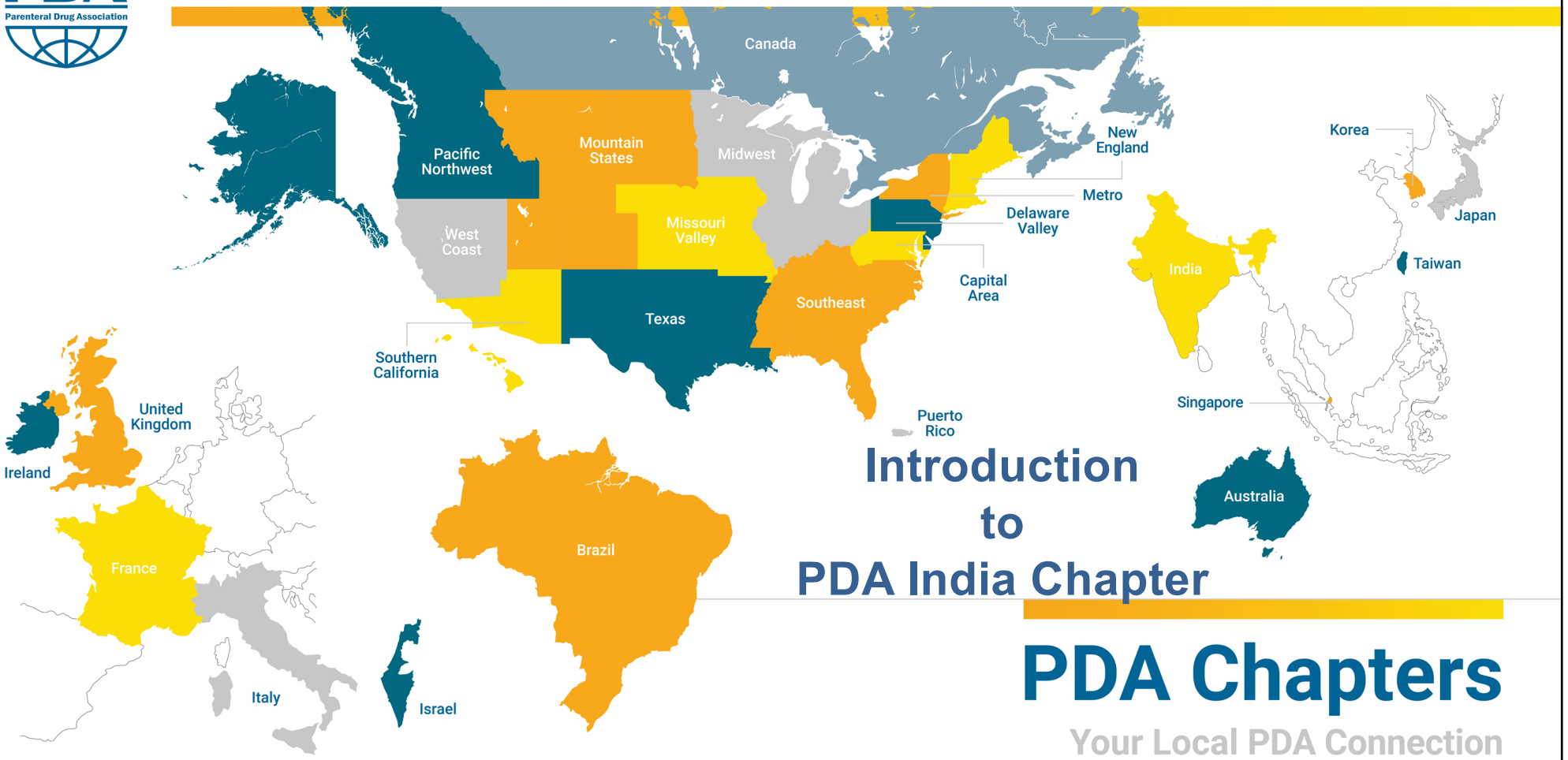
BOARD OF DIRECTORS

PDA® Parenteral Drug Association

More than **2,500** volunteers actively carry out PDA's mission worldwide

Visit **pda.org/volunteer** to learn more

PDA @ IPA-7 ADVANCED GMP WORKSHOP 2022

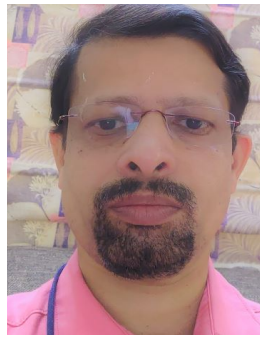


India Chapter Board 2022-2024

Vishal Sharma
President

Dr. Rustom Mody
President Elect

Rishikesh Jaiwant
Secretary



K Raghuram Chandra Rao
Treasurer

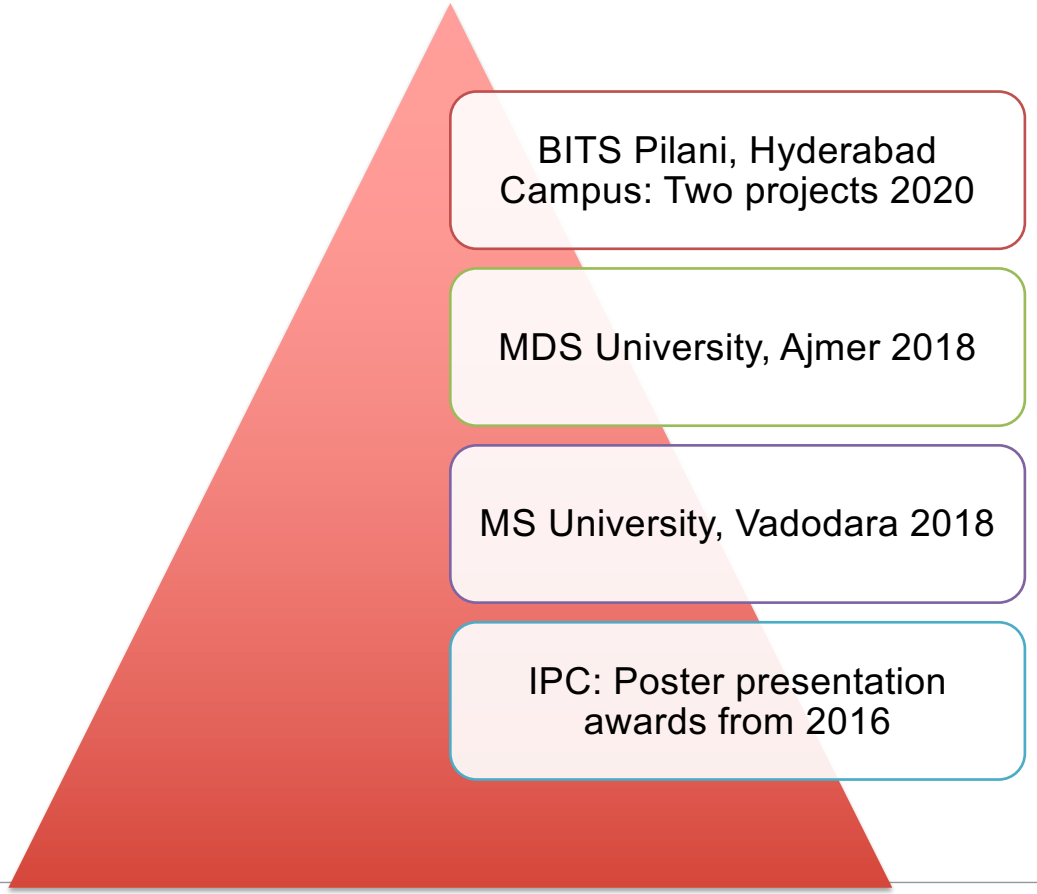
SG Belapure
Past Chair

Pravin Arora
Member

Dr. Sumitra Pillai
Member

Pankaj Shltole
Member

India Chapter: Collaborations with Research Wings

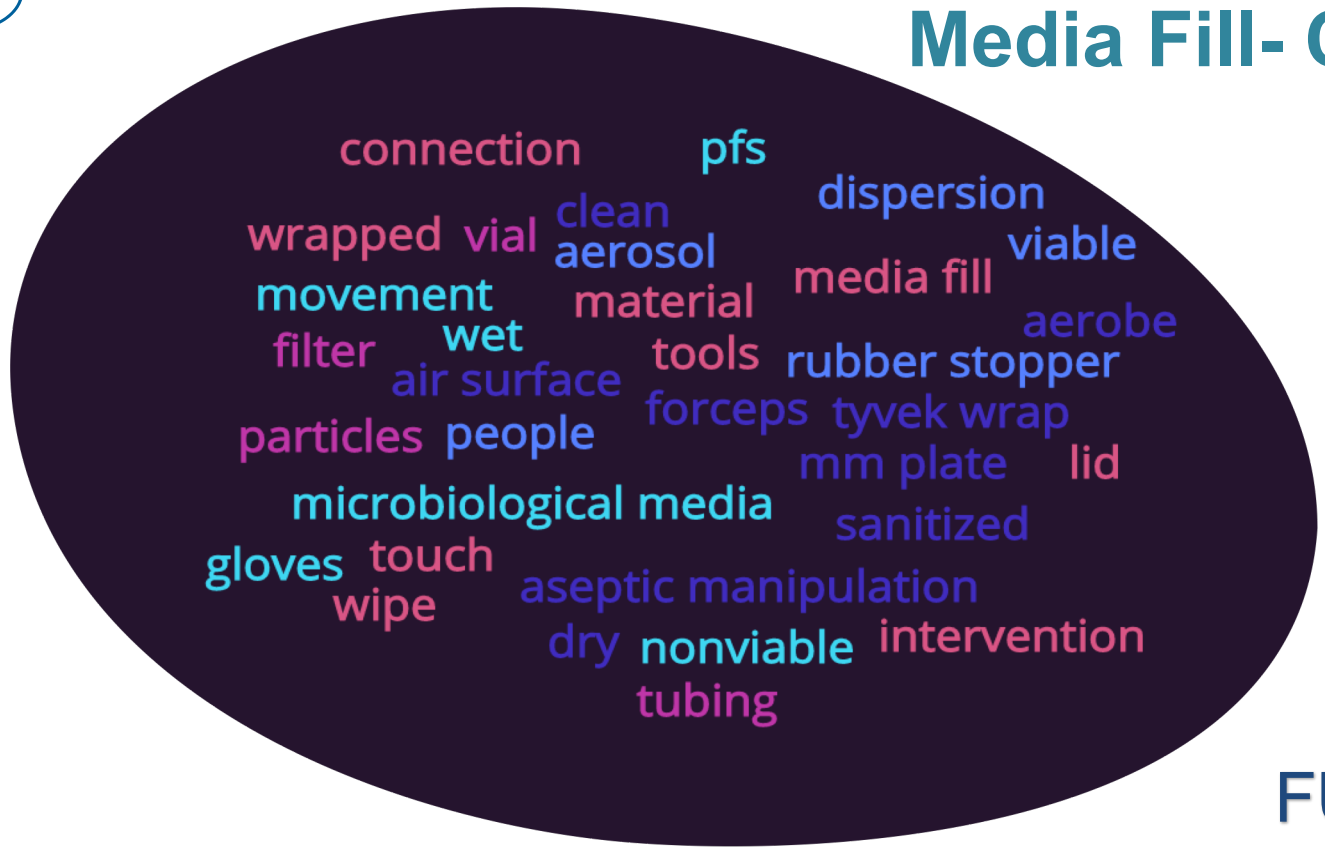


The current PDA Membership Structure!

- PDA has introduced a new, more flexible membership structure.
- Visit www.pda.org/membership/new-membership-structure for details and the answers to Frequently Asked Questions.
- A snapshot of how the tiers are structured-

	New Tiers		
	Essential	Plus	Premium
Standard Member	$150	$250	$350
Academic, Early Career, and Emerging Economy	$75	$125	$245
Health Authority, Students, and Retired	FREE	FREE	$175
Membership Directory	X	X	X
Vote in PDA elections and on proposed bylaws changes	X	X	X
PDA Letter Online	X	X	X
PDA Connect	X	X	X
PDA Volunteer Opportunities	X	X	X
Member Discounts	X	X	X
PDA Technical Publications Portal		X	X
PDA Journal - Limited Access		X	X
Download new TRs for free within 30 days			X
PDA Technical Reports - 1 free download a year of your choice from existing TR/Survey/PtC library			X
PDA Journal - Unlimited Access			X

Media Fill- Current Trends



In Isolators

CURRENT?

For us to be
FUTURE-READY

The ASK for Media Fill in ISOLATORS

References

- PDA TR 22 (Revised 2011)- Process simulation for Aseptically Filled Products
- PDA TR 29 (Revised 2012) - Points to Consider for Cleaning Validation
- Food and Drug Administration (FDA) (2004) Guidance for Industry. Sterile Drug Products Produced By Aseptic Processing – Current Good Manufacturing Practice, FDA Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) and Office of Regulatory Affairs (ORA). Washington DC, and APPENDIX 1: ASEPTIC PROCESSING ISOLATORS
- US FDA- COMPLIANCE PROGRAM GUIDANCE MANUAL- Program-7356.002A- Sterile Drug Process Inspections
- GUIDELINES The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use - Annex 1, Manufacture of Sterile Medicinal Products, 2022
- Task Force- Japan- Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing ; With the support of a Grant for Research on Regulatory Science of Pharmaceuticals and Medical Devices from Ministry of Health, Labour and Welfare of Japan
- Best Practices Document on Media Fill- IPA

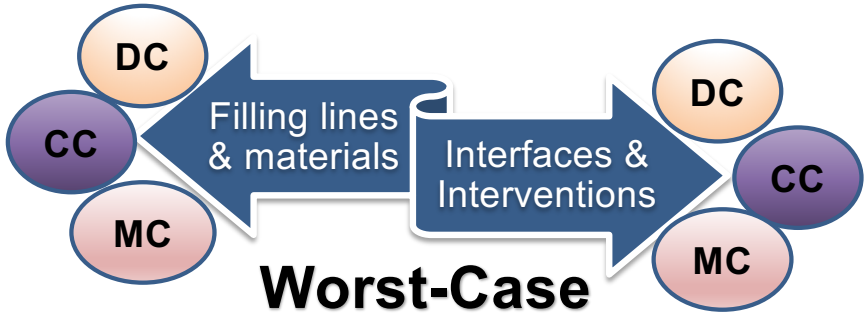
Acknowledgements

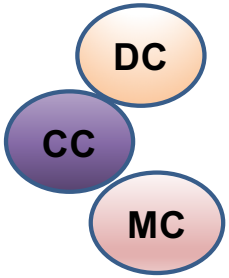
1. **Nitesh Malashiya;** Head Production, Dr Reddy's Laboratories, FTO11
2. **Jayesh Patel,** Lead-investigator/ COE- Aseptic, Sun Pharmaceutical Industries Limited, Halol

Process Simulation- Concepts & Principles

Current Trends: Based on **Scientific Knowledge**, **Experience** and **Regulatory** expectations

Tools to determine Process capability & Identify weakness





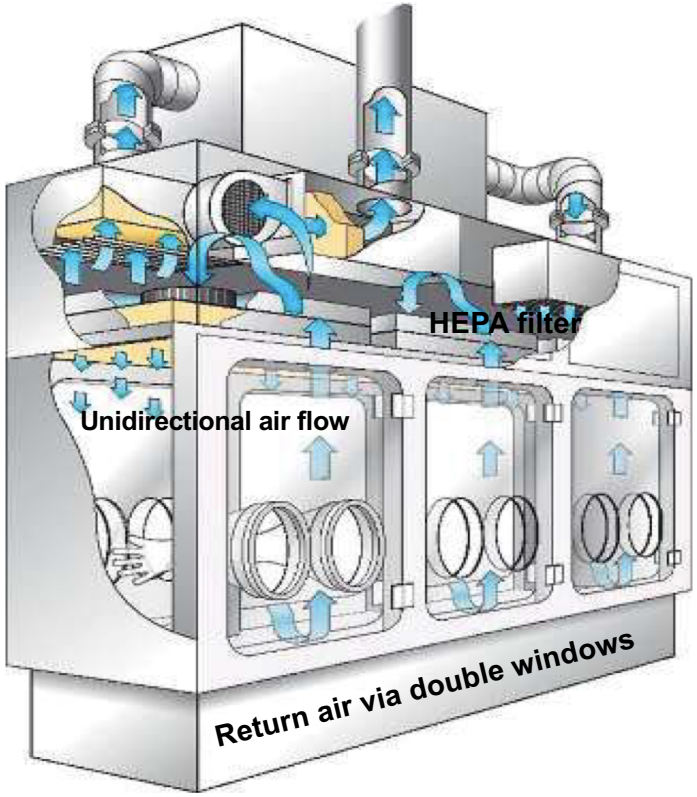
Design Considerations

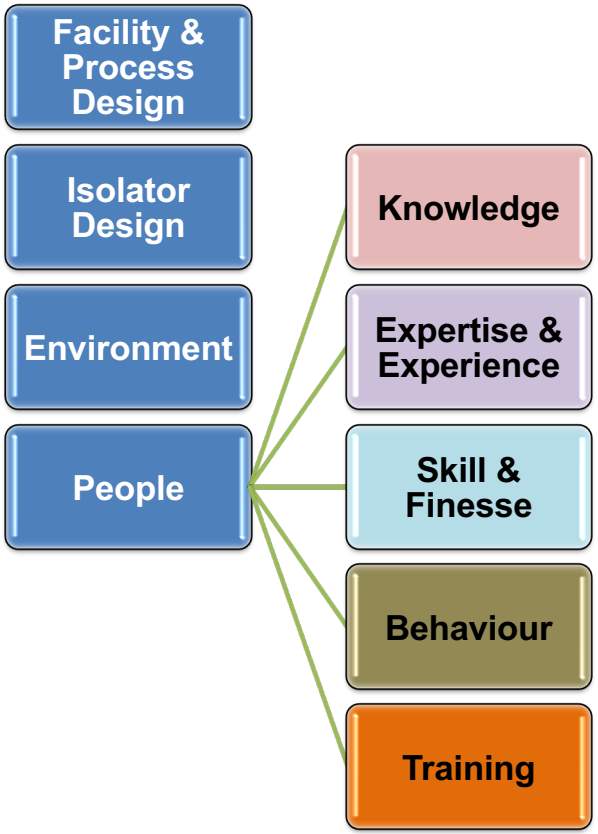
Control Considerations

Monitoring Considerations

Worst-Case- A set of conditions encompassing **processing limits and circumstances**, including those **within** standard operating procedures, that **pose** the greatest chance of process or product **failure** (when compared with ideal conditions). Such conditions have the highest potential to, but do not necessarily always result in product or process failure.

Media Fill in Isolators : Factors of Influence





Facility & Process Design: The SHIFTS

- **Evolution of Grade A filling system over a time to safeguard Aseptic Manufacturing**

LAF Based Filling System

Background: Grade B

RABS Based Filling System

Background: Grade B

Isolator Based Filling System- Open or Closed

Background: Grade C(Open) Grade D(Closed)

Policy for Isolators in the manufacture line up? → **Data Collection** → **Evaluation** → Root Cause Analysis → Action: Reduction/ Elimination

- Facility and its state of being?
- Utilities and its state of being?
- Equipment and its state of being?
- All material, components and its state of being?
- Transfer of material and components and the need?
- Hold time, Duration and the need?
- Interventions and the need?
- # of shifts, time of filling and the need?
- # of containers and the need?
- # of people and the need?
- Operator fatigue and the need?

- **Facility and its state of being?**

Annex 1 –
Manufacture of Sterile Medicinal Products

Refer 4.32 revised Annex 1:
The maximum time interval for requalification of grade A & B areas, ***is 6 months****.*
The maximum time interval for requalification of grade C & D areas, ***is 12 months****.*

Annex 1 - Manufacture of Sterile Medicinal Products
Status of the document: Revision of the 2007 version of Annex 1.

Deadline for coming into operation:
- 25 August 2023 : one year from the date of publication in Eudralex Volume 4
- 25 August 2024 : two years from the date of publication in Eudralex Volume 4 for point 8.123

Worst-Case

Annex 1: Table 4: Examples of operations and grades for aseptic preparation and processing operations	
Grade A	Aseptic assembly of filling equipment.
	Connections made under aseptic conditions (where sterilised product contact surfaces are exposed) that are post the final sterilising grade filter
	These connections should be sterilised by steam-in-place whenever possible.
	Aseptic compounding and mixing.
	Replenishment of sterile bulk product, containers and closures.
	Removal and cooling of unprotected (e.g. with no packaging) items from sterilisers.
	Staging and conveying of sterile primary packaging components in the aseptic filling line while not wrapped.
	Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials
	Loading of a lyophilizer.
Grade B	Background support for grade A (when not in an isolator).
	Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A.
Grade C	Preparation of solutions to be filtered including sampling and dispensing.
Grade D	Cleaning of equipment.
	Handling of components, equipment and accessories after cleaning.
	Assembly under HEPA filtered airflow of cleaned components, equipment and accessories prior to sterilisation.
	Assembly of closed and sterilised SUS using intrinsic sterile connection devices.

If Isolators have Grade A, do we need to worry?

Worst-Case

Annex 1: Table 2: Air Qualification During Qualification			
Grade	**Air sample CFU/m3**	**Settle plates (diameter 90 mm) CFU/4 hours (a)**	**Contact plates (diameter 55 mm) CFU/plate (b)**
A	No growth		
B	10	5	5
C	100	50	25
D	200	100	50

Policy for Isolators in the manufacture line up? → Data Collection → Evaluation → Root Cause Analysis → Action: Reduction/ Elimination

- **Equipment and its state of being?**
- **All material, components and its state of being?**
- **Transfer of material and components and the need?**

Glove positioning

Interventions

A-1: 8.12 The unwrapping, assembly and preparation of sterilised equipment, components and ancillary items with direct or indirect product contact should be treated as an aseptic process and performed in grade A with a grade B background. The filling line set-up and filling of the sterile product should be treated as an aseptic process and performed in grade A with a grade B background. Where an isolator is used, the background should be in accordance with paragraph 4.20.

Areas of concern in Aseptic processing

Annex 1: Section 4.10

- The **transfer** of equipment and materials **into and out** of the cleanrooms and critical zones is one of the greatest potential sources of contamination.
- Any **activities** with the potential to compromise the cleanliness of cleanrooms or the critical zone should be **assessed** and if they cannot be eliminated, appropriate controls should be implemented.

Areas of concern in Aseptic processing

Annex 1: Section 4.11

- The transfer of materials, equipment, and components into the grade A or B areas should be carried out via a **unidirectional** process.
- Where possible, items should be sterilised and **passed into these areas** through double-ended sterilisers (e.g. through a double-door autoclave or depyrogenation oven/tunnel) sealed into the wall.
- Where sterilisation upon transfer of the items is not possible, a procedure which achieves the same objective of **not introducing contamination** should be validated and implemented, (e.g. using an effective transfer disinfection process, rapid transfer systems for isolators or, for gaseous or liquid materials, a bacteria-retentive filter).
- The removal of items from the grade A and B areas (e.g. materials, waste, environmental samples) should be carried out via a separate unidirectional process.
- If this is not possible, time-based separation of movement (incoming/exiting material) by procedure should be considered and controls applied to avoid potential contamination of incoming items.

Areas of concern in Aseptic processing

Annex 1: Section 4.12 ii Material airlocks: used for materials and equipment transfer.

- Only materials and equipment that have been included on an approved list and assessed during validation of the transfer process should be transferred into the grade A or grade B areas via an airlock or pass-through hatches.
- Equipment and materials (intended for use in the grade A area) should be protected when **transiting** through the grade B area.
- Any unapproved items that require transfer should be pre-approved as an exception. Appropriate risk assessment and mitigation measures should be applied and recorded as per the manufacturer's CCS and should include a specific disinfection and monitoring programme approved by quality assurance.
- Pass-through hatches should be designed to protect the higher-grade environment, for example by effective flushing with an active filtered air supply.
- The movement of material or equipment from lower grade or unclassified area to higher-grade clean areas should be subject to cleaning and disinfection **commensurate** with the risk and in line with the CCS.

- **# of shifts, time of filling and the need?**

Ref:

Questions and Answers on Current Good Manufacturing Practice Regulations | Production and Process Controls
https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practice-regulations-production-and-process#10

Media Fill in Isolators- A regulatory POV

What is the acceptable media fill frequency in relation to the number of shifts?

Normally, media fills should be repeated twice per shift per line per year. Is the same frequency expected of a process conducted in an isolator?

Response:

- A firm's justification for the **frequency of media fills in relation to shifts** should be risk based, depending on the **type of operations** and the **media fill study design**.
- For ***closed*, highly automated systems** run on **multiple shifts**, a firm with a **rigorous** media fill design **may be justified** to conduct a **lower number of total media** fill runs.
- Such a program can be appropriate provided that it still ensures performance of media fills for each aseptic processing line at least **semi-annually**.
- The 2004 guidance for industry on *Sterile Drug Products Produced by Aseptic Processing* states that "Activities and interventions representative of each shift, and shift changeover, should be incorporated into the design of the semi-annual qualification program."
- In addition, the EU Annex 1, *Manufacture of Sterile Medicinal Products,* states that "Normally, process simulation tests should be repeated twice a year per shift and process."

Ref:

Questions and Answers on Current Good Manufacturing Practice Regulations | Production and Process Controls
https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practice-regulations-production-and-process#10

Continued…

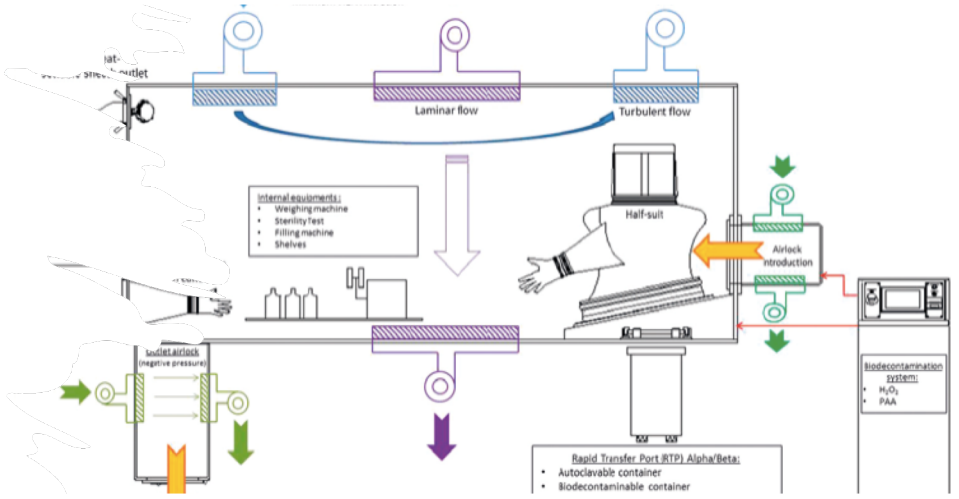
- Certain modern manufacturing designs (isolators and *closed vial* filling) afford isolation of the aseptic process from microbiological contamination risks (e.g., operators and surrounding room environment) throughout processing.
- For such *closed* systems, if the **design** of the processing equipment is **robust** and the extent of **manual manipulation** in the manufacturing process is **minimized**, a firm can consider this information in determining its media fill validation approach.
- For example, it is expected that a conventional aseptic processing line that operates on two shifts be evaluated twice per year per shift and culminate in four media fills.
- However, for aseptic filling conducted in an isolator **over two shifts**, it may be justified to perform **fewer than four media fill runs per year**, while still evaluating the line **semi-annually** to ensure a **continued state of aseptic process control**.
- This lower total number of media fill runs would be based on **sound risk rationale** and would be subject to **re-evaluation** if contamination issues (e.g., product non-sterility, media fill failure, any problematic environmental trends) occur.

Isolator Design:

Turbulent flow

or

Laminar Flow



Media Fill Study Design-
A case study

Media Fill Study Design

A case study

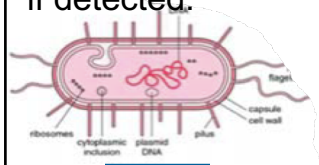
- **Problem:** Low level of Contamination
- **Identification of organism:** Micrococcus
- **Investigation:** Done over 23 days
- **Probable Root Cause:** Personnel related
- **CAPA:** Increased frequency of decontamination, concentration, time & training
- **Repeat observation: ……**

CHAPTER 56:

DRUG QUALITY ASSURANCE

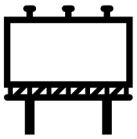
+

A-1 8.19 Aseptic operations (including APS) should be observed on a regular basis by personnel with specific expertise in aseptic processing to verify the correct performance of operations including operator behaviour in the cleanroom and address inappropriate practices if detected.

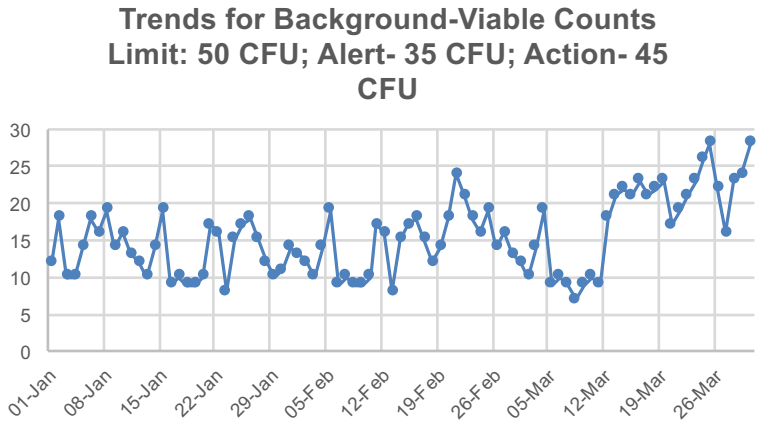


- How does the process used for media fill compare to the aseptic filling of commercial drug products?
- Does the firm accurately evaluate the production operation on a routine basis (changes over time) against the media fill design?
- Does the firm have detailed procedures that describe the media fill process, including frequency, challenge conditions, personnel participation, container / closures, interventions, duration of fill, reconciliation of vials, acceptance criteria, incubation, examination after incubation, actions to take if positive growth is found, etc?

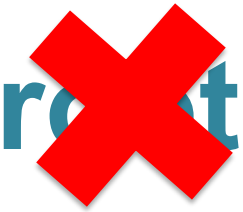
Points for deep dive



P1-P2-P3



Are people always the root cause of media fill failures?

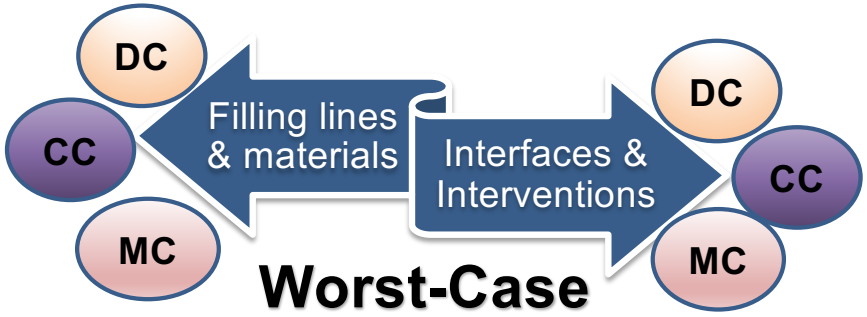


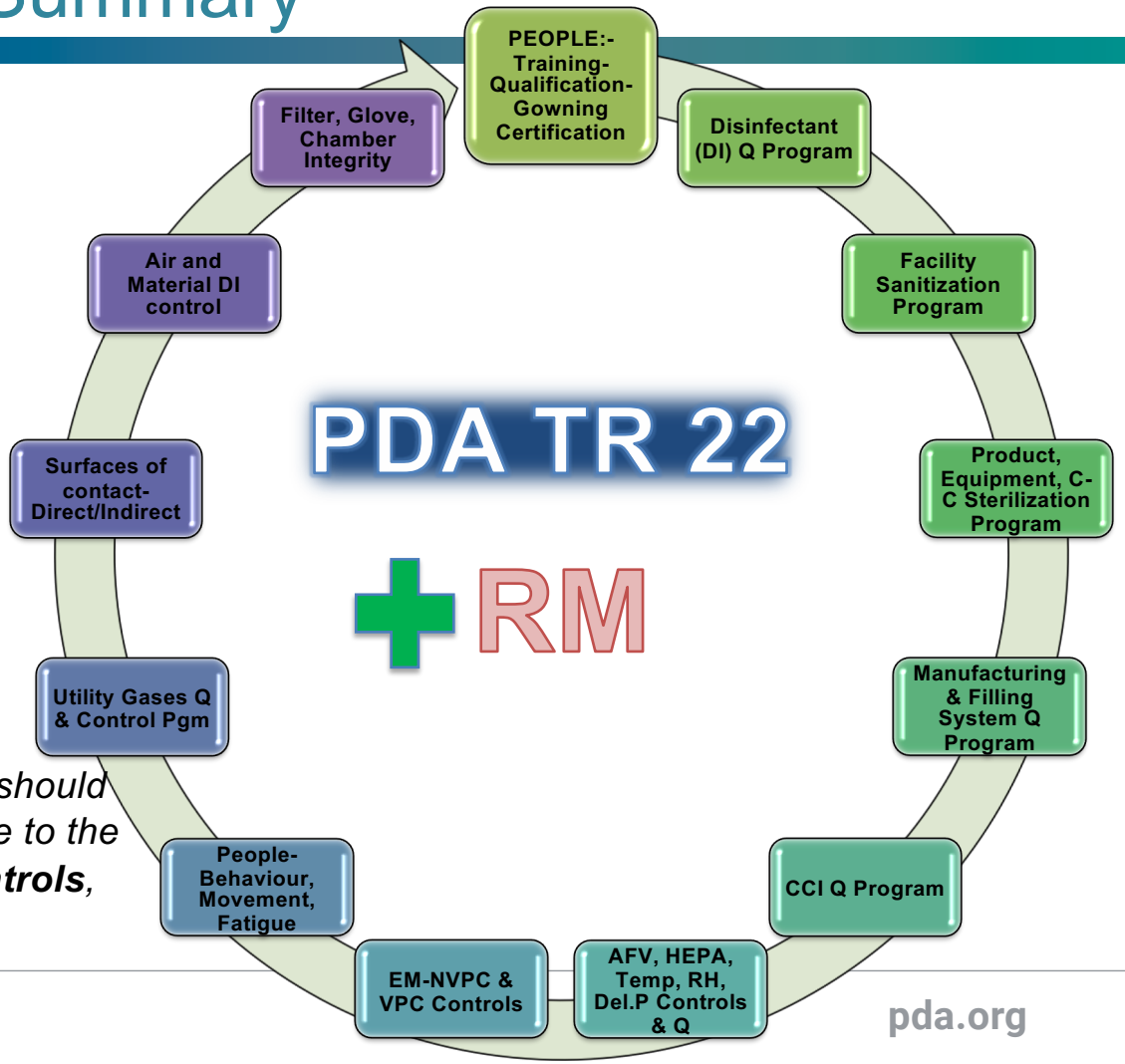
An example
of
Proof of concept

Krämer, I., Federici, M., Kaiser, V. and Thiesen, J. (2016) Media-fill simulation tests in manual and robotic aseptic preparation of injection solutions in syringes, *J Oncol Pharm Pract.*;22(2):195-204

MEDIA FILL STUDIES- IN ISOLATORS														
Parameters ---> Worst case conditions considerations	Facility & Air Flow patterns	Utilities & Supplies	Equipment & Design, Set up-Run-Stop-clean	Materials & Components, sizes, types, pretreatment	Transfer across Grades	Cleaning, Sanitization, Disinfection, Sterilization	Product Pathway, contact time & Hold times	Duration of fill	Batch/Campaign modes	Duration of run	Selection of media	Selection of Container & Closure	People, Number, Roles, types of shedders, decision making,	Interventions (Inherent, Corrective)
DESIGN CONSIDERATIONS? Y/N														
CONTROL CONSIDERATIONS? Y/N														
DETECTION CONSIDERATIONS? Y/N														
Teams involved? Projects/Reg.Affairs/Facility & Engineering/Operations/Quality/Microbiology/ Tech Transfer														
Total Cost per media fill study in INR														
Possibilities for redesigning the study? Y/N														

Isolators-APS/MF : Summary





A-1: 9.32 The effectiveness of the aseptic process should be determined through ***process design****, adherence to the* ***pharmaceutical quality system*** *and* ***process controls****,* ***training****, and* ***evaluation of monitoring data****.*

Final Thoughts

MF in Isolators (Automation & People)

- "*Don't be afraid, but don't be overconfident that AI will solve everything. Risks from new technology will be different, but there will still be risks.*"- Rick Friedman, 2019.
- ***P.S:*** *Today AI asks us human beings to prove that we are not robots!!!*

Many more opportunities..

….For optimization!

Ivy Louis
Member, SAB, PDA Inc.