Advancements in Manufacturing Technology

“Complex Injectables”

Dr. Alex George

Executive Vice President and Head, Injectables & Inhalation Products

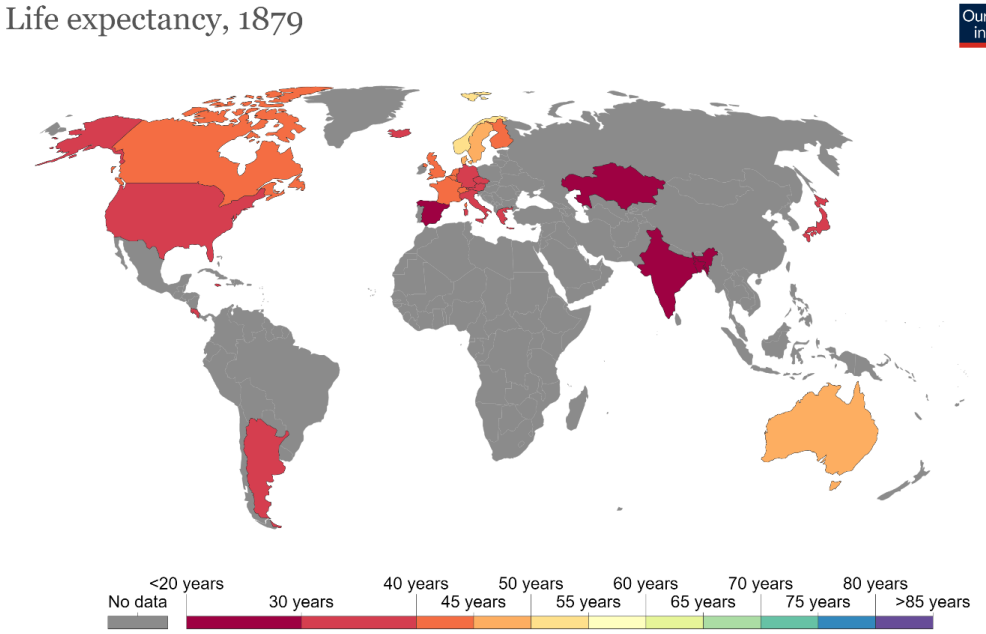
Overview –Advances in Manufacturing Technology

1. Pharma Industy –Introduction & Evolution
2. cGx–Introduction & Development perspective
3. cGx Manufacturing –Hurdles & Mitigation
4. Emerging Technologies & Landscape
5. Passing Thoughts

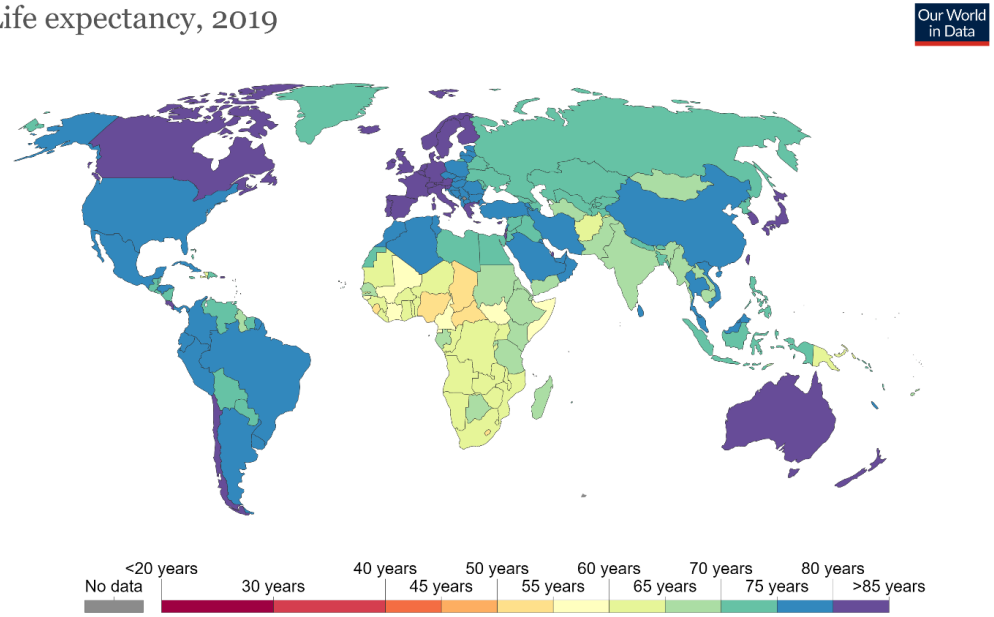
Pharmaceutical Industry

Introduction & Evolution

Pharma Industry –Overview



Source: Riley (2005), Clio Infra (2015), and UN Population Division (2019)
Note: Shown is period life expectancy at birth, the average number of years a newborn would live if the pattern of mortality in the given year were to stay the same throughout its life.
OurWorldInData.org/life-expectancy • CC BY



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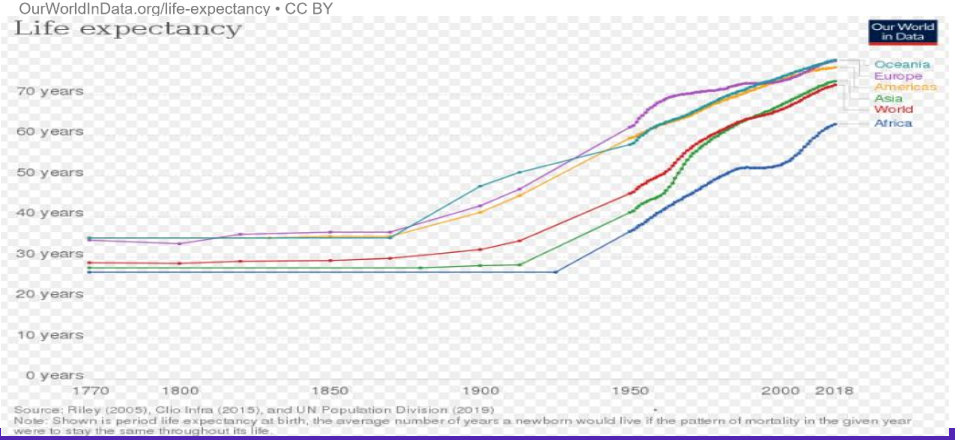
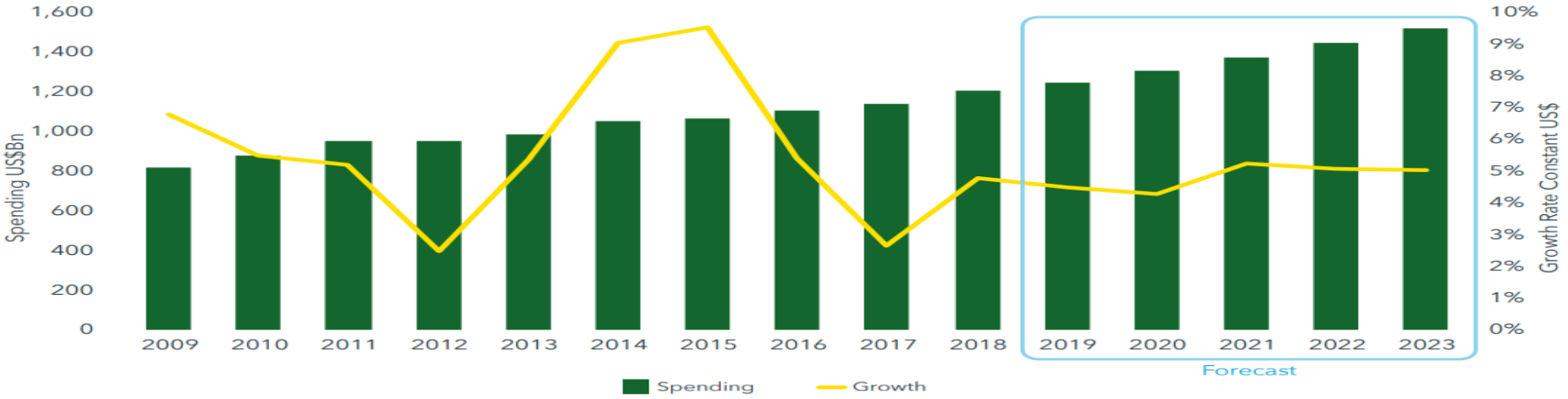


Working In The Pharmaceutical Industry Allows You To Change People's Lives For The Better

Pharma Industry –Overview contd..

A Vibrant Trillion Dollar plus Industry; Growing steady globally



Source: IQVIA Market Prognosis, Sep 2018; IQVIA Institute, Dec 2018

- As of 2018, approximately 1.2 trillion USD had been spent on medicines, up from just 887 billion U.S. dollars in 2010. That number is expected to increase to 1.52 trillion USD by the year 2023
- Global revenue in 2018 was at 1.2 trillion USD where as in 2001 the market was valued at 390 bn USD
- The industry is expected to grow by 160% between 2017 and 2030

We are a global pharmaceutical company

1

Pharmaceutical Services & Active Ingredients

Partner of choice

A leader in generic API supply globally

Customers are generics manufacturers and innovator firms

2

Global Generics

Access to affordable medicines

Finished dosages in distribution- and detailing-driven markets

Key markets: America, India, Russia

Building a sustainable generics business

3

Proprietary Products

Fulfilling unmet medical needs in dermatology & neurology

Building sustainable and profitable proprietary products

Strong pipeline of differentiated formulations

4

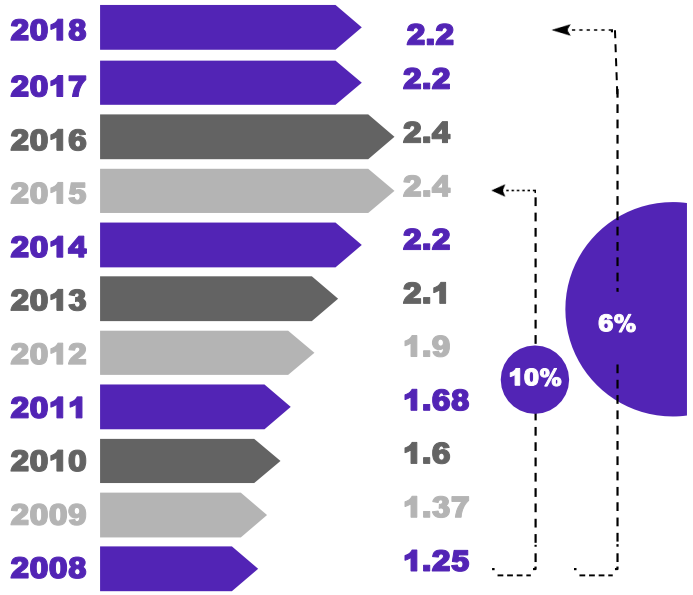
Biologics

High quality global bio-similars

Dr. Reddy's Laboratories leads the industry with four biosimilar products marketed in several countries

Extensive development pipeline

Good Health Can't Wait



We grew at a CAGR of 10% between FY08 & FY15

...with presence in all major regions of the world

Commercial presence in

30

countries

10
API Manufacturing Facilities

14
Formulations Manufacturing Facilities

10
Global R&D Centres

1
Biologics Development Centre

Dr Reddy's is one of the biggest providers of low cost generics of complex drugs to US patients

Azacitidine injection

Indicated for myelodysplastic syndrome

Decitabine injection

Indicated for myelodysplastic syndrome

Simvastatin-Ezetimibe tablets

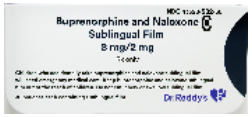
Indicated for hyperlipidemia

Zoledronic acid injection

Indicated for Paget's disease of bone (oncology)

Liposomal doxorubicin injection

Indicated for Ovarian cancer, Multiple Myeloma and Kaposi's sarcoma

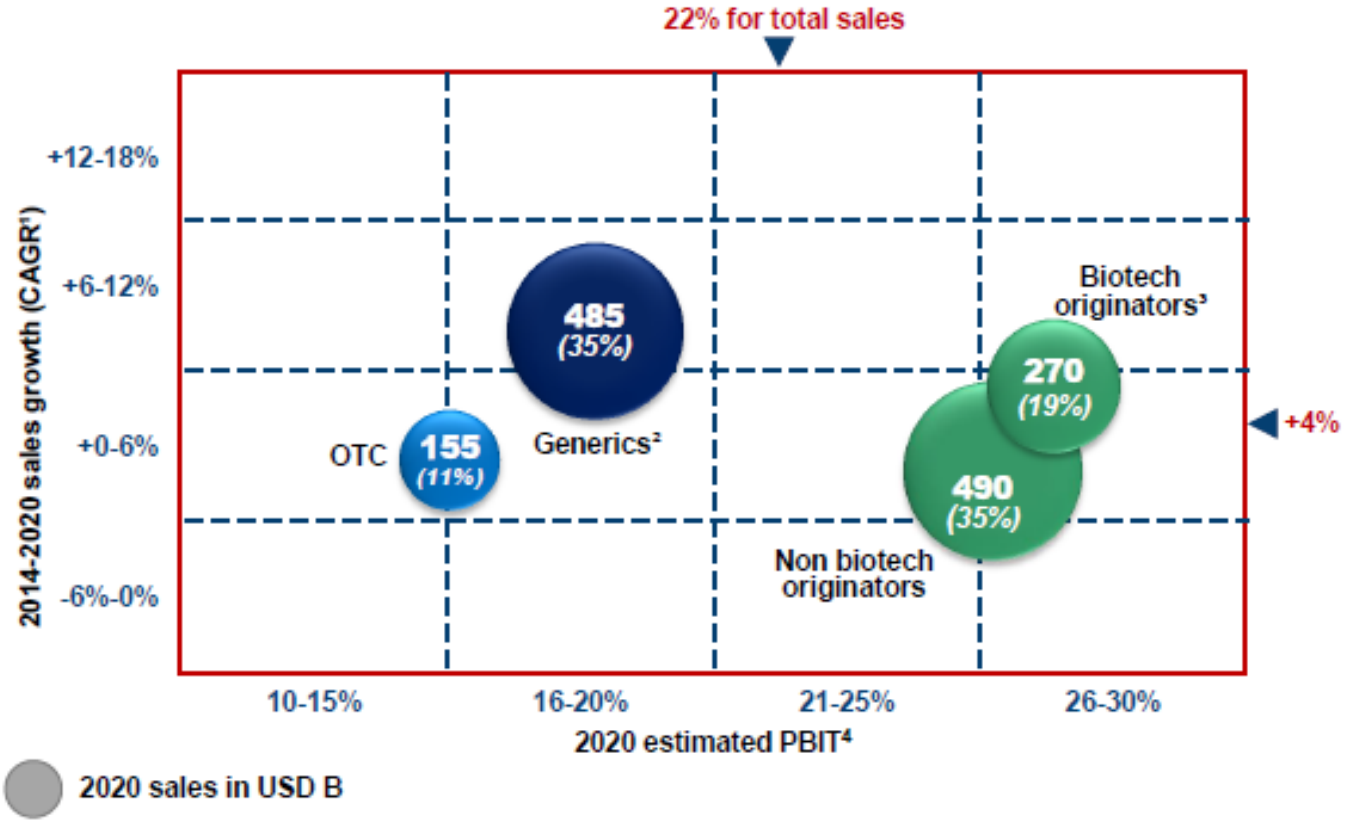


Buprenorphine naloxone sublingual film

Indicated for Opioid dependence

Pharma Industry –Global Trend & cGX Intensification

Market is shifting towards Biologics and Complex Generics



- In 2020, pharma market sales (excluding medical device) should reach USD 1,400 B worldwide with a +4% CAGR between 2014 and 2020
- In 2020, the average profitability rate should stand at 22% of pharma companies sales vs. 25% in 2014
- The OTC segment appears to be the smallest, the least profitable and with the lowest growth rate
- The biotech segment will remain very attractive

Sources : Nicholas Hall's OTC Yearbook 2013 – IMS Health 2014 – Smart Pharma Consulting analyses

¹ Compound annual growth rate – ² Including branded and unbranded generics and biosimilars, excluding OTC – ³ Excluding biosimilars, already included in the "Generics" segment – ⁴ Profits before interests and taxes

Pharma Industry –Global Trend & cGX Intensification

The global pharma market will be mainly driven by demographic factors and a strong willingness of citizens to have access to breakthrough innovation

DRIVERS

1. Population increase and ageing
2. Strong development of Complex Generics to meet the specific needs of the population
3. Stronger demand for new and better medicines
4. Increasing demand for Secondary Care products and Treatment
5. Increasing access to medicines by multiple emerging markets

In terms of "Limited Competition and ROI"

Complex Generics is one of the BEST available options for the Industry

LIMITERS

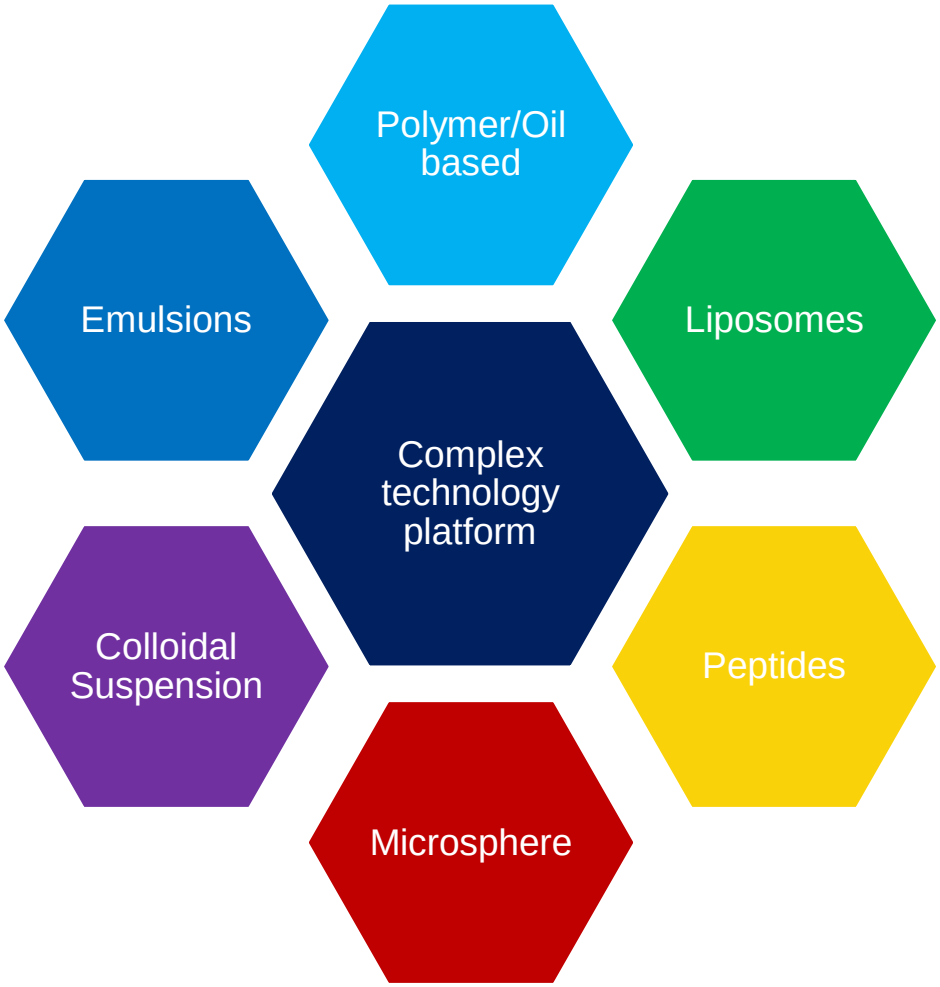
1. Stagnation in R&D productivity and less number of NCE molecules in market
2. Re-purpose push
3. Intensification of competition from plain vanilla generics and biosimilars
4. Increasing price pressure from PAYERs
5. Increasing price sensitivity of customers for OTC offerings

Complex Injectables

Introduction & Development..

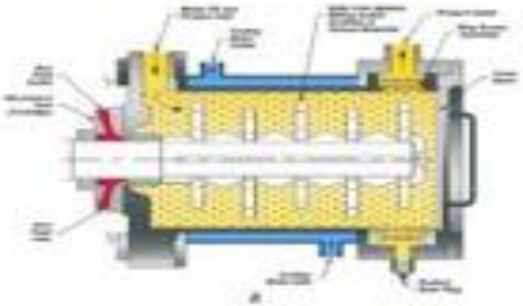
Introduction – Complex Injectable

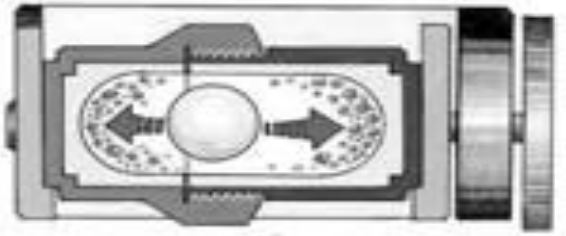
Gamut of Technologies



Where lies the complexity

Complex Injectables –Development Hurdles?





Complex Injectables

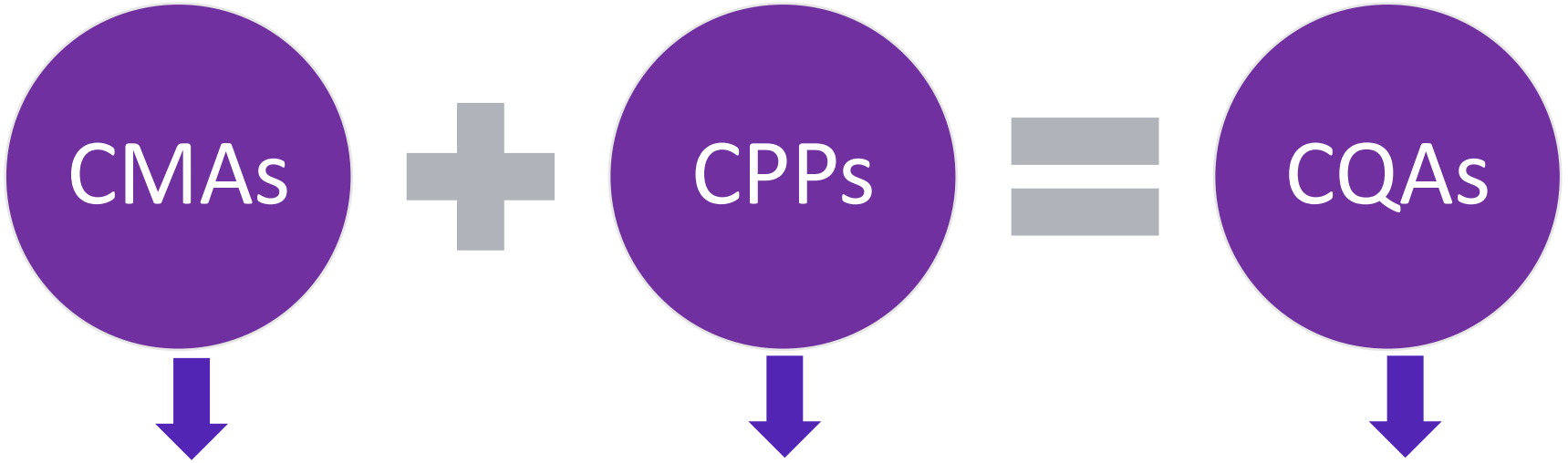
Manufacturing –Hurdles & Mitigation

Complex Injectables –Manufacturing @ Scale Challenges

1. Understanding the Product CQAs and CPPs & CMAs linkage
2. Lack of Lab to Plant Scalability of Transfer functions
3. High Volume & Number of Unit Operations & Interconnects
4. Customized set of dedicated equipment train & Infrastructure
5. Sterlity Assurance @ Scale | CIP,SIP,Media Fill, Isolators etc..
6. Robust & Agile Manufacturing Process @ Scale

1 Understanding the Product CQAs and CPPs & CMAs linkage

Case study : Microsphere technology



- *Polymer IV*
- *Co-monomer ratio*
- *Acid Number*
- *Molecular weight*
- *Crystallinity*
- *Chain-end chemistry*
- *Residual solvents*
- *Residual metals etc…*

- *Emulsification:*
  - *RPM*
  - *Flow Rate*
  - *Temp*
  - *Pressure*
  - *Residence Time*
- *Hardening:*
  - *Extraction rate, T &P*
- *Collection steps:*
  - *Filtration/centrifugation*
  - *Drying*
- *Suspension / Powder filling*

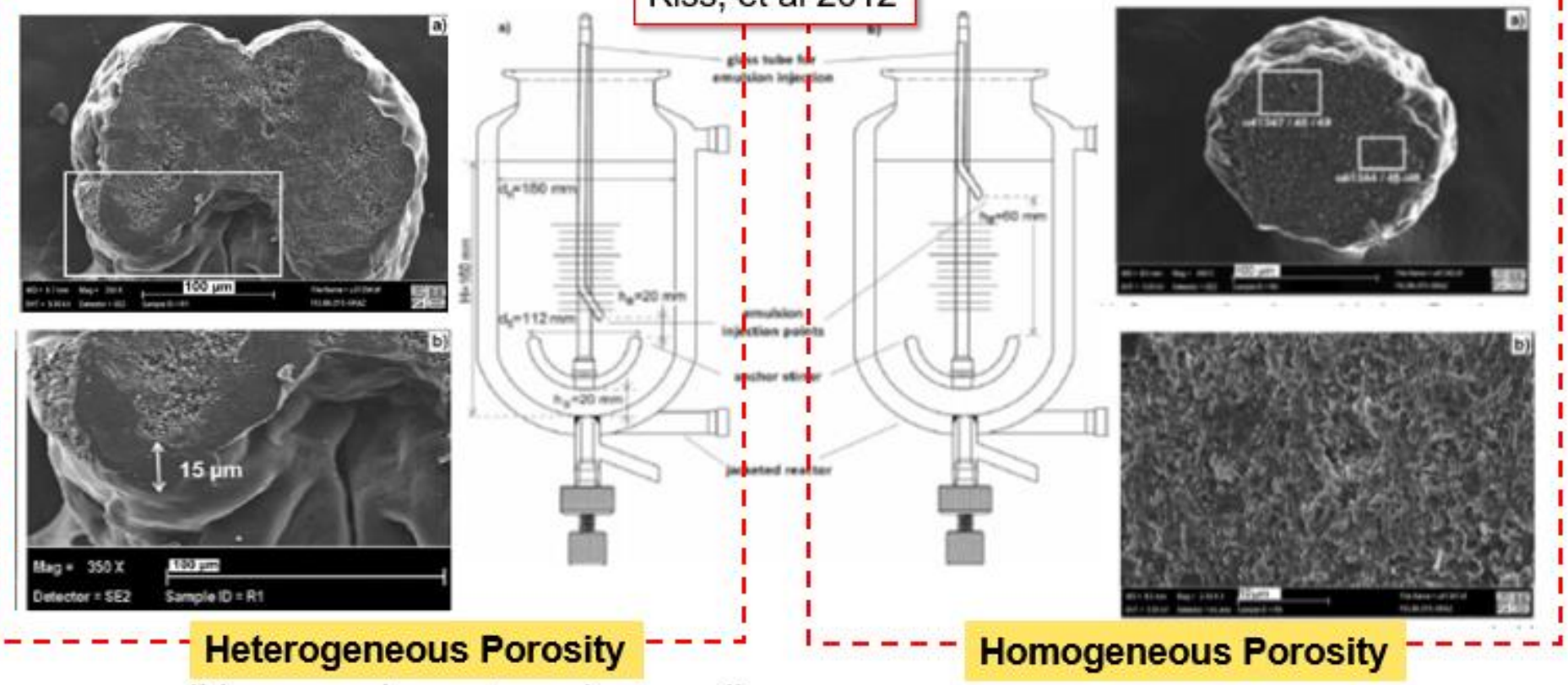
In Process CQAs for each unit operation –Strung together to achieve final CQAs

1 Understanding the Product CQAs and CPPs & CMAs linkage contd..

Microsphere technology

Impact of location of Emulsion Introduction in the Hardening Step

Kiss, et al 2012



Heterogeneous Porosity

Homogeneous Porosity

Process conditions can impact product quality

Important to ensure similarity of process conditions at lab/ plant scales during scale-up

2 Lack of Lab to Plant Scalability of Transfer functions

Microsphere technology

Lab Scale Development

QbD approach
Unit Op Understanding
Advanced Characterization
Modeling & Simulation

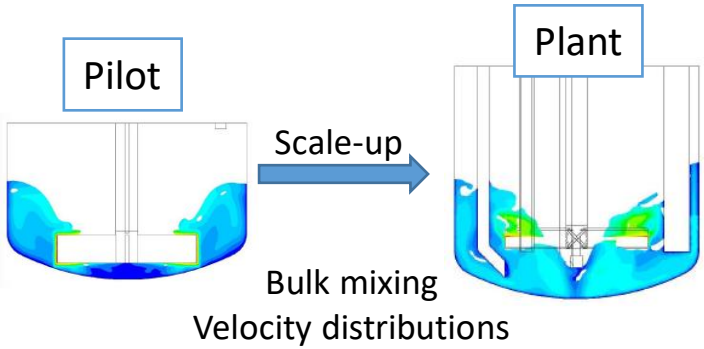
Intermediate Scale

Scale-up Parameters
PAT Tools
Equipment Design

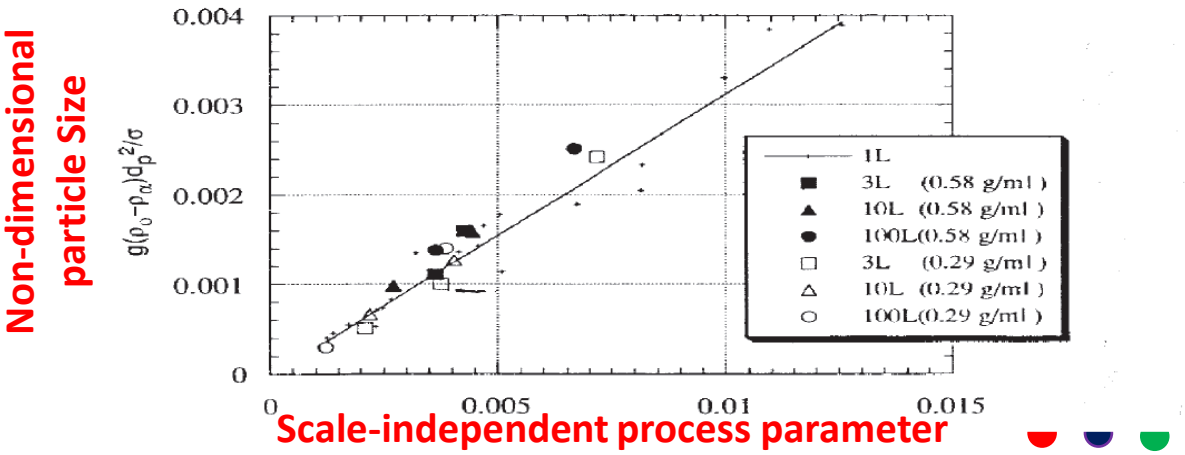
Intermediate Scale

Geometrically Similar Equipment
Verification of Scale-up Strategy
Minimization of Plant Trials

Modeling for Mixing



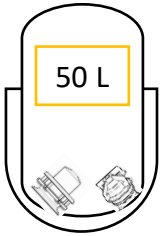
Screening SI & SD Parameters



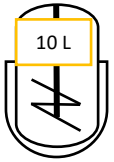
2 Lack of Lab to Plant Scalability of Transfer functions contd..

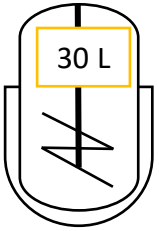
Geomterical Similarity across the scale for right Transfer fucntion

Vessels with GMP & HSH



Vessels with Helical/ Anchor





Bead Mill

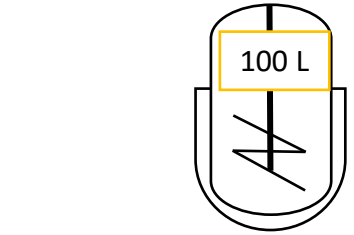
CMX (10L – 100L)

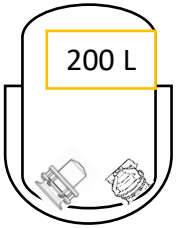
Sonicator

HPH –

Bead Mill

CMX (10L – 100L)





Sonicator

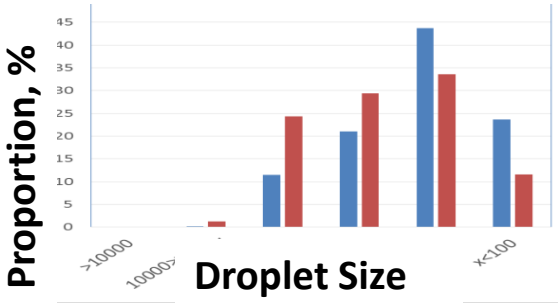
HPH –

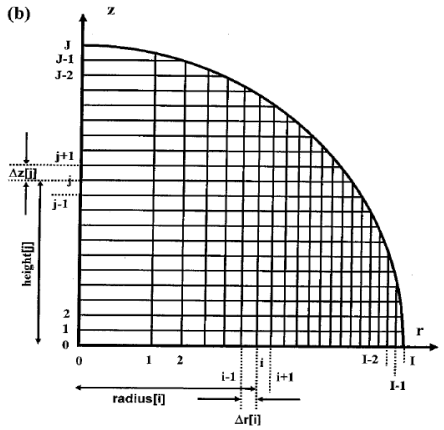
19

2 Lack of Lab to Plant Scalability of Transfer functions contd..

Microsphere technology

Phase Separation

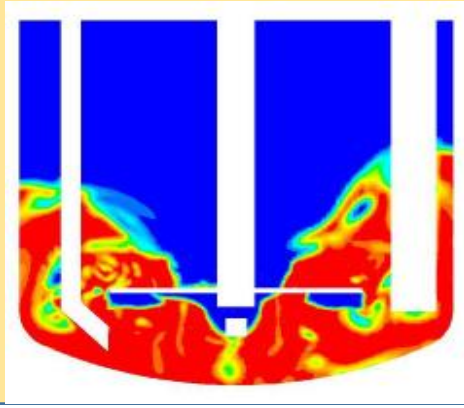




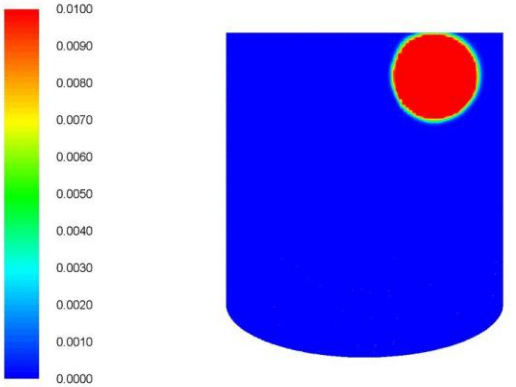
$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial r}\left(D\frac{\partial c}{\partial r}\right) + \frac{D}{r}\frac{\partial c}{\partial r} + \frac{\partial}{\partial z}\left(D\frac{\partial c}{\partial z}\right)$$

Kilo-lab

Intermeidate/Plant Scale



CFD/DEM Simulation



Evaluation whether mixing is adequate and there are no dead zones

3 High Volume & Number of Unit Operations & Interconnects

Managing the vast netwtwork of Equipment Train

- Early Enagement with Vendor and Project team to Finalize the Layout and Utlity area
- Designing the right Qualification for the Area [Grade-A/B/C]
- Skid mounted equipment with CIP/SIP to minimize aseptic interventions
- Automated systems to ensure reproducibility
- Solvent handling systems with required safety procedures
- PAT tools for monitoring particle size, residual s etc
- Suitable drying technologies with aseptic handl (Pharmasep/Refiner/ANFD etc)

Microsphere technology

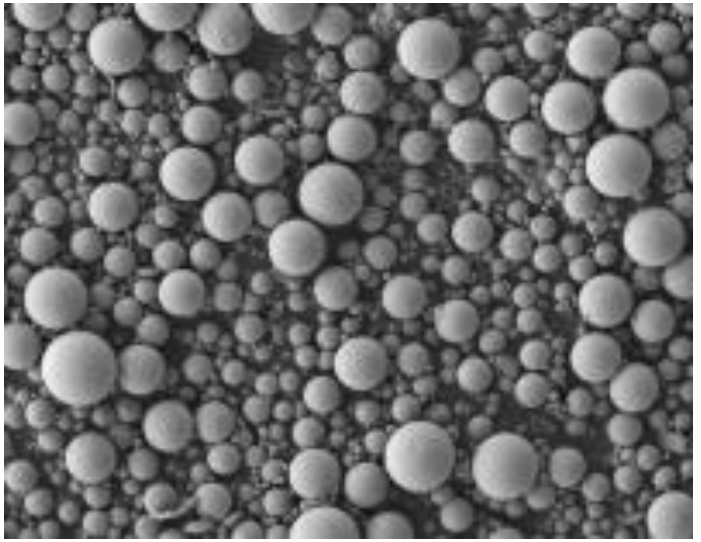
4 Ensuring Reproducibility

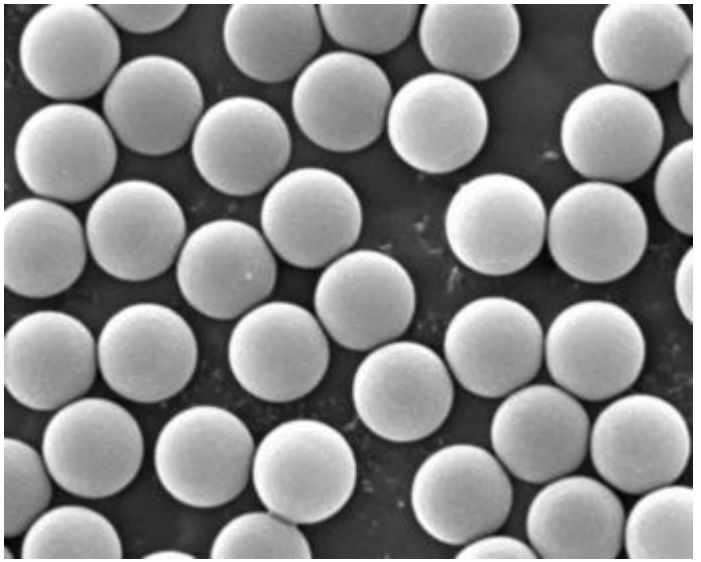
a) Particle Size Distribution (PSD):

Non-uniform particle size distribution (PSD) of microspheres result in poor production yield due to wastage of smaller / larger than desired particles

PSD has critical impact on the several CQAs including :

- Rate of drug release
- Sedimentation behavior of the product
- Ease of syringibility of the product
- Finalization of the needle bore diameter/ gauge

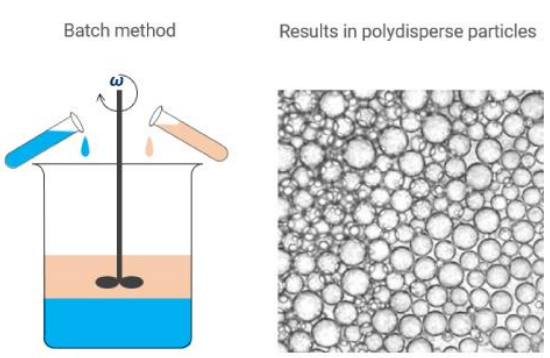


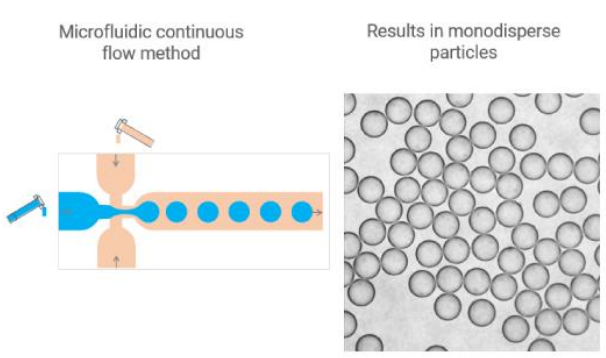


Some Advances in Ensuring Uniformity in Particle Size

The Netherlands based **Emultech's *Microfluidic Emulsification Technology*** produces microspheres using an unique chip with up to 100 identical channels (10, 50 and 100 micron).

The technology claims to produce uniformly sized microspheres in a controlled, predictable and scalable manner.





4 Ensuring Reproducibility

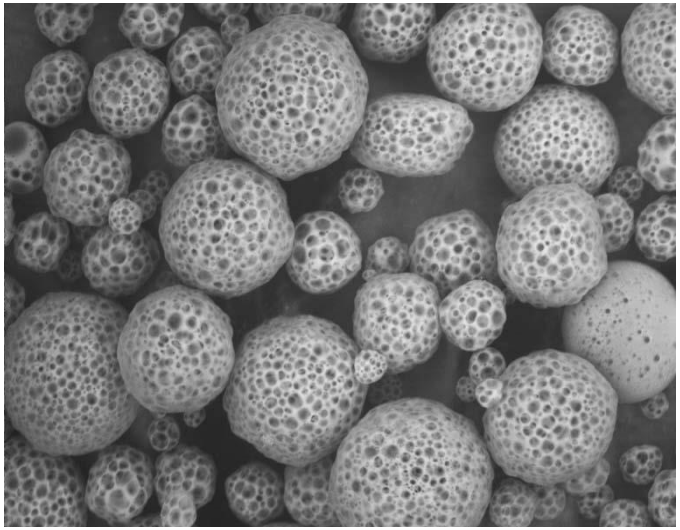
b) Porosity :

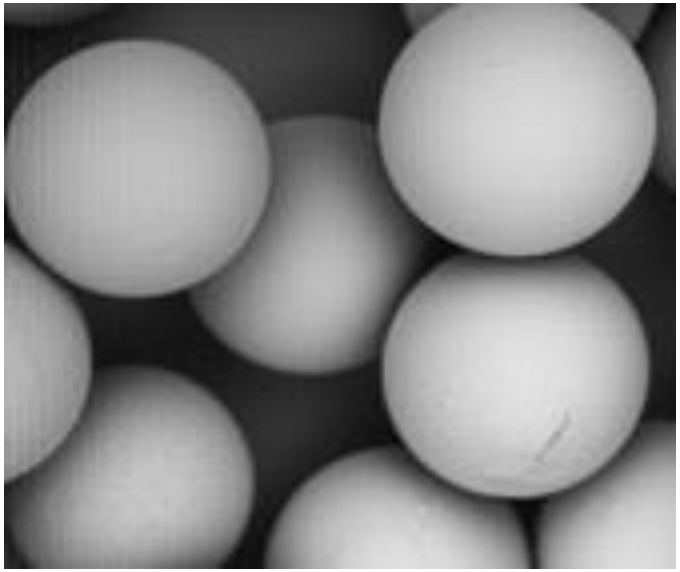
Porosity of microspheres has influence critical CQAs as:

- Burst release
- Overall drug release rate

Automated systems to control CPPs can ensure reproducible porosity:

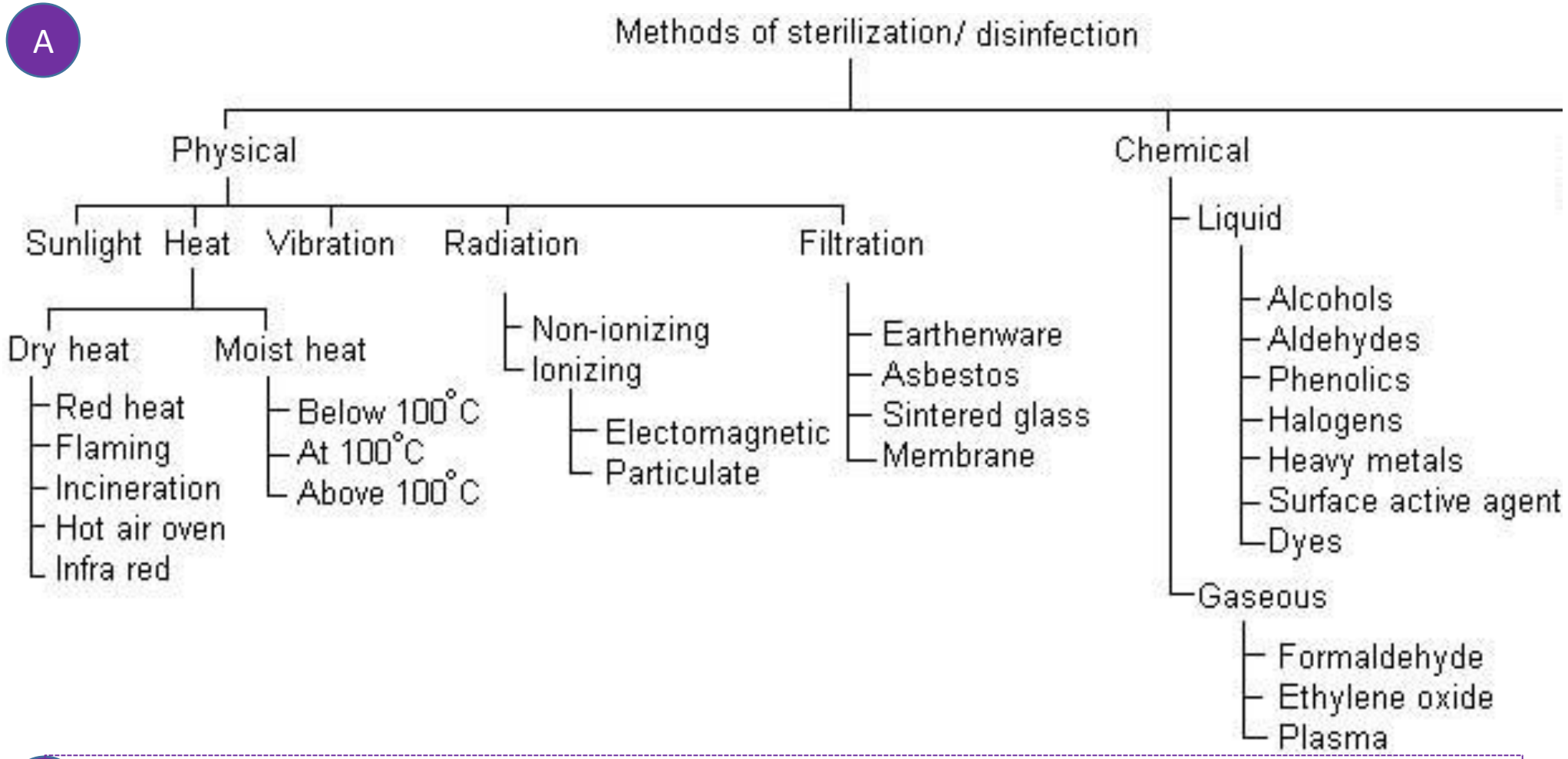
- **Solvent extraction / evaporation stages:**
  - *Temperature*
  - *Pressure*
  - *Vacuum*
- **Product drying stages:**
  - *Temperature*
  - *Pressure*
  - *Vacuum*
  - *Rate of flow of carrier/ drying gas*





5 Sterlity Assurance @ Scale | CIP,SIP,Media Fill, Isolators etc..

A



B Asceptic Manufacturing

B

Aseptic Manufacturing Then, Now and Future trends

History of Parenteral Drugs

- The first experimental injection was done by Christopher Wren on dogs with crude hypodermic needles in 1656. These experiments consisted of using animal bladders (as the syringe) and goose quills (as the needle) to administer drugs such as opium intravenously to dogs. Their main interest was to learn if medicines traditionally administered orally would be effective intravenously.
- In 1831, the first intravenous (IV) therapy of salt, bicarbonate and water was applied to treat cholera patients

Why ,when Parenteral Drugs regulated

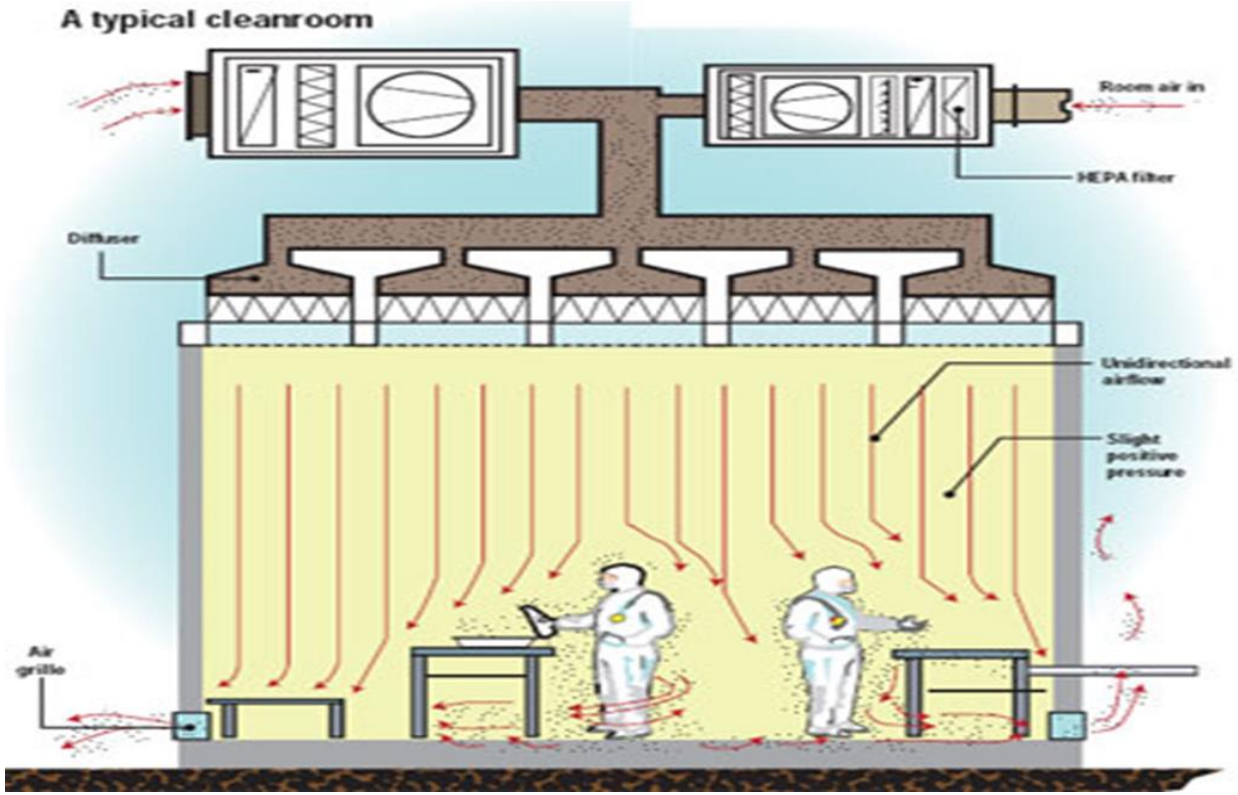
- In 1938, the Food, Drug, and Cosmetic Act was passed by the Congress after the **sulfanilamide incident** where 107 people died due to ingesting this drug dissolved in diethlyene glycol. This Act established FDA which enforced this Act so manufacturers should prove to the government that drug they produce were safe. This provided the legal basis for cGMP and other FDA regulations.

Aseptic Manufacturing Then, Now and Future trends

Dr.Reddy's

First Generation-Aseptic manufacturing- Clean Rooms

- In 1961, clean room technology, including the use of laminar air flow units, high efficient particulate air (HEPA) filters, was introduced. The first clean room classifications was proposed by the US government in 1962



A typical clean room manufacture

- Terminally sterilized Products
- Aseptically filled Products

B

Aseptic Manufacturing Then, Now and Future trends

Second Generation- BARRIER TECHNOLOGY: OPEN & CLOSED RABS

- Open RABS is a simple solution, used extensively in the pharmaceutical sector, to separate the production area from the operator and the external environment. Product protection is only effective if the airflow is active, whereas no protection is offered to the operator when potent compounds are being processed. Easy to install and a cost-effective solution, it is the minimum barrier solution to be used in case of aseptic production environments.

- Closed RABS is an evolution of the “Open” solution, providing a minimal degree of operator protection when potent compounds are being processed.

- Needs Installation in grade B surroundings hence higher operating cost
- Higher Capex investment comparative HVAC (A/B) facilities. Cheaper cost comparative Isolators.

B

Aseptic Manufacturing Then, Now and Future trends

Dr.Reddy's

Current Generation- Aseptic Isolators

- Isolators provide superior environmental control compared with conventional grade A/B aseptic manufacturing operations and restricted access barrier systems (RABS).
- By design, isolators are decontaminated while closed, using validated methods (e.g., controlled application of vapor phase hydrogen peroxide).
- A traditional isolator enclosure consists of a shell, viewing window, glove/sleeve assemblies, supply and exhaust filters, lights, input and output openings (e.g., equipment door airlocks, rapid transfer ports), and various other connection points.

Isolator

- Better confidence on SAL sterility assurance level.
- Can be installed grade C or D area, resulting in low consumables operation cost.
- High capital cost comparative RAB'S

Bio-Valve

4 Emerging Trend –Manufacturing

- Robotic Manufacturing – Powder/Vial Filling
- Robust Manufacturing -QbC through Advanced PAT Technologies
- Seamless inclusion of Big Data Analytics & AI/ML Algorithms
- Process Intensification and precision Manufacturing
- Deeper collaboration with external partners CMO, CRO, CDMOs
- Single Use Technologies and Facilities etc..

4 Emerging Trend -Aseptic Manufacturing

- Single use technologies Mobius bags
- Sterile connectors and disconnectors
- Flexi Isolators to handle potent drugs handling
- Novaseptic bags to handle aseptic sampling in C area
- Charge points to enable powder addition aseptically in non calcified areas
- VHP advancements to surface sanitation specific areas

Thank you

Dr. Reddy's