Advancements in Manufacturing Technology

“Complex Injectables”

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Overview – Advances in Manufacturing Technology

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

Life expectancy, 1879

Life expectancy, 2019

Source: Riley (2005), Cio 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

Working In The Pharmaceutical Industry Allows You To Change People’s Lives For The Better
A Vibrant Trillion Dollar plus Industry; Growing steady globally

- 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

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**Good Health Can’t Wait**

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

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

Commercial presence in 30 countries

- USA
- Russia
- India
- Germany
- Venezuela
- France
- China
- United Kingdom
- Ukraine
- South Africa
- Kazakhstan
- Italy
- Romania
- Australia
- Canada
- Myanmar
- Belarus
- Spain
- Uzbekistan
- Vietnam
- Sri Lanka
- Jamaica
- New Zealand
- Switzerland
- Netherlands
- Brazil
- Mexico
- Colombia
- Japan
- Malaysia

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

**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

In terms of “Limited Competition and ROI”

Complex Generics is one of the BEST available options for the Industry.
Complex Injectables
Introduction & Development..
Introduction – Complex Injectable

**Gamut of Technologies**
- Polymer/Oil based
- Emulsions
- Complex technology platform
- Colloidal Suspension
- Liposomes
- Peptides
- Microsphere

**Where lies the complexity**
- API & Formulation Development
- Pharmaco-vigilance
- Innovative and Affordable Medicines
- Cost, Quality & Availability
- Scale-up & Manufacturing
- Portfolio, Sales & Marketing
- Regulatory Approval
- Regulatory & IP Diligence
- Regulatory Inspections
Complex Injectables – Development Hurdles?

1. Requires advanced characterization tools and techniques.
2. Needs a customized set of equipment even at lab scale.
3. High investment in PAT and QbC Technologies.
4. Steep RM, PPM, and experimentation costs, leading to longer development cycles.
5. Nuturing and maintaining the right talent flow.

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Dr. Reddy's Laboratories Ltd.
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. Sterility Assurance @ Scale | CIP, SIP, Media Fill, Isolators etc..
6. Robust & Agile Manufacturing Process @ Scale
Understanding the Product CQAs and CPPs & CMAs linkage

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

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

**CQAs**

*Case study: Microsphere technology*

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

Process conditions can impact product quality

Important to ensure similarity of process conditions at lab/ plant scales during scale-up
Lack of Lab to Plant Scalability of Transfer functions

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
- Non-dimensional particle Size
- Screenin SI & SD Parameters

Scale-independent process parameter
Lack of Lab to Plant Scalability of Transfer functions contd..

**Geomterical Similarity across the scale for right Transfer function**

Vessels with GMP & HSH

10 L 10 L 50 L 100 L 200 L

Vessels with Helical/ Anchor

10 L 30 L 100 L

Bead Mill

CMX (10L – 100L)

Sonicator

HPH –

Bead Mill

CMX (10L – 100L)

Sonicator

HPH –
Lack of Lab to Plant Scalability of Transfer functions contd..

Microsphere technology

Phase Separation

Droplet Size

Proportion, %

Kilo-lab

Intermeidate/Plant Scale

CFD/DEM Simulation

Evaluation whether mixing is adequate and there are no dead zones

\[ \frac{\partial c}{\partial t} = \frac{\partial}{\partial r} \left( D \frac{\partial c}{\partial r} \right) + \frac{D}{r} \frac{\partial c}{\partial r} + \frac{\partial}{\partial z} \left( D \frac{\partial c}{\partial z} \right) \]
High Volume & Number of Unit Operations & Interconnects

Managing the vast network of Equipment Train

- Early Engagement with Vendor and Project team to Finalize the Layout and Utility 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 solvents etc
- Suitable drying technologies with aseptic handling (Pharmasep/Refiner/ANFD etc)
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.
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
Methods of sterilization/disinfection

**Physical**
- Sunlight
- Heat
- Vibration
- Radiation

**Chemical**
- Filtration
  - Non-ionizing
    - Ionizing
      - Electromagnetic
      - Particulate
  - Earthenware
  - Asbestos
  - Sintered glass
  - Membrane

**Liquid**
- Alcohols
- Aldehydes
- Phenolics
- Halogens
- Heavy metals
- Surface active agent
- Dyes

**Gaseous**
- Formaldehyde
- Ethylene oxide
- Plasma

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Asceptic Manufacturing
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 diethylene 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.
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.
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.
Aseptic Manufacturing Then, Now and Future trends

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.

- 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
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.
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