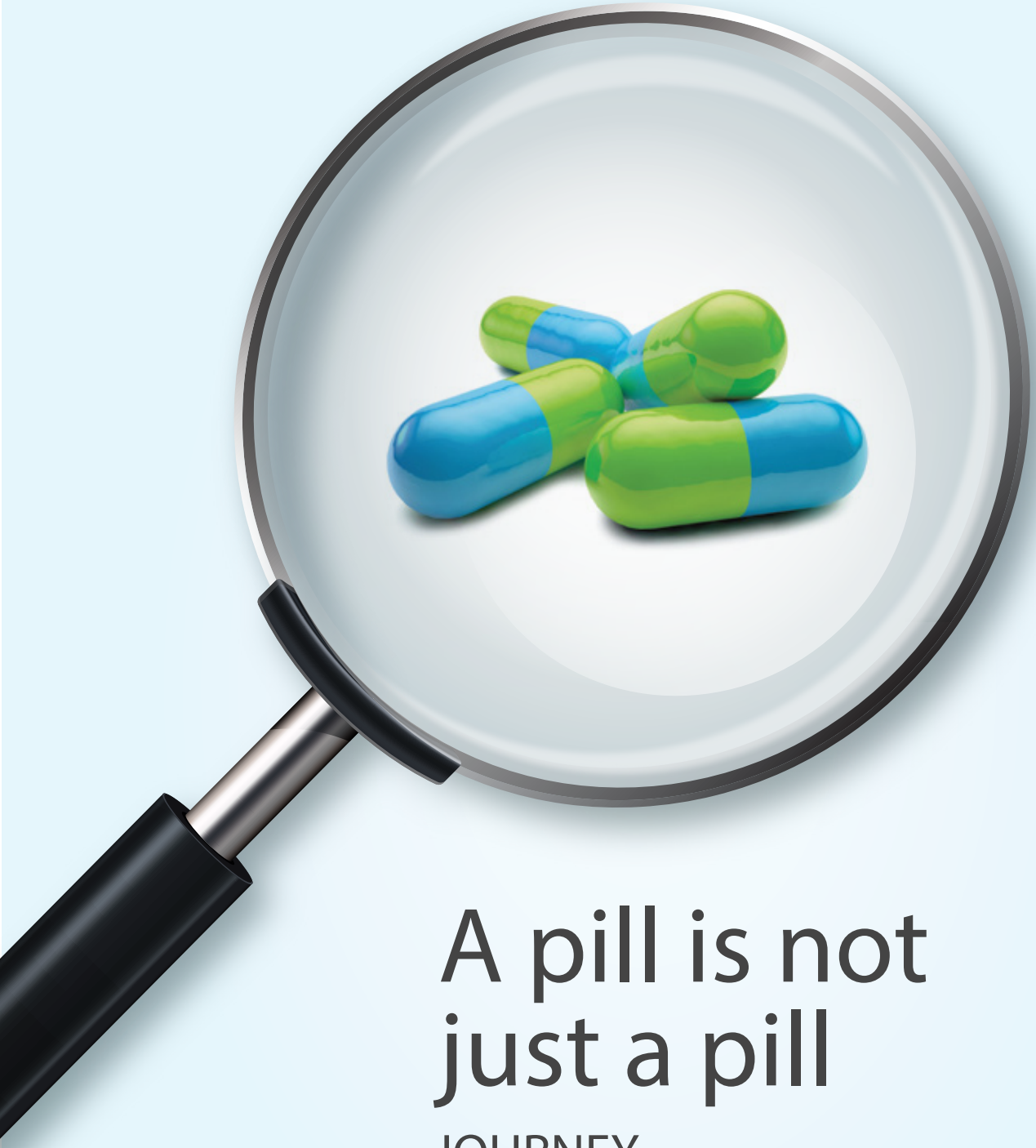
OPPI



A pill is not just a pill

JOURNEY TOWARDS EXCELLENCE IN QUALITY

OPPI Quality Summit 2018

Foreword

"Quality should be embedded in every stage of the medicine-making process and across the delivery chain – from the R&D laboratory to the pharmacy where the patient buys the drugs"

Each time we pop a pill, feed syrup to our children, vaccinate our babies or inject a medicine into our critically-ill loved ones, there is hope, that it will work. But, we are totally oblivious to the untold story of the medicine. While it owes its existence to research and discovery, the intrinsic value of the pill in its living form lies in its quality. Quality does not confine itself to manufacturing alone. It includes packaging, labelling, transportation and storage of the medicine. All these elements in the supply chain are critical for a medicine to retain its effectiveness.

Quality in general is a comparison to standards. Pharmaceutical quality is very specific because for each pharma product like a tablet or capsule, there are specifications. And within tablets there are individual specifications for each individual product. There is a specification for each pharma dosage form and there is also a quality specification for each therapy area product that they must comply with to be able to assert that the products meet quality specifications.

Millions of people all over the world are alive and in good health today because they have "trusted" the pill to do its job. "Trust"- the result of the doctor—patient relationship and in the pill that is expected to do its work. Good manufacturing practices, good distribution practices, good storage practices and good quality control practices make for a "good" pill. Thus, making for a positive end to the story of the pill being more than just a pill!

Keeping the patient at the centre of all our activities, the Organisation of Pharmaceutical Producers of India (OPPI) in collaboration with the Department of Pharmaceuticals (DoP), the major industry associations, viz, the Indian Pharmaceutical Alliance (IPA), and the Indian Drug Manufacturers Association (IDMA) organised the first-of-its-kind, Quality Summit 2018, to set an agenda that would:

- Align on the importance of setting and adopting best-in-class global quality standards for the pharmaceutical industry;
- Bring all stakeholders together – regulators, industry and governments, both State and Central – to create the enabling conditions for achieving this goal,
- Define the quality roadmap for India.

It is imperative to build a quality culture in the country. As an industry association we believe that it is critical for the industry to provide quality medicines to the millions of patients in the country, today. The conversations on quality have just begun to be heard. This report documents the key learnings from the Summit. While the government is working towards upgrading quality standards in the country, industry representatives, industry associations and patient groups need to play their role in delivering quality medicines.

Quality is a continuous journey, not a destination. We must keep working at it in a sustained fashion.

A.Vaidheesh
President – OPPI
Vice President, South Asia and Managing Director, India.
Glaxo SmithKline Pharmaceuticals Ltd

Kanchana TK
Director General – OPPI

Acknowledgements

OPPI would like to acknowledge the team from McKinsey & Company for their insights in this whitepaper.

We acknowledge Dr Sanjit Singh Lamba, Chair – OPPI Technical & Supply Chain Committee & Managing Director, Eisai Pharmaceuticals India Pvt Ltd, for his guidance and technical input in the making of this report.

We acknowledge Kanchana TK, Director General, OPPI, whose vision and direction has helped in making this study a – reality. We would like to thank our colleagues from the industry, D.G. Shah, Indian Pharmaceutical Alliance and Daara Patel, Indian Drug Manufacturers' Association, who participated in the discussions on quality.

Finally, we acknowledge the efforts of our OPPI– colleagues, Nitika Garg – Director Research, who has been the primary lead on this project and Bhavna Singh – Director Communications, for design and editorial support.

OPPI

INTERVIEW OF DR SANJIT SINGH LAMBA CHAIR — OPPI TECHNICAL & SUPPLY CHAIN COMMITTEE & MANAGING DIRECTOR, EISAI PHARMACEUTICALS INDIA PVT LTD

SPEAKS ON QUALITY BY DESIGN (QBD) PRINCIPLES AND THE BENEFITS OF GLOBAL GUIDELINES TO IMPROVE THE QUALITY OF PHARMACEUTICAL PRODUCTS

How can formulation scientists implement QbD principles as defined in ICH Q8 (R2)? What are the other global guidelines that need to be followed?

FDA initiated Quality by Design (QbD) and Process Analytical Technology (PAT)- principles in 2003 with the purpose of building quality into the product right from the beginning of manufacturing (Food and Drug Administration, 2006). The traditional Quality by Testing (QbT) approach tests product quality by checking it against the approved regulatory specifications at the end of manufacturing stream. QbD principles promote innovation and continuous improvement of the product. Knowledge based commercial manufacturing ensures enough regulatory flexibility for setting specifications and post approval changes. Product and process are designed using innovative risk-based techniques to meet predefined quality objectives, thereby satisfying the most critical patient needs and regulatory requirements at low cost. Innovative approaches such as quality management programs, process capability measurements, six sigma, lean manufacturing and continuous improvement programs can be adopted to improve the quality of pharmaceutical products. Understanding the relationship between critical material and critical process attributes, culminates in process control and continuous improvement.

» The first crucial step in any formulation development is to understand the product profile which is called as Quality Target Product Profile (QTPP) in terms of regulatory

» Once QTPP is identified, formulation scientists need to define the - “potential” critical qualities or attributes of the product (CQAs)

» Risk assessment to be carried out to link raw material attributes and process parameters to CQAs, based on risk assessment control strategy shall be designed and implemented

» Once control strategy is implemented, there is a need to manage product life cycle within the design and which becomes part of continual improvement

What are the other global guidelines that need to be followed?

» The following guidelines are — crucial for product development

- ICH Q9 Quality Risk Management
- ICH Q8 (R2) Pharmaceutical Development
- Q10 Pharmaceutical Quality Systems

What are the benefits of implementing QbD principles at the formulation development stage?

There are many benefits of QbD at formulation development stage, few of them are listed below which are crucial to deliver cost-efficient approach for delivering high-quality drug substances and drug products consistently:

» Product is developed /built considering customer (patient's) need

» Robust process is developed as it focuses on control strategy rather than testing

» Overall development is systematic and multivariate experiments are conducted to understand the process and product which establish a design space

» The process can be adjustable within design space rather than fixed process

» Product life cycle is managed as a preventive action rather than reactive problem solving

Are there most costs involved as it means more rigorous testing and documentation? What are the ROI, payoff, benefits?

» The cost involved during development depends on the product profile and process. Proper risk assessment is key to avoid more experimentation, testing and documentation

» If the control strategy and design space is well-established then definitely there will be benefits considering the product scale-up and commercialization which can eliminate the risk of product failure and consistency in the manufacturing

» Avoid delay in the process validation. In current scenario more efforts are required during process validation which can be minimized

» Process can be changed within the design space (PAR values) which helps to avoid the regulatory filings updation, variations and follow-ups

The above points can save cost in terms of both time and money

Can you give some examples of how using QbD in FR&D in your projects has resulted in savings in time, costs, regulatory hurdles, when a product is in the process of being scaled up or moved to production stages?

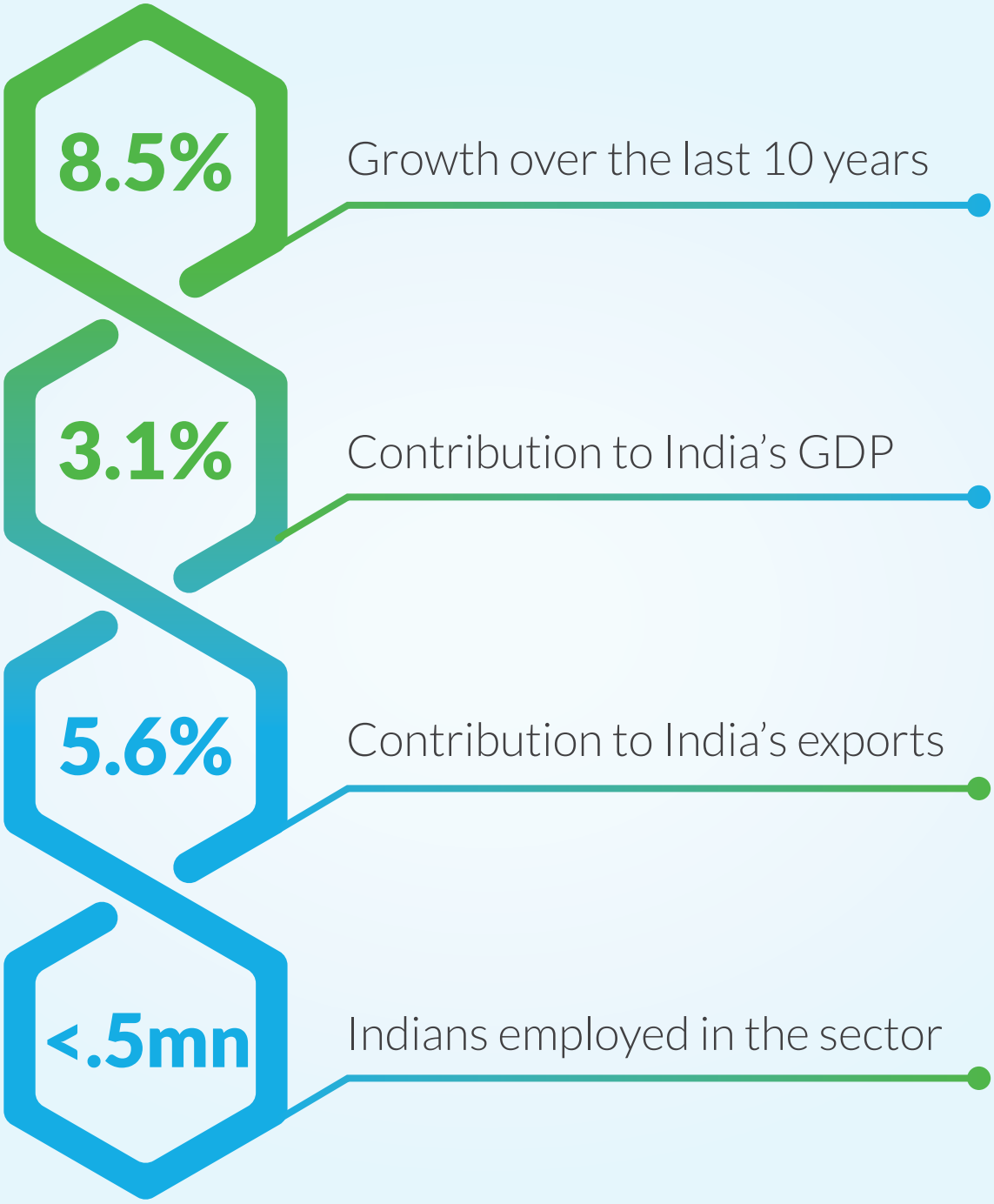
One of the products we are manufacturing for the Japanese market is a case in itself. During commercial manufacturing we observed extended drying time for intermediate stage which resulted in about 7 days delay in batch cycle and which is huge, considering the product demand and supply.

Considering above, it was required to change the input quantity of solvents in the process. When we approached the regulator, they accepted this change as a very minor change. This is because we had considered a change within the design space and it was well mentioned and explained in the filing dossier.

This is a classic example of how a well-defined design space can be helpful for continuous manufacturing and to provide uninterrupted supply of the quality product at a competitive cost structure.

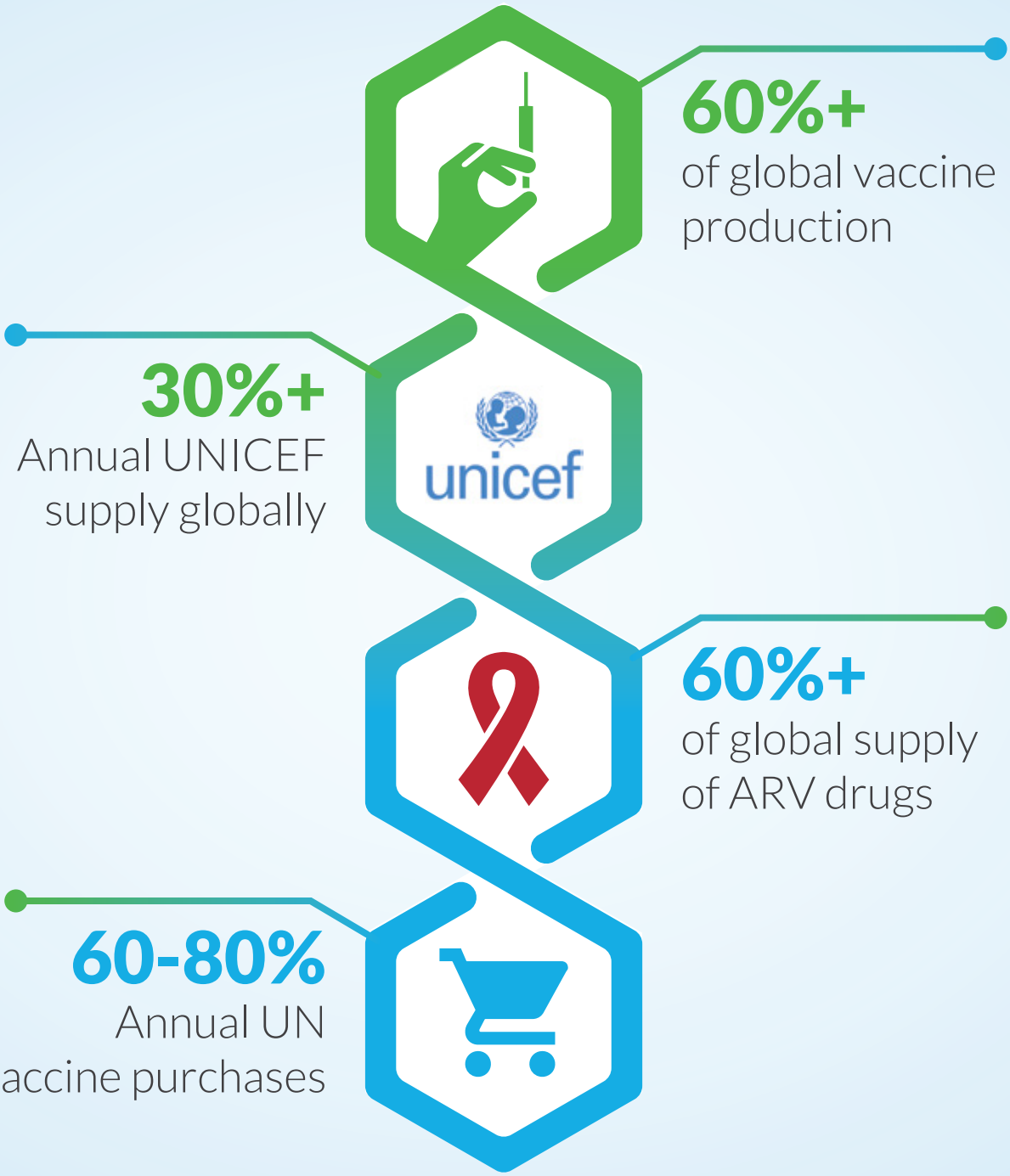
SOURCE: Express Pharma, Special GMP, May 2018

INDIAN PHARMA INDUSTRY HAS CONTRIBUTED IMMENSELY TO DRIVING HEALTHCARE OBJECTIVES AND ECONOMIC GROWTH IN INDIA



SOURCE: The Economist Intelligence Unit, IBEF and The Hindustan Times, The Economic Times

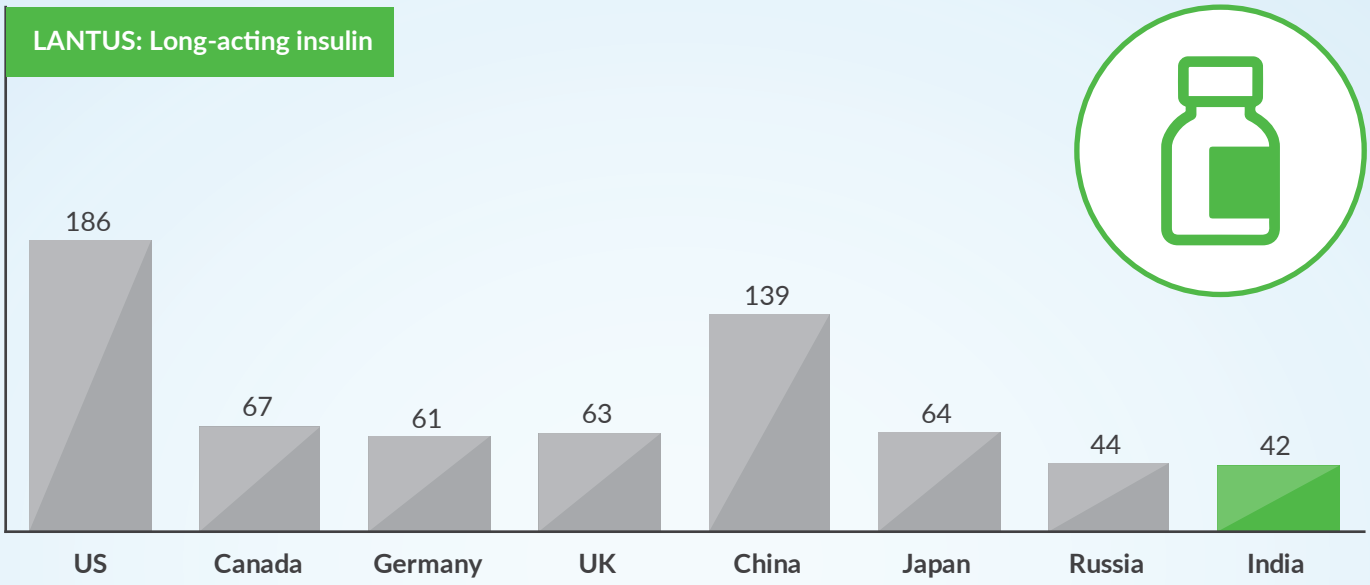
INDIA HAS CONTRIBUTED NOT JUST TO THE HEALTH OUTCOMES IN INDIA BUT ALSO GLOBALLY

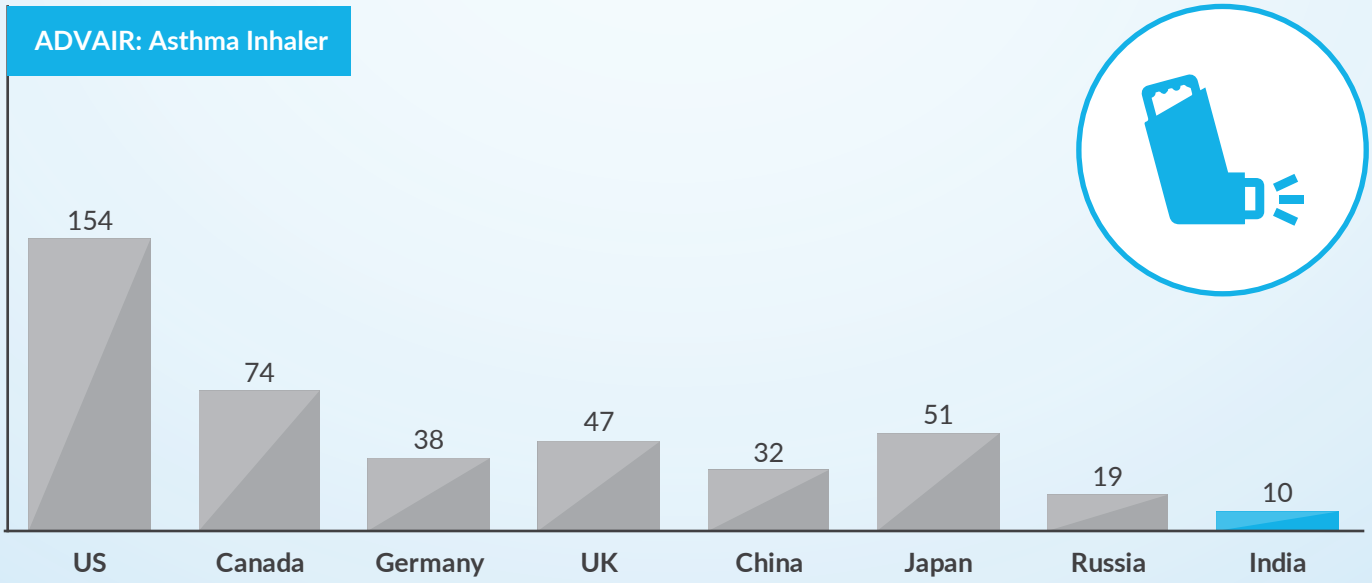


SOURCE: Quality Excellence: The next frontier for Indian pharma industry, IPA whitepaper 2016; "Affordable Efficacious Medicines – All Roads Lead to India" report by IDMA; "Vaccines Market in India" report by Netherlands Office of Science and Technology

WE CONTINUE TO DRIVE AVAILABILITY OF HIGH QUALITY DRUGS AT LOW COSTS

Comparative price of drugs (USD per month)





SOURCE: www.Bloomberg.com

HOWEVER, MANY INSTANCES OF QUALITY ISSUES RELATED TO PRODUCTS MANUFACTURED IN INDIA HAVE SURFACED

Drug quality is one of the major challenges faced by the industry and has been reported extensively in the public domain

Quality of generic drugs in question

Drugs recalled six times over the last three months – six batches have failed the quality standards. Bureau of Pharma Public Sector Undertakings of India, which oversees the distribution of drugs in the generic drug stores, do not have a quality control manager.

Drugs sold in India not of standard quality

Drug regulator USFDA raised concerns on the quality and efficacy of medicines being sold in India. This is perhaps the first instance that a foreign drug regulator has spoken about the quality of medicines being sold in the country.

Indian drugs: not what the doctor ordered

Last year, Israeli generics company, Teva recalled 40,000 bottles of medicine manufactured for it by an Indian company.

4.5% of the drugs in Indian market are substandard

Substandard drugs are less effective, causing diseases to run a longer course and may even require a new prescription drug treatment. Substandard drugs also contribute to anti-bacterial resistance, a threat that has doubled in India in the last five years.

SOURCE: The Hindu, The Economic Times, The Financial Times, www.Indiaspend.com

GOALS OF MEDICINE QUALITY ASSURANCE PROGRAM

To make certain that each medicine reaching a patient is safe, effective, and of standard quality

QUALITY IN MFG

Obtaining quality products that are safe and effective and manufactured through **good manufacturing practices**

QUALITY IN SCM

Maintaining quality products through appropriate **storage, distribution**, **monitoring** and **use** by prescribers and patients

WHO-GMP

BASICS OF GMP AND SCHEDULE M

- **Good Manufacturing Practices** (GMP also referred to as 'cGMP' or 'current Good Manufacturing Practice') is the aspect of quality assurance that ensures medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the product specification
- **Schedule M** is a part of Drug and Cosmetics Act 1940. It lays down guidelines of GMP for pharmaceuticals that must be followed by pharmaceutical manufacturing units in India
- The **flexibility** in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement
- Accordingly, the **"C" in cGMP** stands for "**current**," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations

SCHEDULE M TO WHO GMP AND BEYOND...

1. Schedule M
2. WHO GMP
3. PIC/S Pharmaceutical Inspection Co-operation Scheme
4. **USFDA, MHRA, PMDA**

By implementing WHO GMP and PIC/S , India can aim to meet stringent global standards.

WHO-GMP

FDA

MHRA Regulating Medicines and Medical Devices

pmda

COMPARISON OF WHO AND SCHEDULE M – OVERVIEW

Not much difference with respect to basic GMP requirements

WHO GMP guidelines evolved to the modern quality management system concepts of ICH Q9 and Q10

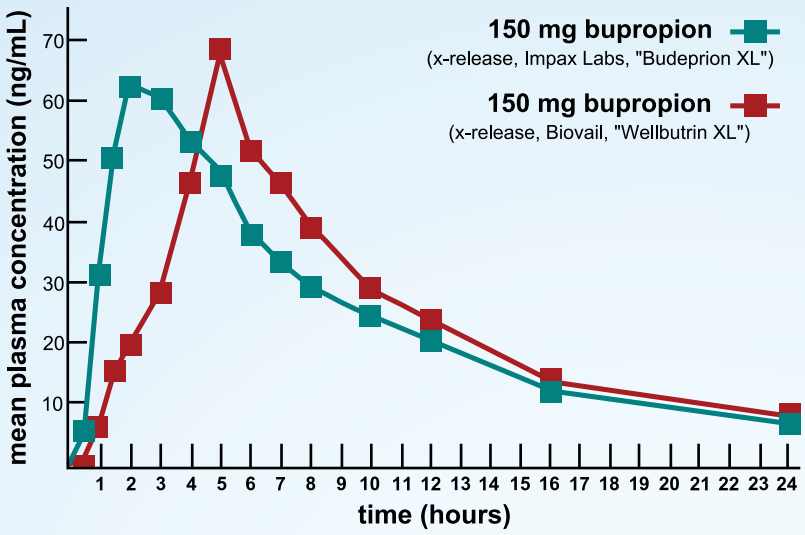
WHO GMP – Quality Risk Management Principles are integrated with every aspect of Quality Management System

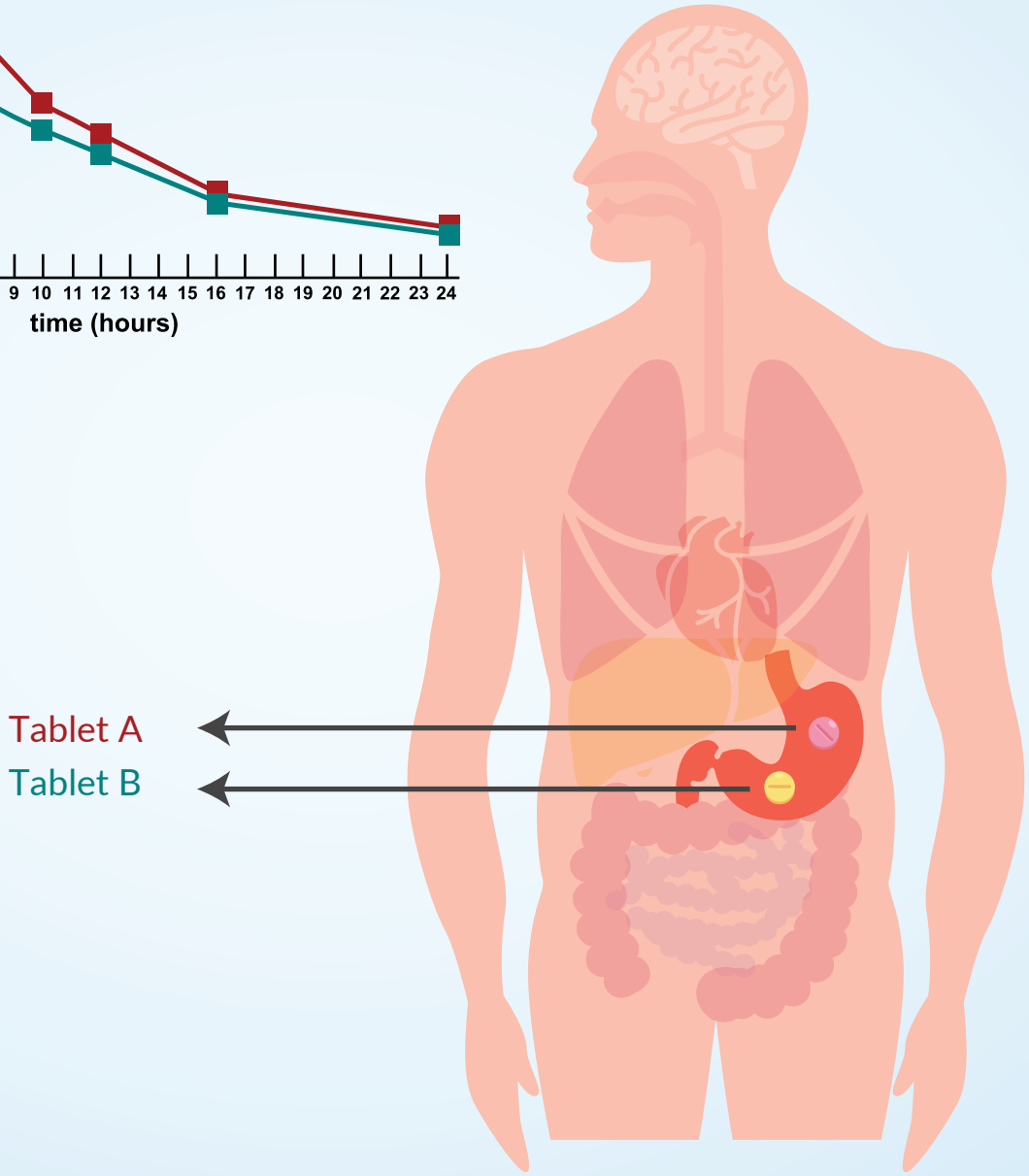
Data Integrity elements are clearly defined in WHO guidance

WHO technical reports clearly spell out the requirements of modern quality systems, e.g.: Sampling, HVAC, Hold studies, Good warehousing and distribution practices etc.

* Data integrity refers to maintaining and assuring the accuracy and consistency of data over the entire data life-cycle

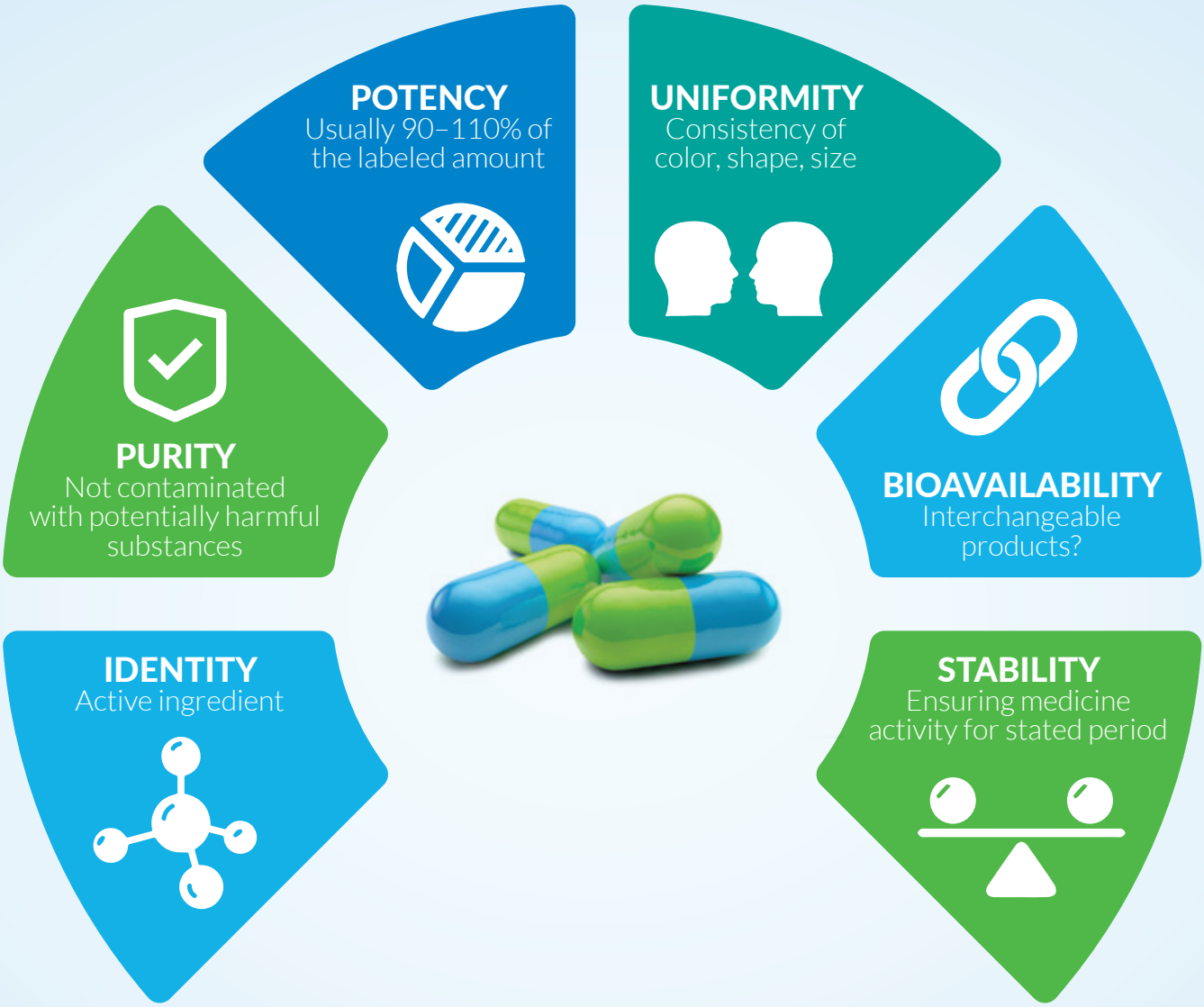
PHARMACEUTICAL EQUIVALENT vs BIOEQUIVALENT





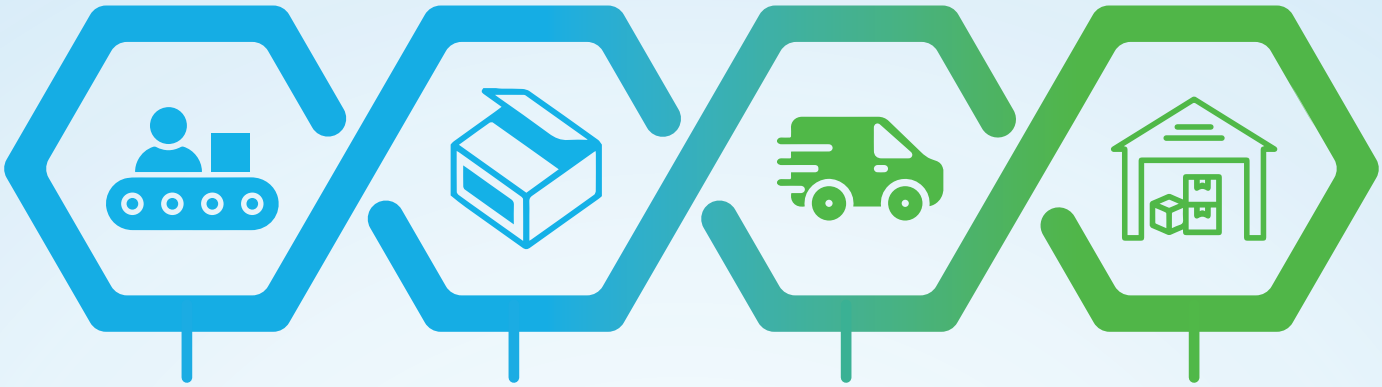
- Tablet A is different in bioequivalency from Tablet B if the rate and extent of its availability in blood stream is different
- Therefore, the two tablets may look the same but are not the same

DETERMINANTS OF MEDICINE QUALITY



Identity, purity, potency, uniformity are defined in pharmacopoeias and stated in certificate of analysis (COA) of each lot of the product

IMPACT OF LOW-QUALITY MEDICINES



Low quality / Poor quality

- **Lack of therapeutic effect** — Prolonged illness
- **Toxic & adverse reaction** — Death
- **Waste of limited financial resources**
- **Loss of credibility**
- **Distress to patients & their family members**

HOW IS MEDICINE QUALITY ASSURED?

Development

The objective of the development phase is "Quality to be built into the Product" – Quality by Design

Manufacturing

The objective of this phase is to manufacture under Good Manufacturing Practice guidelines

Distribution

The objective of distribution is also to properly store, handle and protect the goods and supply them to consumers in good condition

PROCESSES

CONTROLS

Adequate temperature control, security, and cleanliness

- **Man** – Competent personnel, proficient in cGMP and thorough understanding of the process
- **Machine** – High precision, well-controlled, high process capability
- **Material** – Strict supplier controls, incoming testing and consistency
- **Method** – Operational controls, clear written instructions

Developing a flexible and robust product through risk management principles. Critical process parameters and product specifications are well defined.

Effective controls throughout the Product Life Cycle ensure Product Quality and Patient Safety

QUALITY IN COMPLETE VALUE CHAIN

Procurement
- Raw material
- Intermediates
- Packaging material

Manufacturing
- Granulation
- Blending
- Tablet compression
- Tablet coating
- Tablet packing

Logistics
- Multiple legs
- Ground transport
- Air /sea route
- Temperature monitoring

Warehousing
- Finished product storage
- Maintain storage conditions
- Documentation (invoicing, packing list etc)

- Finished goods
- Patient
- Pharmacovigilance
- Periodic safety update reports
- Adverse drug reactions

THE QUALITY GAP

Product quality or robustness

- Variability in processes & method robustness needed for consistent quality
- Inability to consistently identify root cause of quality issues. Insufficient focus on continuous improvement

Quality systems & standards vis-à-vis best practices

- Gaps in key quality processes e.g., complaint management, pharmacovigilance vis-à-vis best practices

Facilities & infrastructure

- Gaps related to buildings, equipment & other physical infrastructure
- Need to upgrade IT-infrastructure to maintain data reliability

Quality culture & capabilities

- Insufficient industry-ready talent and Internal training processes
- Limited line ownership of quality across functions and levels

Discipline & governance

- Gaps in ensuring adherence to standards or SOPs
- Limited use of metrics around product quality (e.g. deviations, variability - CpK)

Special Case: MSMEs

- Revised guidelines classify MSME based on annual sales turnover
  - Micro: up to 5 cr
  - Small: up to 75 cr
  - Medium: up to 250 cr
- There are an estimated 4,000+ MSMEs in India with limited clarity on split across Micro, Small & Medium categories
- Many MSMEs have not made adequate investments, nor do they have the resources (human, financial) to address these issues

THE GAP – REGULATORY PERSPECTIVE

Standards not in line with best-in-class

- Schedule M provides robust guidelines but needs to be upgraded to global standards. Need to adopt WHO GMP & develop a roadmap for PIC/S

Variable adherence to standards

- Low adherence to Schedule M guidelines for many pharmaceutical manufacturers. Need to ensure 100% compliance

Need for regulations on other stakeholders

- Regulations largely applied to pharmaceutical manufacturers. Need to extend to other stake-holders in value chain e.g., distributors, pharmacies

Variability in Central and State drug approvals

- In several cases the State and Central drug approvals are not harmonized

DIFFERENT STAKEHOLDERS NEED TO PLAY AN IMPORTANT ROLE TO OVERCOME QUALITY CHALLENGES

Pharmaceutical manufacturers

Activities

Stage 1

Achieve 100% compliance to regulatory guidelines

- Ensure sites achieve full compliance vis-à-vis regulatory guidelines

Stage 2

Put in place robust quality systems

- Instill the right quality processes (e.g., data reliability, lab controls)
- Improve product robustness and put in place continuous improvement practices
- Upgrade facilities & infrastructure
- Design the right quality organization with adequate resources
- Create a strong discipline to achieve high quality

Stage 3

Achieve excellence in quality on a sustainable basis

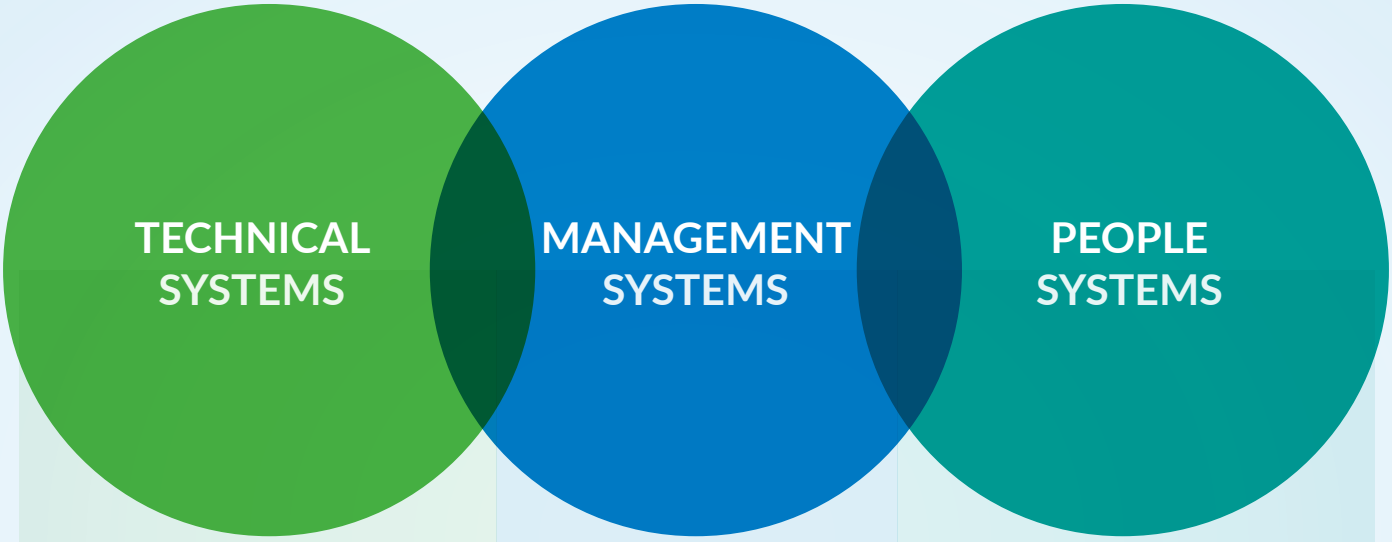
- Build a robust quality culture across the network
- Develop capabilities in quality excellence across all cohorts
- Adopt mechanization / automation (even at low cost) to ensure error-proofing

Around 80% of the pharma manufacturers are at Stage 1. Most of the rest have progressed only to Stage 2. Very few are close to Stage 3 — achieving excellence in quality.

PHARMACOS NEED TO TAKE INITIATIVES ACROSS TECHNICAL, MANAGEMENT & PEOPLE SYSTEMS

Pharmaceutical manufacturers

Illustrative list of interventions – variable application based on which stage the pharmaco lies in



Putting in place best-in-class technical systems & processes which are core to the quality system

- Understanding of unit operations
- Data reliability
- Quality Risk Management
- Product & process robustness
- Supplier Quality Management
- Investigation / Root cause assessment of non-conformances
- Good Documentation Practices

Setting up formal quality performance management tools (e.g., metrics, governance, roles) supported by the right quality organisation to drive results

- Quality metrics (cascaded from the CEO to the shop floor level)
- Visual & real-time performance management
- Robust governance mechanism
- Strong quality organization
- Clarity in roles & responsibilities with KRAs

Creating a robust quality culture & capabilities from senior management to the shop floor level – building the right skills, mindsets, behaviours and ownership

- Openness & transparency
- Shop floor connect -Gemba
- Cross-functional collaboration
- Leadership role modelling
- Addressing specific capability gaps
- Upgrading training systems

WE HAVE IDENTIFIED 5 PRIORITY AREAS FOR THE INDUSTRY

Pharmaceutical manufacturers

Maintain uniform baseline quality standards across units and for both domestic and export markets

Upgrade to a robust QMS that incorporates industry best practices

Embed a quality culture driven by top and middle managers

Build technical, managerial and behavioural capabilities across all levels in the organization

Establish basic to drive consistency in quality by reducing manual processes

GOVERNMENT AND REGULATORY PERSPECTIVE – SEVERAL INITIATIVES HAVE BEEN TAKEN TO IMPROVE QUALITY STANDARDS IN INDIA

Government and Regulators

1. Creation of national digital database of pharmaceutical manufacturers and their medicines (SUGAM) to facilitate easy inspections and ensure quality
2. Stringent penalties under Drugs & Cosmetics (Amendment) Act 2008 for manufacture of spurious and adulterated drugs, with select offences made cognizable and non-bailable
3. Mandatory bioequivalence studies/ bioavailability tests in India for drugs before market launch – Health Ministry
4. Ban on import of raw material from 10 Chinese drug companies by DCGI for supplying APIs due to lack of mandatory drug manufacturing standards
5. Hiring and skill-building of inspectors for GMP enforcement done for the current batch

SOURCE: The Economic Times, www.fda.up.nic.in; ET Healthworld, The Economic Times, expert conversations

REGULATORS IN VARIOUS COUNTRIES ARE ALSO TAKING STEPS TO DRIVE QUALITY IMPROVEMENT

Government and Regulators

China Interventions	What they mean?
GMP implementation/ inspection	• Initiatives to further screen out low-quality pharmacos. e.g., unannounced inspections, CFDA inspection capacity expansion, and preparation to join PIC/S • By 2015 end, 25% of pharmacos' licenses revoked due to new GMP implementation
Quality consistency evaluation (QCE)	• All Gx approved without quality consistency evaluation vs. off-patent originators to conduct QCE • Registration to be revoked if pharmaco fails to complete QCE before next registration renewal
Quality consideration in tendering	• Encourage favourable consideration in provincial tendering for those who passed QCE
Gx registration	• CFDA reform, including clear goals to accelerate registration timeline • Clinical data self-inspection • Accelerated approval for queuing applications

6 POTENTIAL THEMES EMERGE FOR GOVERNMENT AND REGULATORY AGENCIES IN INDIA

Government and Regulators

Regulatory agencies (Central and State)

- **Adopt WHO GMP** as the baseline for quality standards across Indian sites
- **Develop roadmap to join PIC/S,** allowing further harmonization of GMP standards and quality systems
- **Strengthen drug filing requirements in India** to introduce adequate checks to ensure robustness of new products filed & approved.
- **Extend regulatory and quality checks till last mile,** including distributors and retailers
- **Cooperation with other regulators** to join audit & skill building sessions in a stage-wise process

Government

- **Provide requisite financial support to ensure baseline standards** met by all including MSME sites in India and bring policy changes

INDUSTRY ASSOCIATIONS CAN PLAY A KEY ROLE IN DRIVING THE DRUG QUALITY OBJECTIVE IN THE COUNTRY

Industry associations

Build awareness about the importance of quality and the current gaps vis-à-vis baseline quality standards

Hold sessions for regulators with industry and industry associations to support interaction and skill building

Create a common platform for industry players to understand / identify opportunities and adopt best practices

Quality is not a one-time activity, it is a journey. A journey, that we all have to take together to remain the leading supplier of highest quality drugs to patients in India and the world.

OPPI

Organisation of Pharmaceutical Producers of India
Peninsula Chambers, Ground Floor, Peninsula Corporate Park
G.K. Marg, Lower Parel, Mumbai 400 013,
Tel: +91 22 2491 8123, 2491 2486, 66627007
www.indiaoppi.com

Follow us on: