pharma mantra
Quality Advisory Consultancy

Challenges in Pharmaceutical Project Management

New Product Development, Manufacturing Scale up & Commercialization

8thMarch, 2018
Hotel Orchid, Mumbai

Udaykumar K. Rakibe
M.Pharm., M.B.A.
Pharmantra.expert@gmail.com

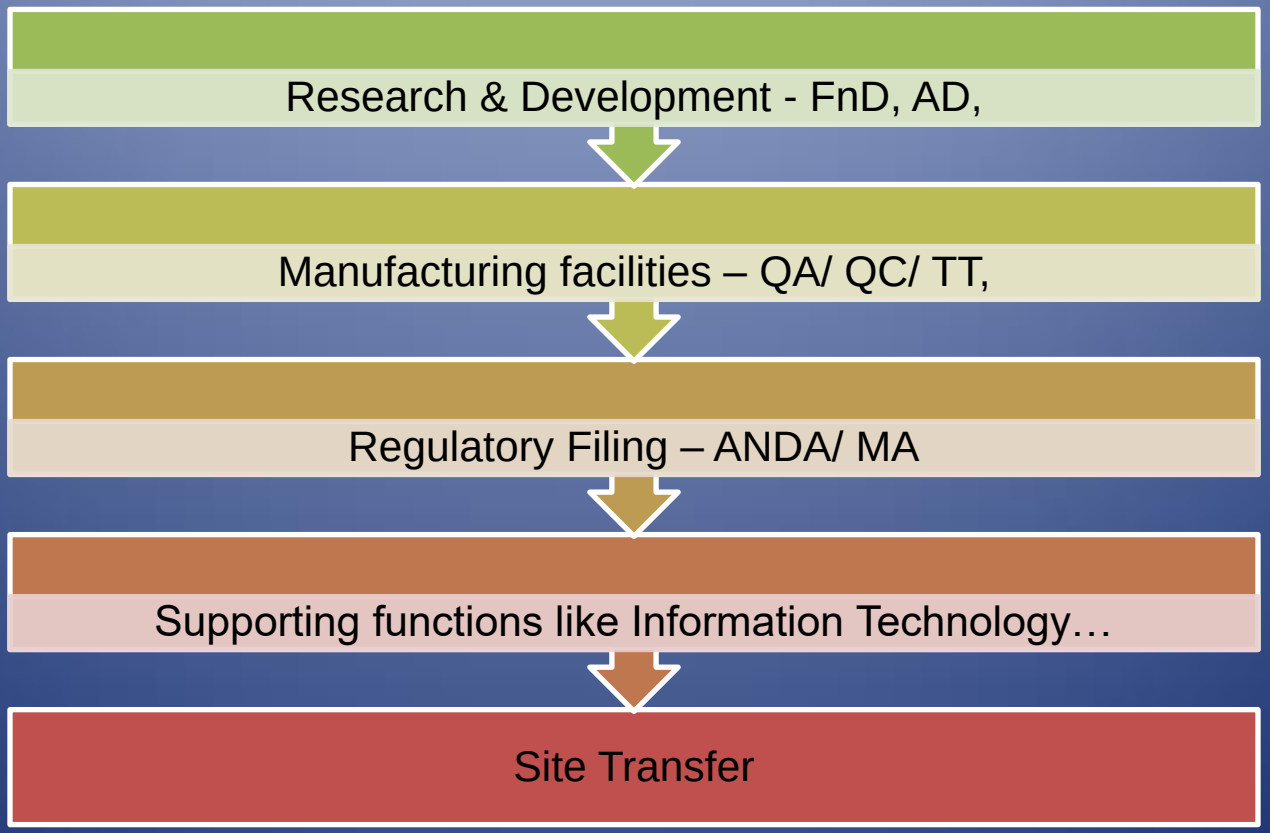
Challenges in Pharmaceutical Project Management

pharma mantra
Quality Advisory Consultancy

1. **Purpose**
2. **Scope**
3. **References**
4. **Challenges**
   - ❑ Project scale-up challenges/process validation/failure mitigation at manufacturing scale.
   - ❑ Scaling manufacturing to meet commercial requirements
5. **Case Studies.**

Scope

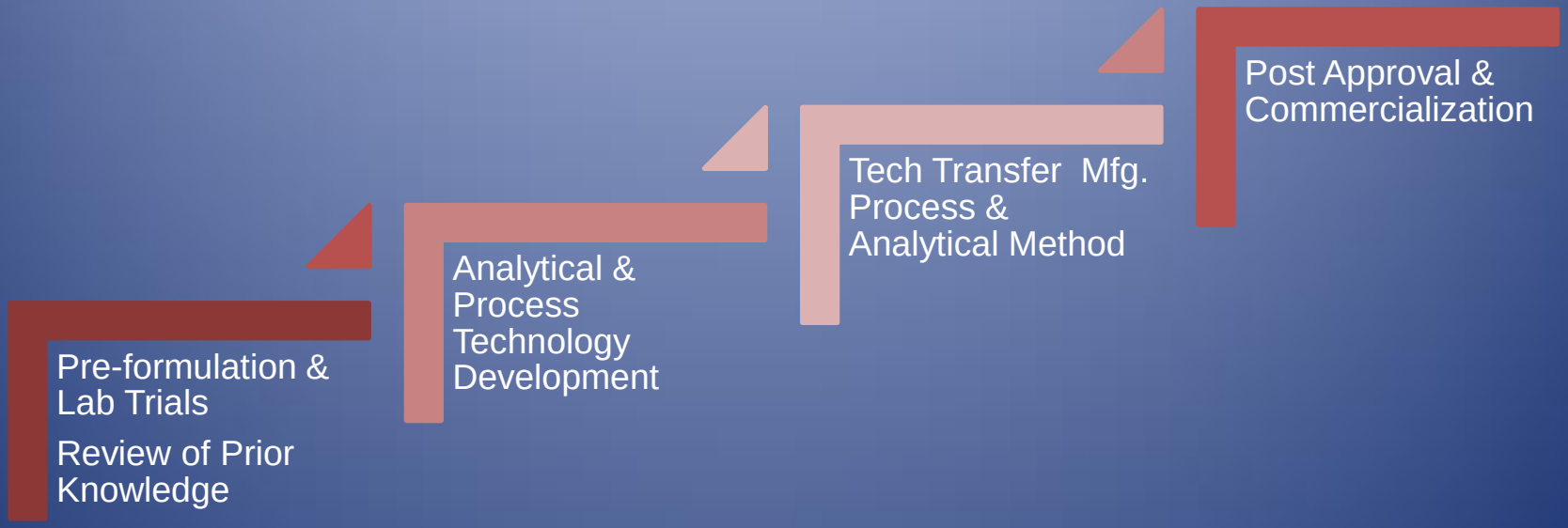
This is applicable to Development & Scaling manufacturing & analytical process/ methods to meet Bio-batch and commercial requirements including all the post scale-up changes - investigations conducted at –



pharma mantra
Quality Advisory Consultancy

Purpose

To describe the Challenges in Pharmaceutical Project Management, Project scale-up challenges/process validation/failure mitigation at manufacturing scale.



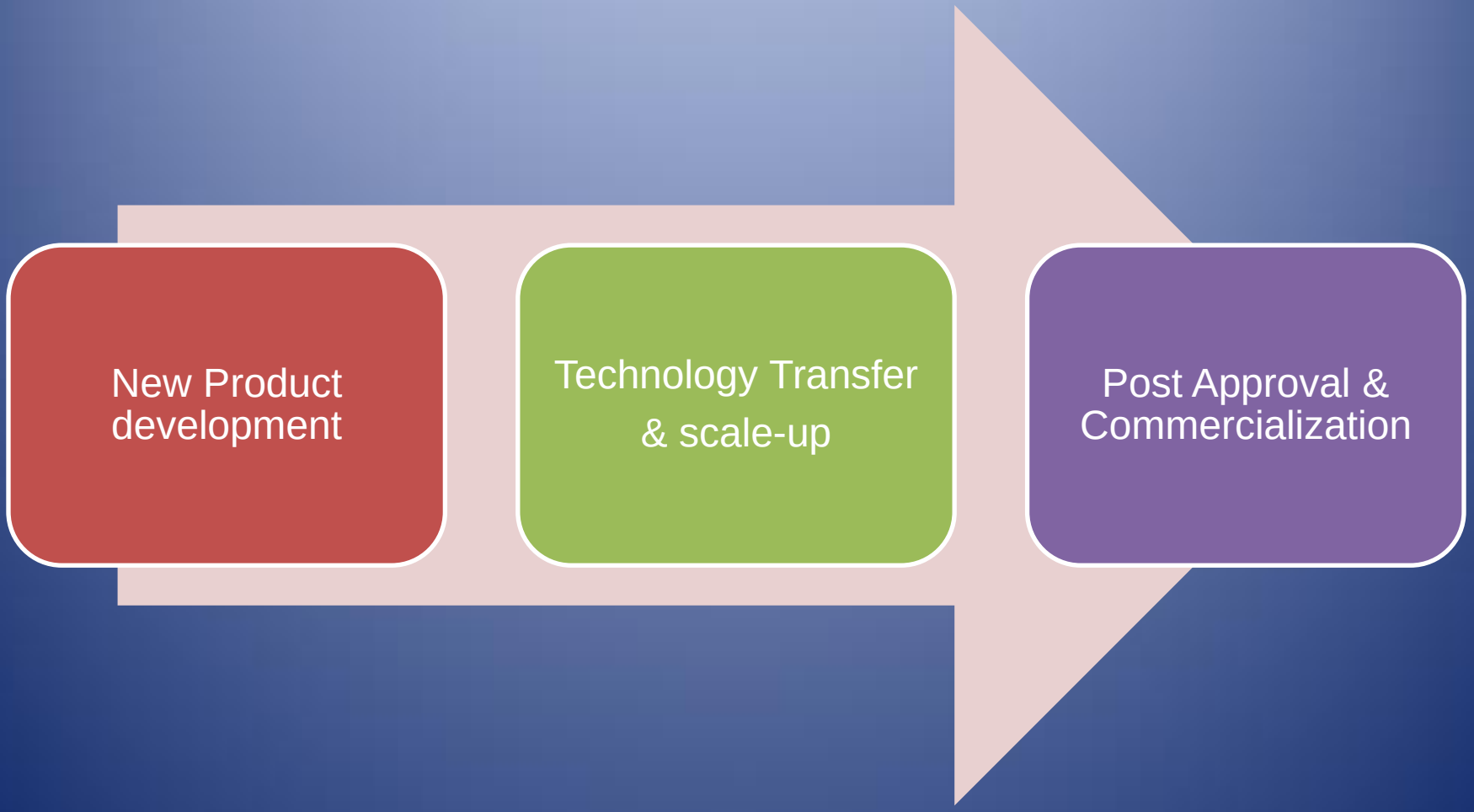
pharma mantra
Quality Advisory Consultancy

References

1. Guidance for Industry and FDA Staff , Early Development Considerations for Innovative Combination Products, 2006
2. Process Validation FDA Guidance, 2011
3. WHO TRS970 2012, Pharmaceutical development of multisource (generic) finished pharmaceutical products Q8(R2) Pharmaceutical Development
4. ICH Q8 (2) - Pharmaceutical Development
5. ICH Q9 - Quality Risk Management.
6. ICH Q10 – Quality System, Management Review
7. EU Guidelines to GMP, Chapter 1, Quality Management
8. Guidance to Industry-Quality systems approach to Pharmaceutical cGMP regulations-September 2006.
9. Product Lifecycle Management for the Pharmaceutical Industry , An Oracle White Paper.
10. An Analysis Of FDA FY2017 Drug GMP Warning Letters, By Barbara Unger, Unger Consulting Inc.
11. Learning and Unlearning of 3 decades….

Challenges

pharma mantra
Quality Advisory Consultancy



Challenges –

pharma mantra
Quality Advisory Consultancy

New Product development

- Prior Knowledge
- Regulatory expectation
- Guidance
- Process Technology
- Method of Analysis
- Q8(2)QbD
- Design Space
- PAT
- eDocumentation
- Data Integrity

Technology Transfer & Manufacturing scale-up

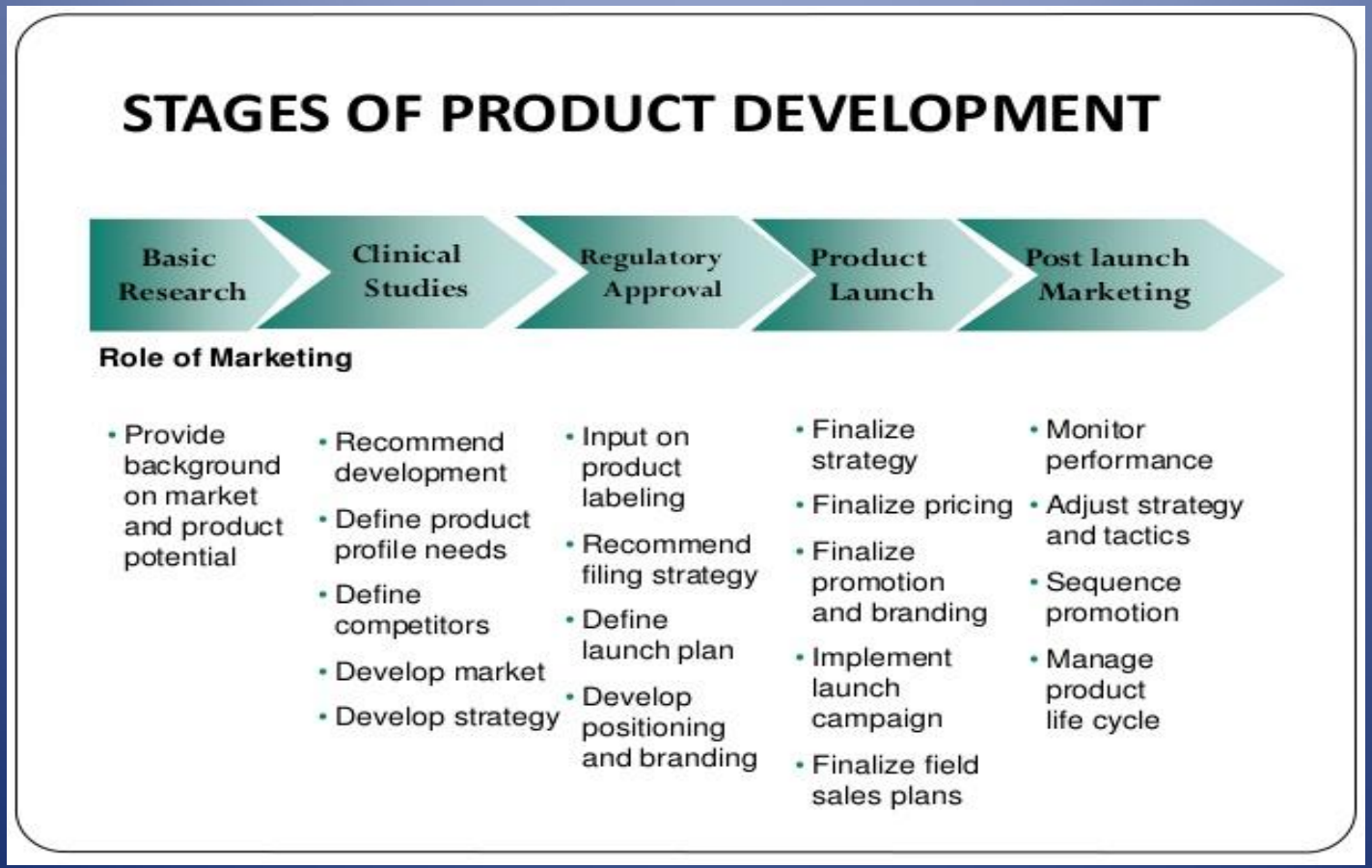
- Scale-up
- Clinical/ exhibit batches
- Change in the mfg/ analytical method
- Change control
- Q9 Risk Assessment
- Q10 Quality System
- Management Review
- eDocumentation
- Data Integrity

Post Approval - Commercialisation

- Process for investigation and analysis of any failure,
- Incident or discrepancy in order to identify the root cause/probable cause.
- To provide a brief description of investigation methods and documentation to assist the investigation team.

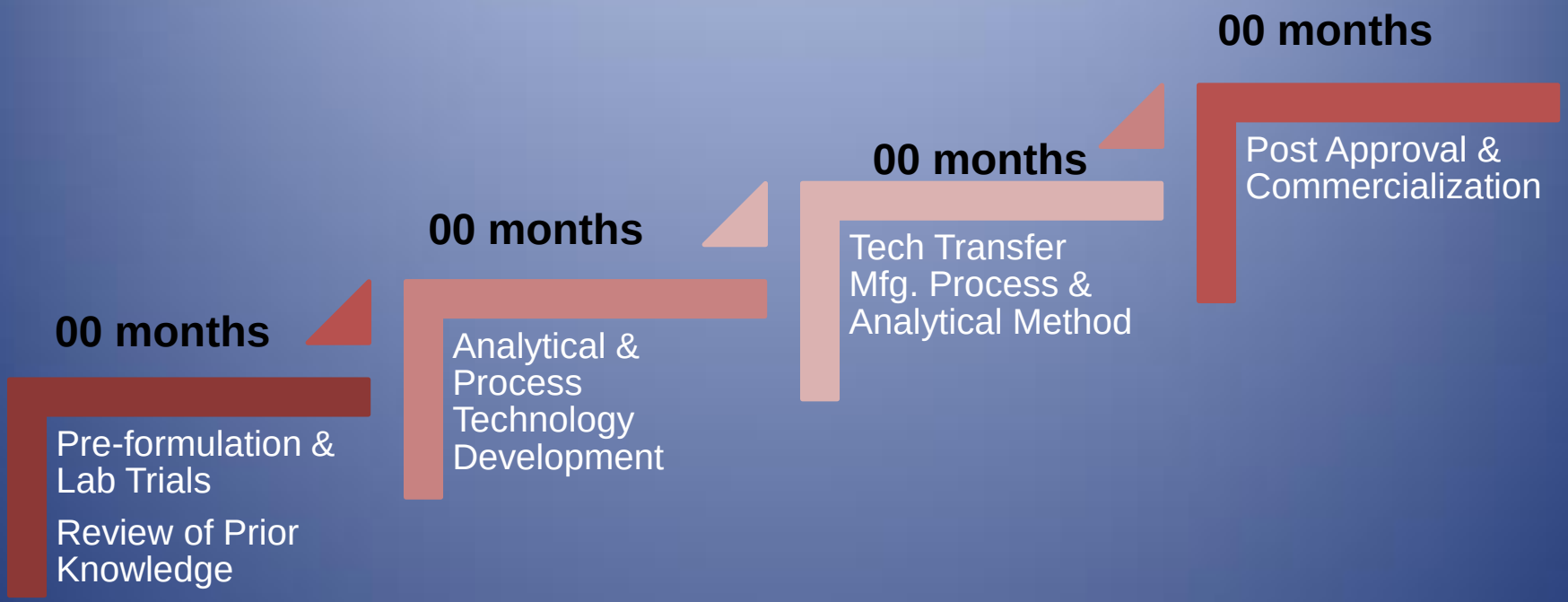
Challenges

Right Candidate Proposal…



Challenges –

pharma mantra
Quality Advisory Consultancy



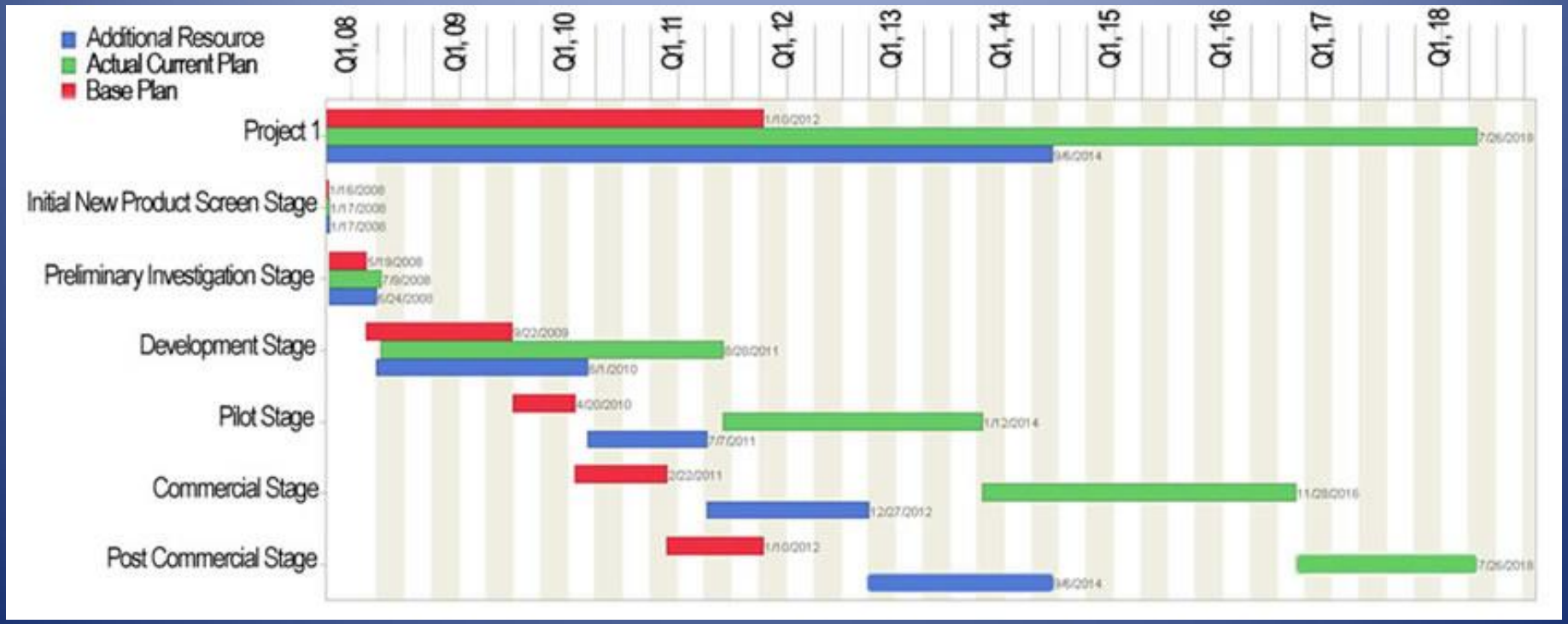
Note: Timelines….appox.

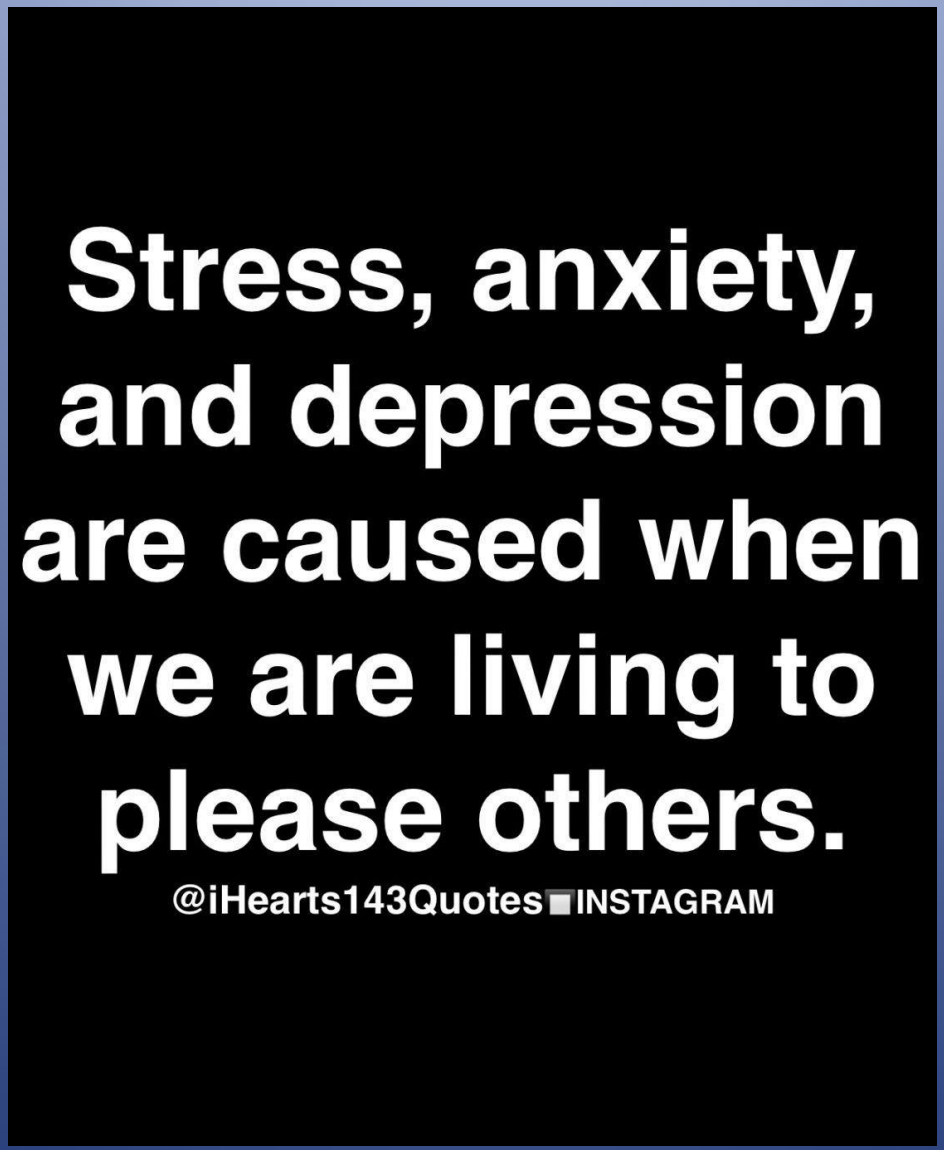
- ✓ **NCE** **12 to 20 Years**
- ✓ **Generics** **03 to 05 Years**

Challenges –
New Product Development

pharma mantra
Quality Advisory Consultancy

Project Management at Development




Stress, anxiety, and depression are caused when we are living to please others.
@iHearts143Quotes INSTAGRAM

Bhagavad Gita: Chapter 4, Verse 34

pharma mantra
Quality Advisory Consultancy

तद्विद्धि प्रणिपातेन परिप्रश्नेन सेवया |
उपदेक्ष्यन्ति ते ज्ञानं ज्ञानिनस्तत्त्वदर्शिन: || 34||

tad viddhi praṇipātena paripraśhnena sevayā
upadekṣhyanti te jñānaṁ jñāninas tattva-darśhinaḥ

tat *viddhi* *pranipātena*—by approaching a spiritual master; *paripraśhnena*—by humble inquiries; *sevayā*—by rendering service; *upadekṣhyanti*—can impart; *te*—unto you; *jñānam*—knowledge; *jñāninaḥ*—the enlightened; *tattva-darśhinah*—those who have realized the Truth

BG 4.34: Learn the Truth by approaching a spiritual master. Inquire from him with reverence and render service unto him. Such an enlightened Saint can impart knowledge unto you because he has seen the Truth.

On hearing that sacrifice should be performed in knowledge, the natural question that follows is, how can we obtain spiritual knowledge?

Shree Krishna gives the answer in this verse.

He says: 1) Approach a spiritual master. 2) Inquire from him submissively. 3) Render service to him.

Guidance- Product Development

Guidance for Industry and FDA Staff

Early Development Considerations for Innovative Combination Products

U.S. Department of Health and Human Services Food and Drug Administration Office of the Commissioner Office of Combination Products (OCP) September 2006

Guidance- Product Development

pharma mantra
Quality Advisory Consultancy

Guidance for Industry and FDA Staff

TABLE OF CONTENTS

Guidance- Product Development

Guidance for Industry and FDA Staff

TABLE OF CONTENTS

Guidance- Product Development

Guidance for Industry and FDA Staff

Background

FDA recognizes that innovative technologies may raise a spectrum of scientific and ***technical development issues.*** Combination products are increasingly incorporating cutting edge, novel technologies that hold great promise for advancing patient care. Innovative drug, biological product, device combinations have the potential to make treatments safer, more effective, or more convenient or acceptable to patients.

Some of these developmental challenges may not be readily apparent. For example, although a combination product may be comprised of an already approved drug and an already approved device, ***new scientific and technical issues may emerge*** when the drug and device are combined or used together.

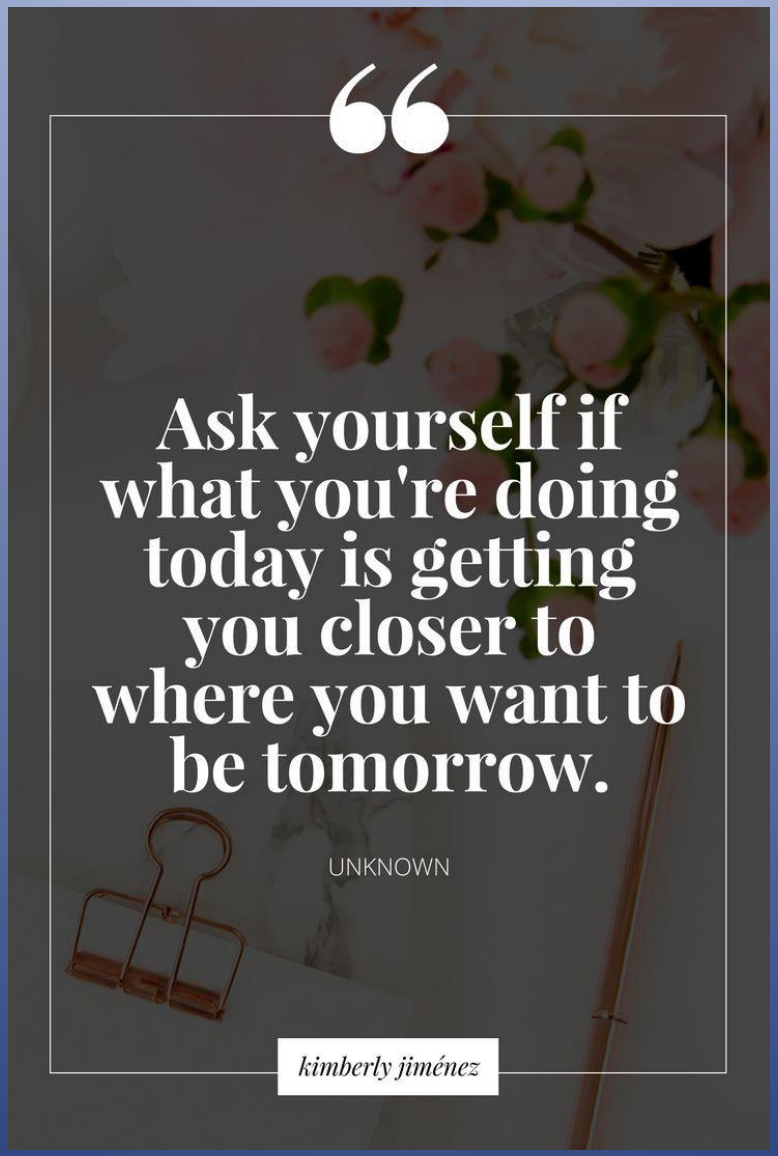
FDA believes it is important to address the scientific and technical issues raised by innovative combination products in order to develop efficient, appropriate techniques and methods to ensure the safety, effectiveness, and quality of the combination product.

Guidance- Product Development

Guidance for Industry and FDA Staff

III. GENERAL DEVELOPMENT CONSIDERATIONS

As with other medical products, combination product development typically focuses on the scientific and technical issues raised by the particular product being developed. For a combination product, these scientific/technical issues will ordinarily reflect the combination product itself as well as its constituent parts. When combining products such as drugs or biologics and devices that are customarily developed using different regulatory paradigms, certain critical developmental issues, such as the interaction of the drug/biologic and device constituents, may not be readily apparent. Further, ***because of the breadth, innovation and complexity of combination products, there is no single developmental paradigm appropriate for all combination products.***


Ask yourself if what you're doing today is getting you closer to where you want to be tomorrow.
UNKNOWN
kimberly jiménez

Guidance- Product Development

Guidance for Industry and FDA Staff

IV. CURRENTLY MARKETED PRODUCT CONSIDERATIONS

Prior FDA approval and/or clearance of a particular constituent part of a combination product is often an excellent starting point for considering the appropriate data to establish safety and effectiveness for its use in a combination product.

FDA recommends that developers fully consider what is already established about a constituent part; i.e., what existing information and data are available, to avoid duplication and ensure a more timely and efficient development process.

While this prior information is often very helpful, developers should recognize that additional data and information may be necessary to address the scientific and technical issues raised by the new use of the constituent in the combination product. These issues may be raised by combining the constituent parts or by new uses for the constituent in the combination product, such as a new indication for use, a different target population, a new route of administration, or by different local or systemic exposure profiles once the products are combined. For example, developers should consider:

Guidance- Product Development

Guidance for Industry and FDA Staff

IV. CURRENTLY MARKETED PRODUCT CONSIDERATIONS

For example, developers should consider:

- Are the constituent parts already approved for an indication?
- Is the indication for a given constituent part similar to that proposed for the combination product?
- Does the combination product broaden the indication or intended target population beyond that of the approved constituent part?
- Does the combination product expose the patient to a new route of administration or a new local or systemic exposure profile for an existing indication?
- Is the drug formulation different than that used in the already approved drug?
- Does the device design need to be modified for the new use?
- Is the device constituent used in an area of the body that is different than its existing approval?

Guidance- Product Development

Guidance for Industry and FDA Staff

IV. CURRENTLY MARKETED PRODUCT CONSIDERATIONS

For example, developers should consider:

- Are the device and drug constituents **chemically, physically**, or otherwise combined into a single entity?
- Changes in the **stability or activity of a drug constituent** when used together with an energy emitting device.
- Does the device function as a delivery system, a method to prepare a final dosage form, and/or does it provide active therapeutic benefit? *f*
- Is there any other ***change in design or formulation*** that may affect the safety/effectiveness of any existing constituent part or the combination product as a whole? *f*
- Is a marketed device being proposed for use with a drug constituent that is a new molecular entity? *f*
- Is a marketed drug being proposed for use with a complex new device?

Guidance- Product Development

Guidance for Industry and FDA Staff

V. PERSPECTIVES BY CONSTITUENT PART

A. Device constituent considerations

For new device constituent parts, some safety and/or effectiveness testing of the device alone may be necessary before or along with the studies to establish the safety and effectiveness of the combination product as a whole.

Consideration should also be given to the potential interaction (desired or undesired) between the device and the drug/biological constituents. For example, it may be appropriate to conduct studies to evaluate the potential for the following:

- Leachables/extractables of the device materials into the drug/biologic substance or final combination product;
- Changes in stability of the drug constituent when delivered by the device or when used as a coating on the device;
- Drug adhesion/absorption to the device materials that could change the delivered dose;
- Presence of inactive breakdown products or manufacturing residues from device manufacture that may affect safety, or device actions that could change the drug performance characteristics at the time of use; or

Changes in the stability or activity of a drug constituent when used together with an energy 271 emitting device.

Guidance- Product Development

Guidance for Industry and FDA Staff

V. PERSPECTIVES BY CONSTITUENT PART

B. Manufacturing considerations

Manufacturing, scale-up, and quality management are important considerations during the development of a combination product. Manufacturing methodologies affect both premarket development and postmarket regulation. FDA encourages consideration of the manufacturing issues posed by the scientific and technical aspects of the drug, biological product, and device constituent parts, and of the combination product as a whole.

FDA also encourages developers to carefully consider the effect of the manufacturing methods on the interaction of the constituent parts. For example, the stability of a combination product as a whole may be different than that of the separate constituent parts. Certain drug or biological product constituent parts may be altered or destroyed by terminal sterilization techniques. For constituent parts that use aseptic manufacturing techniques, developers are encouraged to implement manufacturing techniques to ensure aseptic control for the combination product.

Guidance- Product Development

Guidance for Industry and FDA Staff

V. PERSPECTIVES BY CONSTITUENT PART

C. Reliance on information not developed by the applicant

Investigational or marketing applications often contain trade secret or confidential commercial information. In some instances, developers may wish to provide all necessary information in one marketing application. However, for combination products being developed by more than one manufacturer, there may be a desire to provide necessary information to FDA while maintaining the confidentiality of each manufacturer's intellectual property. This can be accomplished by the application holder submitting to FDA a letter of authorized cross reference from the owner of the referenced material. This letter would grant FDA permission to consider the referenced material in its review of the current application. In general, the referenced information may be available from two sources:

1. Existing application: An existing investigational application (IND or IDE) or an existing marketing application (NDA, BLA, PMA or 510(k)) may provide information relevant to a new developer's application. In some instances, the application being cross referenced may be under co-review for use in the combination product. In other instances, the cross-referenced application may be approved for other purposes, but may have information relevant to the new use.

Guidance- Product Development

Guidance for Industry and FDA Staff

V. PERSPECTIVES BY CONSTITUENT PART

C. Reliance on information not developed by the applicant

Continued…

2. Master file: Master files provide an administrative method to submit confidential information to FDA when an appropriate investigational or marketing application for the constituent is not available. A master file is not a substitute for an investigational or marketing application. FDA neither approves nor disapproves master files; rather, information in a master file is considered in the context of a particular investigational or marketing application. It should be recognized that the information in a master file may be sufficient to support a marketing application for one product, while additional information may be necessary to support its use in another product. For example, this may occur when specific issues raised by the new use of a constituent are not addressed in the master file. Such information could be provided by supplementing the existing master file, or by providing the necessary information in the application under review.

Guidance- Product Development

Guidance for Industry and FDA Staff

VII. EARLY INTERACTION AND COMMUNICATION WITH FDA

FDA strongly encourages early communication and discussion between developers, FDA review components and, as appropriate, OCP. Early dialogue allows developers to obtain initial feedback on the kinds of preclinical and clinical testing that may be necessary.

Such communication may identify critical issues for product development and help to ensure an efficient development and approval process.

Further, early and frequent communication provides the opportunity for FDA to establish its intercenter review team and to develop the appropriate scientific expertise to facilitate timely and efficient reviews of any future submissions.


The biggest shortage of all is the shortage of common sense
theviennablog.com

Challenges – Regulatory Actions

Regulatory Perspective:

Detailed summary of the drug GMP warning letters issued in FY2017, as well as a comparison of trends since fiscal year 2013. The data presented herein for FY2017, ending Sept. 31, 2017, is based on drug GMP warning letters posted by the FDA no later than Oct. 25, 2017.

Table 1: Drug GMP Warning Letters

	FY2013	FY2014	FY2015	FY2016	FY2017
Total	**41***	**49****	**42**	**102**	**114*****
Compounding pharmacies	**3** (7%)	**27** (55%)	**24** (57%)	**56** (55%)	**45** (39%)
U.S. (non-compounders)	**13** (32%)	**4** (8%)	**3** (7%)	**11** (11%)	**20** (17.5%)
OUS	**25** (61%)	**18** (37%)	**16** (38%)	**35** (34%)	**49** (43%)
Breakdown by Facility Type (U.S. & OUS), Excluding Compounding Pharmacies					
API sites	**5**	**8**	**9**	**19**	**19**
Drug product (non-compounders)	**29**	**12**	**9**	**23**	**46**
API and drug product	**3**	**2**	**1**	**4**	**3**

*Includes one repackager not counted as either API or drug product
**Includes one warning letter regarding combination products, considered drug product
***Includes one warning letter to a contract laboratory, not counted as either API or drug product

Challenges – Regulatory Actions

Regulatory Perspective:

Warning letters issued to API sites increased since FY2013, and the number is the same this year as it was last year. The most significant change is the doubling in the number of warning letters issued to drug product sites, doubling from 23 in FY2016 to 46 in FY2017. India received the highest number of warning letters issued to a single country over the five-year period. China received the next highest number of warning letters, followed closely by Europe. For the past two years, China received more warning letters than India, though overall, India comes in first.

Table 2: Drug GMP Warning Letters Issued Regarding Sites Outside the U.S.

Country / Geography	FY2013	FY2014	FY2015	FY2016	FY2017	TOTAL
India	7	7	8	10	14	46
China	2	4	2	15	17	40
Europe	7	3	3	5	8	26
Canada	4	1	1		3	9
Taiwan	1			2		3
Japan	2			1	3	6
Hong Kong		1				1
Australia	1	1				2
Brazil				2	1	3
New Zealand			1			1
Jamaica	1					1
Mexico		1				1
Thailand			1			1
South Korea					2	2
Singapore					1	1

Challenges – Regulatory Actions

Import Alerts Associated With Warning Letters

Forty-nine warning letters were issued regarding sites outside the U.S., and 20 of these had associated import alerts for failure to comply with drug GMPs or refusal of an inspection. So not only did these firms have the expense associated with remediation of the warning letter, they are prevented from selling product from these sites in the U.S., excluding FDA-identified medically necessary products. Table 3 shows the distribution of the import alerts associated with warning letters in FY2017. China and India, taken together, account for 80 percent of the import alerts associated with warning letters.

Table 3: Import Alerts Associated With FY2017 Warning Letters

Country	FY2017 Warning Letters	Number of Warning Letters Subject to Import Alerts
China	17	10
India	14	6
Spain	1	1
Canada	3	2
South Korea	2	1

Challenges – Regulatory Actions

Data Integrity Deficiencies In Warning Letters

An Analysis Of FDA FY2017 Drug GMP Warning Letters. Table 4 shows the number of warning letters issued both inside and outside the U.S. that included references to data management and data integrity. Data integrity deficiencies in warning letters continue to identify the predicate rule(s) to which firms did not adhere. Figure 4 provides a graphic representation of the data. The percentage of warning letters that cite data integrity deficiencies issued to sites in the U.S. is very similar when compared to warning letters issued outside the U.S., though the absolute numbers differ. The numbers and percentages have decreased between FY2016 and FY2017.

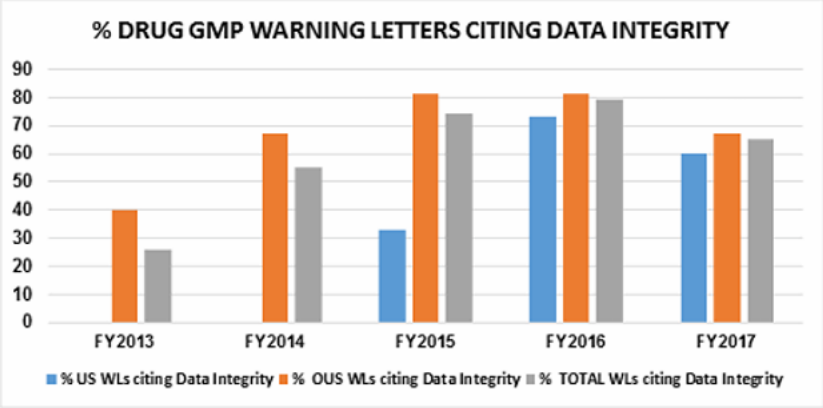
pharma mantra
Quality Advisory Consultancy

Challenges – Regulatory Actions

Data Integrity Deficiencies In Warning Letters

Table 4: Data Integrity Deficiencies in Warning Letters, Excluding Compounding Pharmacies

	FY2013	FY2014	FY2015	FY2016	FY2017
Total WLs	38	22	19	46	69
U.S. WL sites with data integrity	0 of 13 (0%)	0 of 4 (0%)	1 of 3 (33%)	8 of 11 (73%)	12 of 20 (60%)
OUS sites with data integrity	10 of 25 (40%)	12 of 18 (67%)	13 of 16 (81%)	29 of 35 (81%)	33 of 49 (67%)
Total number of warning letters citing data integrity	10 (26%)	12 (55%)	14 (74%)	37 of 46 (79%)	45 of 69 (65%)



Challenges – Regulatory Actions

Data Integrity Deficiencies In Warning Letters

For warning letters issued to sites outside the U.S. in FY2017, Figure 6 compares the intervals between inspection and warning letters, and inspection and imposition of an import alert.

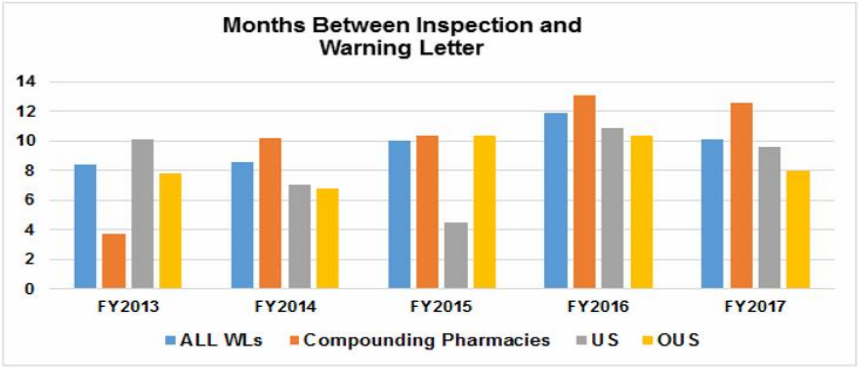
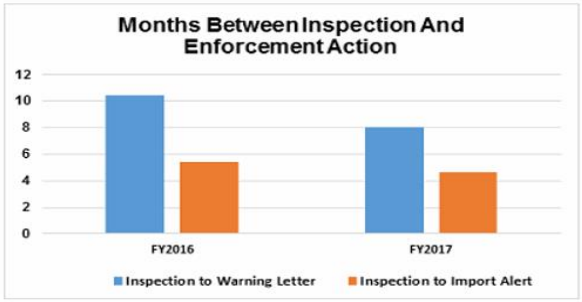


Figure 5



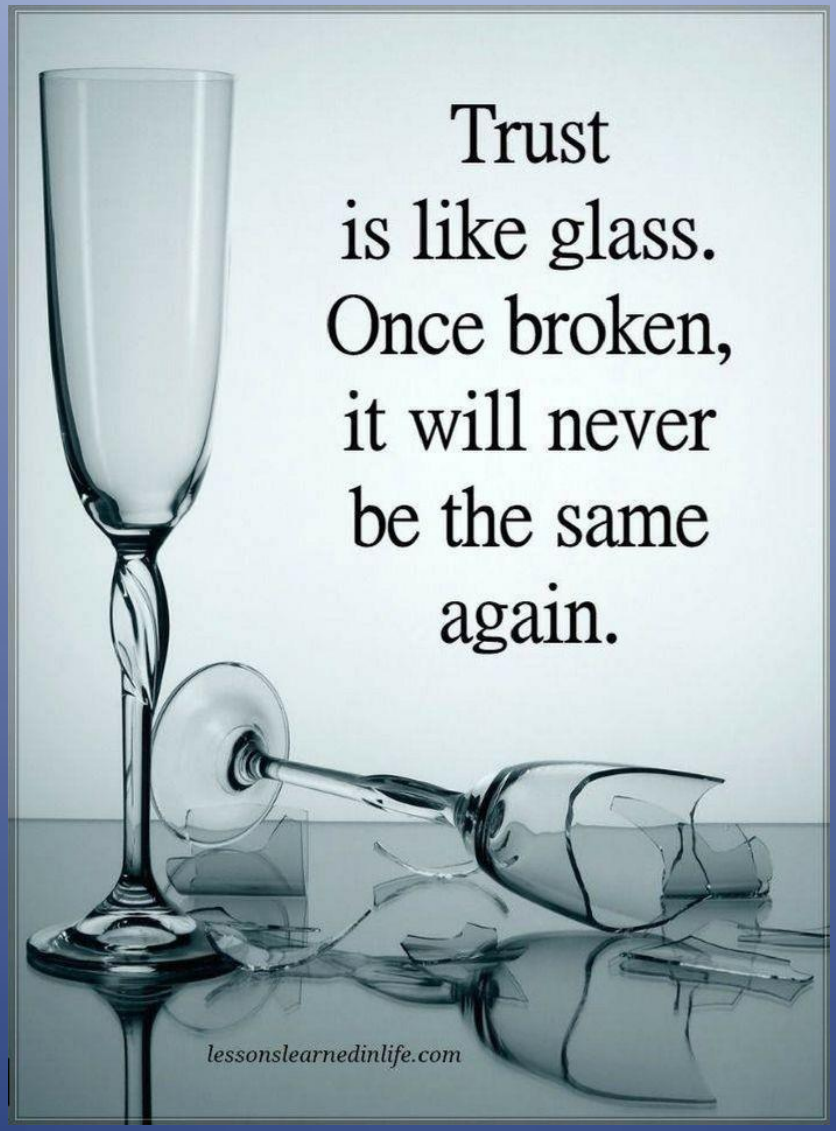
pharma mantra
Quality Advisory Consultancy

Challenges – Regulatory Actions

Conclusion - Data Integrity Deficiencies In Warning Letters

Overall, in FY2018, look for the following trends in enforcement actions:

1. Continued focus on compounding pharmacies
2. Continued focus on data integrity and data governance
3. Continued focus on sites outside the U.S., including China, India, and South Korea.
4. We might see some decline in inspections in some EU countries based on the MRA.
5. Contract manufacturers and laboratories and those that contract for their services will see continued attention by the FDA.
6. There likely will be increased attention in process validation, particularly ongoing process monitoring, as required in both the FDA and EMA validation guidance.
7. Homeopathic product manufacturers and stem cell product manufacturers will see additional enforcement actions based on their overall potential impact on public health and the FDA's stated focus to improve risk based enforcement in those areas.


Trust
is like glass.
Once broken,
it will never
be the same
again.
lessonslearnedinlife.com

Bhagavad Gita: Chapter 4, Verse 22

pharma mantra
Quality Advisory Consultancy

यदृच्छालाभसन्तुष्टो द्वन्द्वातीतो विमत्सरः |
समः सिद्धावसिद्धौ च कृत्वापि न निबध्यते || 22||

yadṛichchhā-lābha-santuṣhṭo dvandvātīto vimatsaraḥ
samaḥ siddhāvasiddhau cha kṛitvāpi na nibadhyate

- ***yadrichchhā*—which comes of its own accord; *lābha*—gain; *santushtah*—contented; *dvandva*—duality; *atītah*—surpassed; *vimatsarah*—free from envy; *samah*—equipoised; *siddhau*—in success; *asiddhau*—failure; *cha*—and; *kritvā*—performing; *api*—even; *na*—never; *nibadhyate*—is bound**

BG 4.22: Content with whatever gain comes of its own accord, and free from envy, they are beyond the dualities of life. Being equipoised in success and failure, they are not bound by their actions, even while performing all kinds of activities.

While living in this world, nobody can hope to neutralize the dualities to have only positive experiences. Then how can we successfully deal with the dualities that come our way in life? The solution is to take these dualities in stride, by learning to rise above them in equipoise in all situations. This happens when we develop detachment to the fruits of our actions, concerning ourselves merely with doing our duty in life without yearning for the results.

Guidance- Product Development

Guidance for Industry

Q8(R2) Pharmaceutical Development

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER)

November 2009 ICH

Revision 2

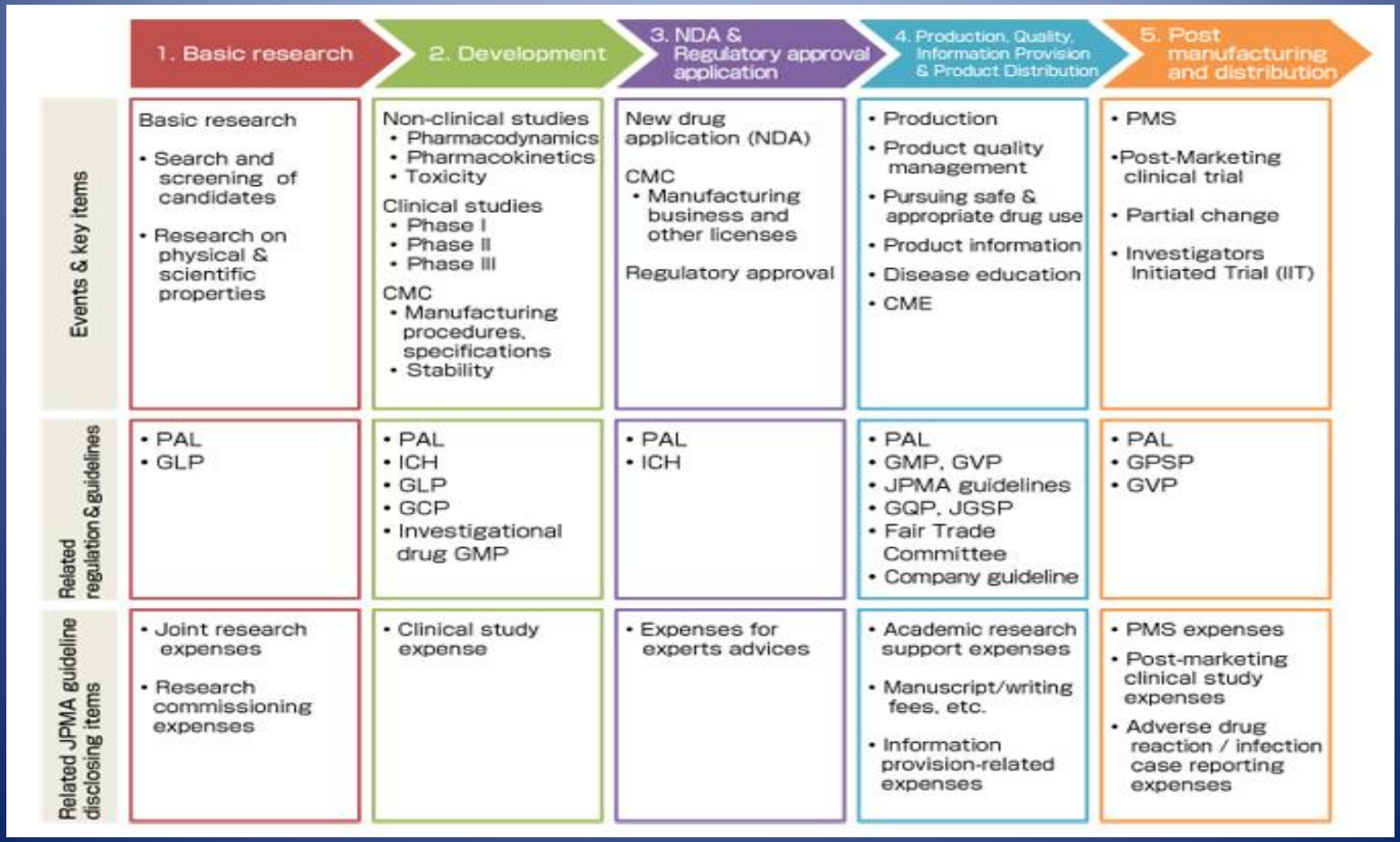
pharma mantra
Quality Advisory Consultancy

Stages – Product Development

Early	Late
Organizational Goal	
Seek truth	Seek success
Organizational Strength	
Establish novel products' promise or lack thereof	Take products to market
Organizational Approach	
Reduce risk	Maximize value
Maintain loyalty to the experiment	Maintain loyalty to the product
Focus on scientific method	Focus on commercialization
Operate with low fixed costs, low capital requirement	Operate with high fixed costs, high capital requirement
Work in small, experiment-based teams	Work in large, product-based teams
Emphasize testing	Emphasize refining

pharma mantra
Quality Advisory Consultancy

Stages – Product Development



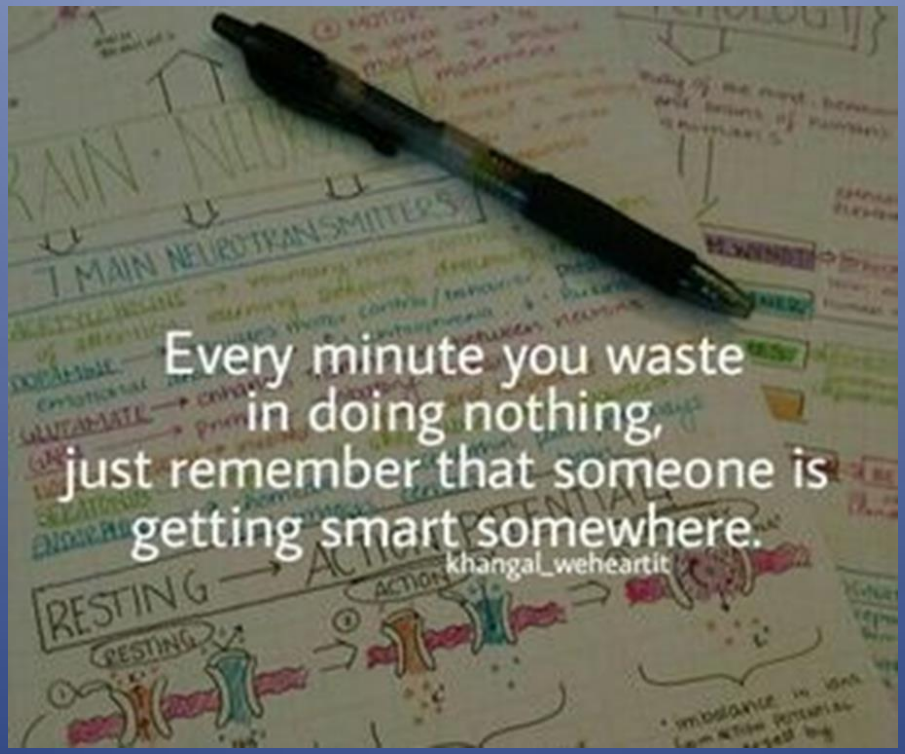
	1. Basic research	2. Development	3. NDA & Regulatory approval application	4. Production, Quality, Information Provision & Product Distribution	5. Post manufacturing and distribution
Events & key items	Basic research • Search and screening of candidates • Research on physical & scientific properties	Non-clinical studies • Pharmacodynamics • Pharmacokinetics • Toxicity Clinical studies • Phase I • Phase II • Phase III CMC • Manufacturing procedures, specifications • Stability	New drug application (NDA) CMC • Manufacturing business and other licenses Regulatory approval	• Production • Product quality management • Pursuing safe & appropriate drug use • Product information • Disease education • CME	• PMS •Post-Marketing clinical trial • Partial change • Investigators Initiated Trial (IIT)
Related regulation & guidelines	• PAL • GLP	• PAL • ICH • GLP • GCP • Investigational drug GMP	• PAL • ICH	• PAL • GMP, GVP • JPMA guidelines • GQP, JGSP • Fair Trade Committee • Company guideline	• PAL • GPSP • GVP
Related JPMA guideline disclosing items	• Joint research expenses • Research commissioning expenses	• Clinical study expense	• Expenses for experts advices	• Academic research support expenses • Manuscript/writing fees, etc. • Information provision-related expenses	• PMS expenses • Post-marketing clinical study expenses • Adverse drug reaction / infection case reporting expenses

Guidance- Product Development

Q8(R2) Pharmaceutical Development

PHARMACEUTICAL DEVELOPMENT — PARENT GUIDANCE

PHARMACEUTICAL DEVELOPMENT — ANNEX



Guidance- Product Development

Q8(R2) Pharmaceutical Development

PHARMACEUTICAL DEVELOPMENT — PARENT GUIDANCE

I. INTRODUCTION

II. PHARMACEUTICAL DEVELOPMENT

A. Components of the Drug Product

1. Drug Substance
2. Excipients

B. Drug Product

1. Formulation Development
2. Overages
3. Physicochemical and Biological Properties

C. Manufacturing Process Development

D. Container Closure System

E. Microbiological Attributes

F. Compatibility

III. GLOSSARY

Guidance- Product Development

Q8(R2) Pharmaceutical Development

PHARMACEUTICAL DEVELOPMENT — ANNEX

I. INTRODUCTION

II. ELEMENTS OF PHARMACEUTICAL DEVELOPMENT

A. Quality Target Product Profile

B. Critical Quality Attributes

C. Risk Assessment: Linking Material Attributes and Process Parameters to Drug Product CQAs

D. Design Space

1. Selection of Variables
2. Describing a Design Space in a Submission
3. Unit Operation Design Space(s)
4. Relationship of Design Space to Scale and Equipment
5. Design Space Versus Proven Acceptable Ranges
6. Design Space and Edge of Failure

E. Control Strategy

F. Product Lifecycle Management and Continual Improvement

Guidance- Product Development

Q8(R2) Pharmaceutical Development

PHARMACEUTICAL DEVELOPMENT — ANNEX

III. SUBMISSION OF PHARMACEUTICAL DEVELOPMENT AND RELATED INFORMATION IN COMMON TECHNICAL DOCUMENT (CTD)

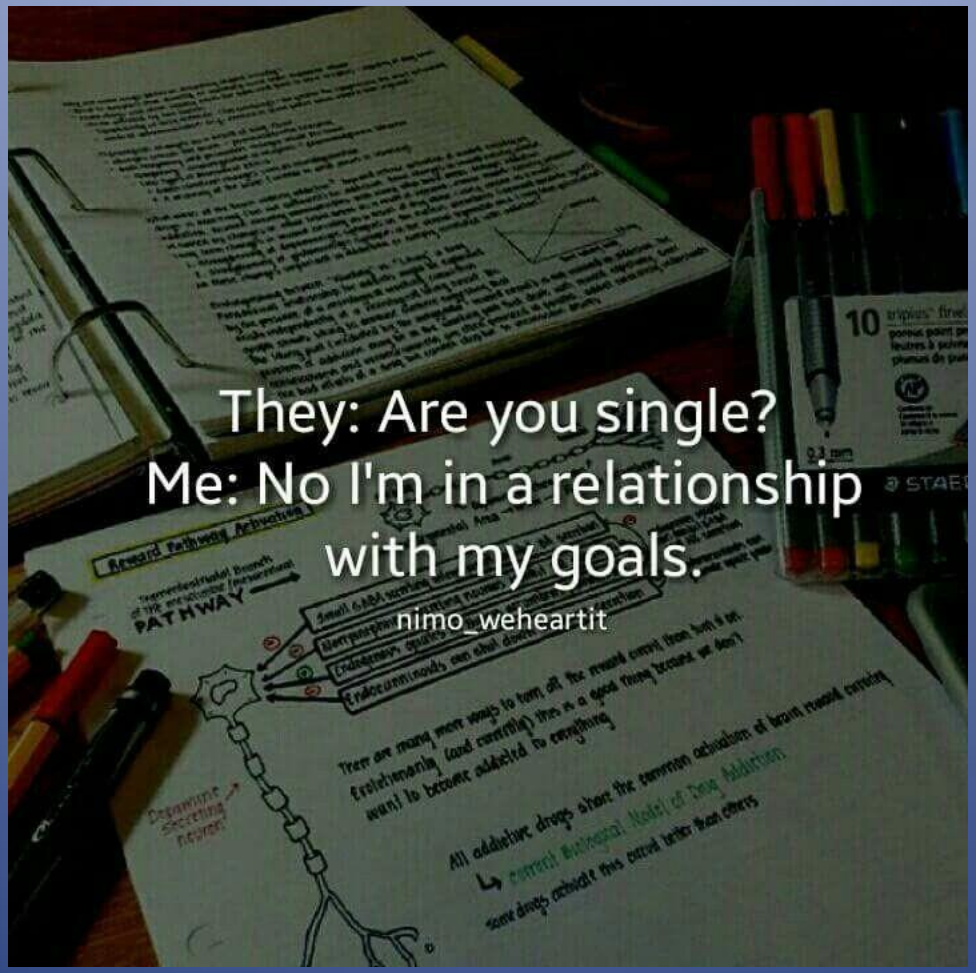
FORMAT (3)

A. Quality Risk Management and Product and Process Development
B. Design Space
C. Control Strategy
D. Drug Substance Related Information

IV. GLOSSARY

Appendix 1. Differing Approaches to Pharmaceutical Development

Appendix 2. Illustrative Examples


They: Are you single?
Me: No I'm in a relationship with my goals.
nimo_weheartit

Guidance- Product Development

Pharmaceutical product development: A quality by design approach

QbD principles, when implemented, lead to a successful ***product development***, subsequent prompt regulatory approval, reduce ***exhaustive validation burden***, and significantly reduce post-approval changes.

The key elements of QbD viz., ***target product quality profile, critical quality attributes, risk assessments, design space, control strategy, product lifecycle management, and continual improvement*** are used to understand the performance of dosage forms within design space. Design of experiments, risk assessment tools, and process analytical technology are also vital for their role in QbD.

This review underlines the importance of QbD in inculcating science-based approach in pharmaceutical product development.

The application of QbD in pharmaceutical product development is systematic, involving multivariate experiments utilizing ***process analytical technology (PAT)*** and other tests to identify ***critical quality attributes (CQAs) based on risk assessments (RAs).*** The QbD begins with predefined objectives and requires an understanding how formulation and process variables influence product quality.

Guidance- Product Development

Pharmaceutical product development: A quality by design approach

The concepts of QbD in the new ICH guidance, ICH Q8 (R2), will help industry for a successful product development and expedite regulatory approval. A successful product development strategy requires thorough understanding of QbD principles and the tools for establishing the QbD strategy.

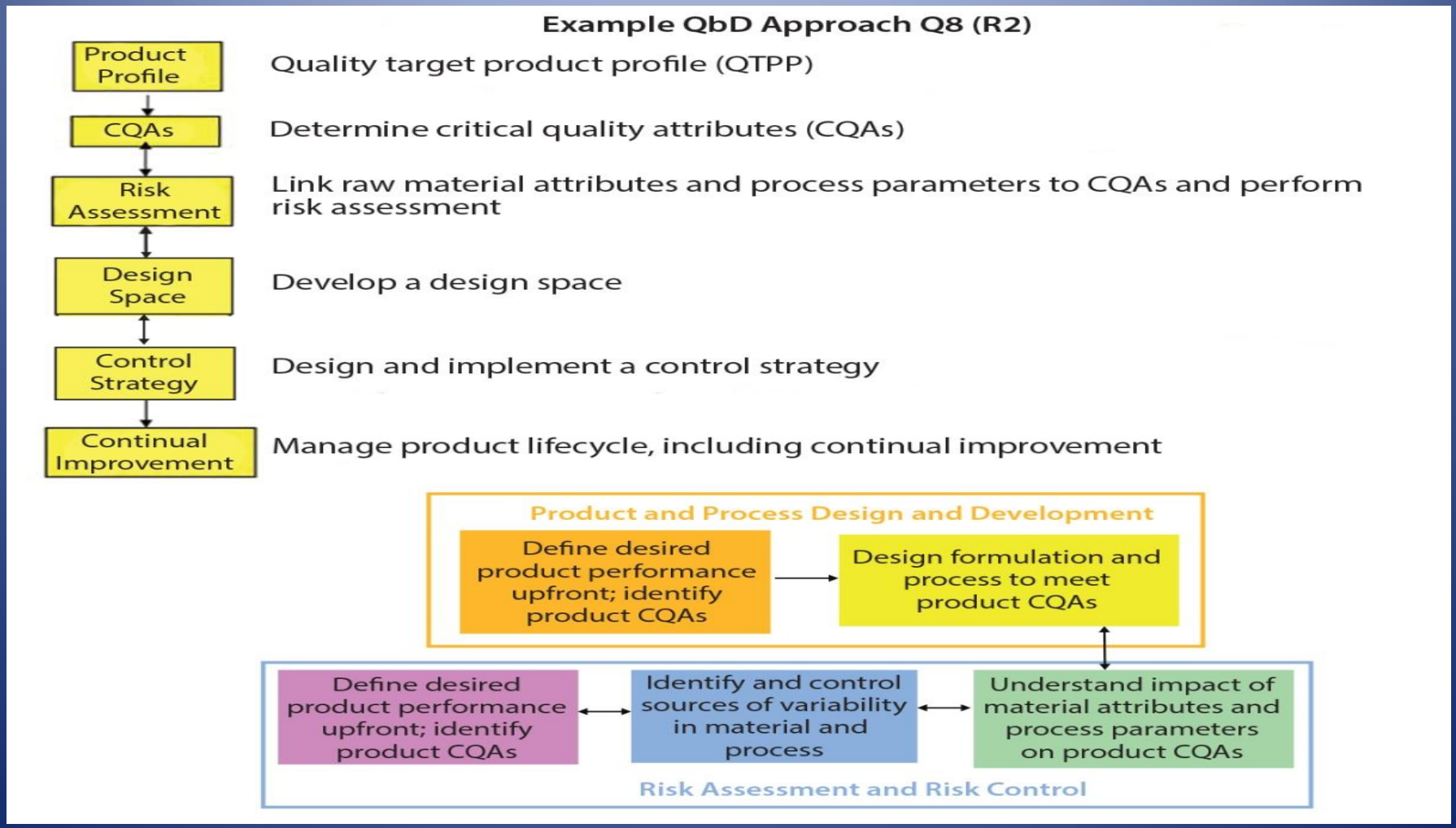
Science and risk-based product development strategy are carried out with the help of QbD. Design of experiments, risk assessment tools, and PAT are the major tools for the establishment of QbD principles.

Establishment of a design space by QbD provides an opportunity for flexibility in constructing a more meaningful design space. The changes in product and process can be managed better with QbD.

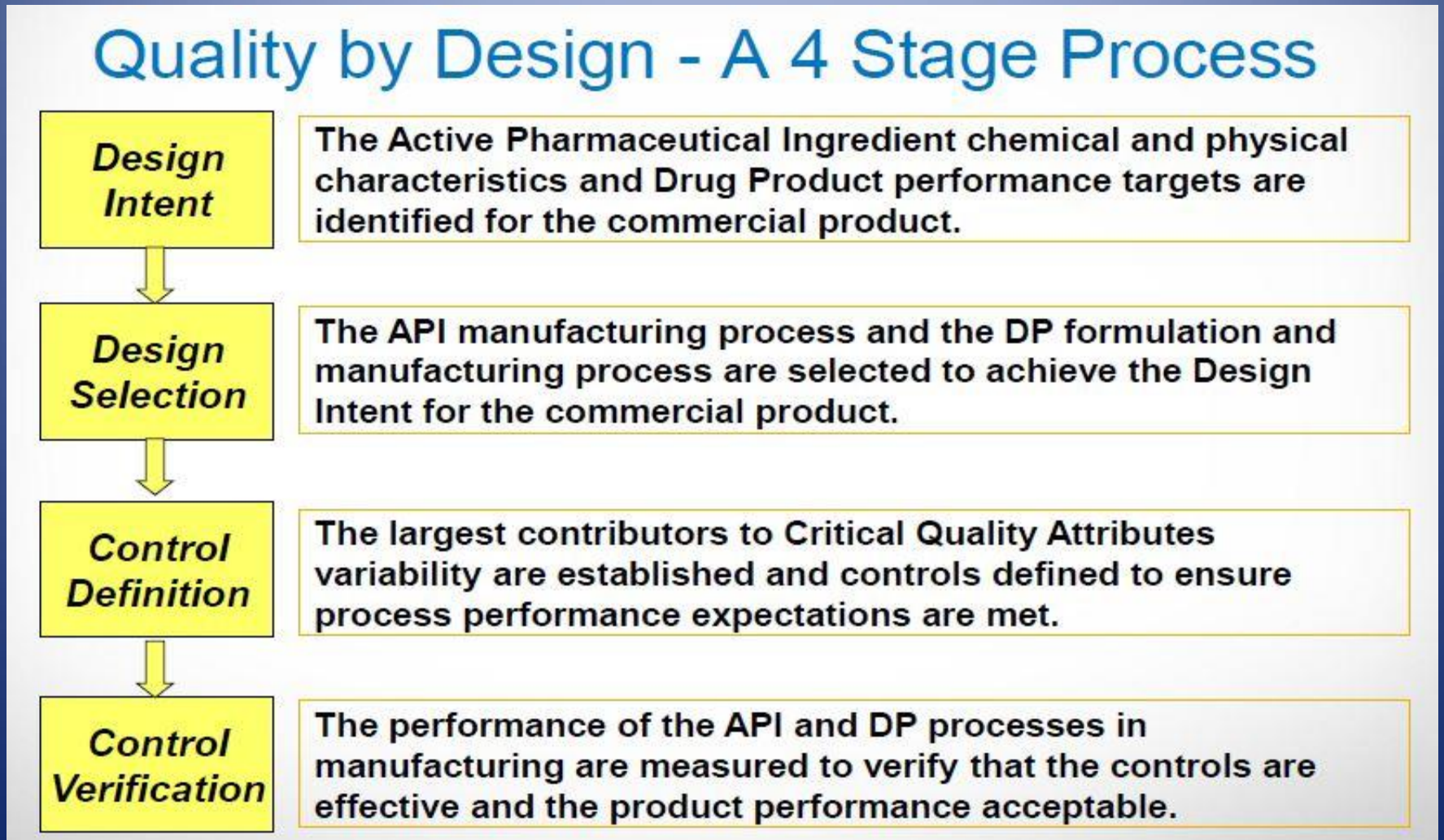
Manufacturers can execute certain changes without filing prior approval supplements and can simply notify regulatory authority in annual reports. The economic and resource drain due to exhaustive validation requirements can significantly be minimized. The application of QbD principles can change the chemistry, manufacturing, and control regulatory process into a science and risk-based assessment.


You can do anything,
but not everything.
Anonymous
WHOLE BODY LIVING

Stages – Product Development



Stages – Product Development



Guidance- Product Development

ICH Q9 QUALITY RISK MANAGEMENT

ICH Harmonised Tripartite Guideline Having reached Step 4 of the ICH Process at the ICH Steering Committee meeting on 9 November 2005, this guideline is recommended for adoption to the three regulatory parties to ICH

TABLE OF CONTENTS

Guidance- Product Development

ICH Q9 QUALITY RISK MANAGEMENT

ICH Harmonised Tripartite Guideline Having reached Step 4 of the ICH Process at the ICH Steering Committee meeting on 9 November 2005, this guideline is recommended for adoption to the three regulatory parties to ICH

TABLE OF CONTENTS

Guidance- Product Development

ICH Q9 QUALITY RISK MANAGEMENT

ICH Harmonised Tripartite Guideline Having reached Step 4 of the ICH Process at the ICH Steering Committee meeting on 9 November 2005, this guideline is recommended for adoption to the three regulatory parties to ICH

TABLE OF CONTENTS

Guidance- Product Development

ICH Q9 QUALITY RISK MANAGEMENT

1. INTRODUCTION

Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of quality risk management in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, ***the importance of quality systems has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system***

It specifically ***provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk based decisions, both by regulators and industry***, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle.

2. SCOPE This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug (medicinal) products, biological and biotechnological products).

Guidance- Product Development

ICH Q9 QUALITY RISK MANAGEMENT

3. PRINCIPLES OF QUALITY RISK MANAGEMENT Two primary principles of quality risk management are:

• The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and

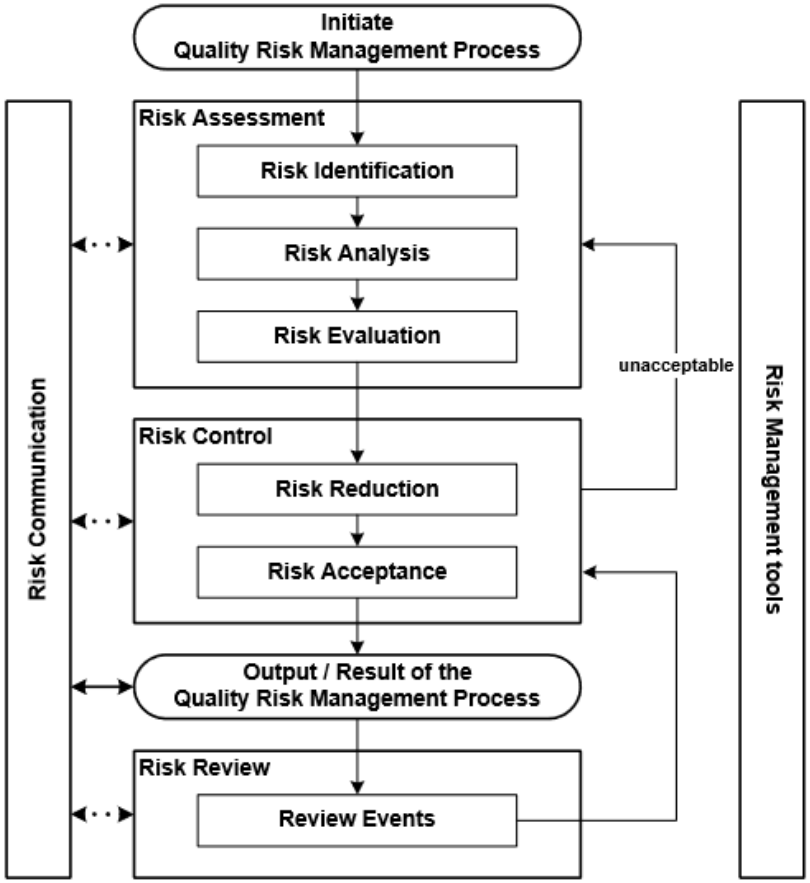
• The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

4. GENERAL QUALITY RISK MANAGEMENT PROCESS Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

4.1 ***Responsibilities Quality risk management activities*** are usually, but not always, undertaken by interdisciplinary teams. ***When teams are formed, they should include experts from the appropriate areas (e.g., quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical) in addition to individuals who are knowledgeable about the quality risk management process.***

Guidance- Product Development

Figure 1: Overview of a typical quality risk management process



pharma mantra
Quality Advisory Consultancy

Guidance- Product Development

ICH Q9 QUALITY RISK MANAGEMENT

II.3 Quality Risk Management as Part of development

- To ***design a quality product*** and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8);
- To enhance ***knowledge of product performance*** over a wide range of material attributes (e.g., particle size distribution, moisture content, flow properties), processing options and process parameters;
- To ***assess the critical attributes*** of raw materials, solvents, Active Pharmaceutical Ingredient (API) starting materials, APIs, excipients, or packaging materials;
- To ***establish appropriate specifications***, identify critical process parameters and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing);
- To ***decrease variability*** of quality attributes: • reduce product and material defects; • reduce manufacturing defects.
- To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer; To make use of the “design space” concept (see ICH Q8).

Guidance- Product Development

ICH Q9 QUALITY RISK MANAGEMENT

II.4 Quality Risk Management for Facilities, Equipment and Utilities Design of facility / equipment

- To determine appropriate zones when designing ***buildings and facilities***,

  e.g., • flow of material and personnel;
  • minimize contamination;
  • pest control measures;
  • prevention of mix-ups;
  • open versus closed equipment;
  • clean rooms versus isolator technologies;
  • dedicated or segregated facilities / equipment.

- To determine appropriate ***product contact materials*** for equipment and containers (e.g., selection of stainless steel grade, gaskets, lubricants);
- To determine ***appropriate utilities*** (e.g., steam, gases, power source, compressed air, heating, ventilation and air conditioning (HVAC), water);
- To determine ***appropriate preventive maintenance*** for associated equipment (e.g., inventory of necessary spare parts).

Guidance- Product Development

ICH Q9 QUALITY RISK MANAGEMENT

II.6 Quality Risk Management as Part of Production Validation

- To identify the scope and extent of verification, qualification and validation activities (e.g., ***analytical methods, processes, equipment and cleaning methods***;
- To determine the extent for follow-up activities (e.g., ***sampling, monitoring and revalidation***);
- To distinguish between critical and non-critical process steps to facilitate design of a validation study. In-process sampling & testing
- To evaluate the frequency and extent of in-process control testing (e.g., to **justify reduced testing** under conditions of proven control);
- To evaluate and ***justify the use of process analytical technologies (PAT)*** in conjunction with parametric and real time release. Production planning
- To determine ***appropriate production planning*** (e.g., dedicated, campaign and concurrent production process sequences).

Guidance- Product Development

ICH Q9 QUALITY RISK MANAGEMENT

II.7 Quality Risk Management as Part of Laboratory Control and Stability Studies ***Out of specification results***

- ***To identify potential root causes and corrective actions*** during the investigation of out of specification results. Retest period / expiration date
- ***To evaluate adequacy of storage and testing of intermediates, excipients and starting materials.***

II.8 Quality Risk Management as Part of Packaging and Labelling

- Design of packages - To design the secondary package for the protection of primary packaged product (e.g., to ensure ***product authenticity, label legibility***).
- Selection of container closure system To determine the critical parameters of the container closure system.
- Label controls - To design label control procedures based on the ***potential for mix-ups involving*** different product labels, including different versions of the same label.

Guidance- Product Development

WHO TRS Annex3 970

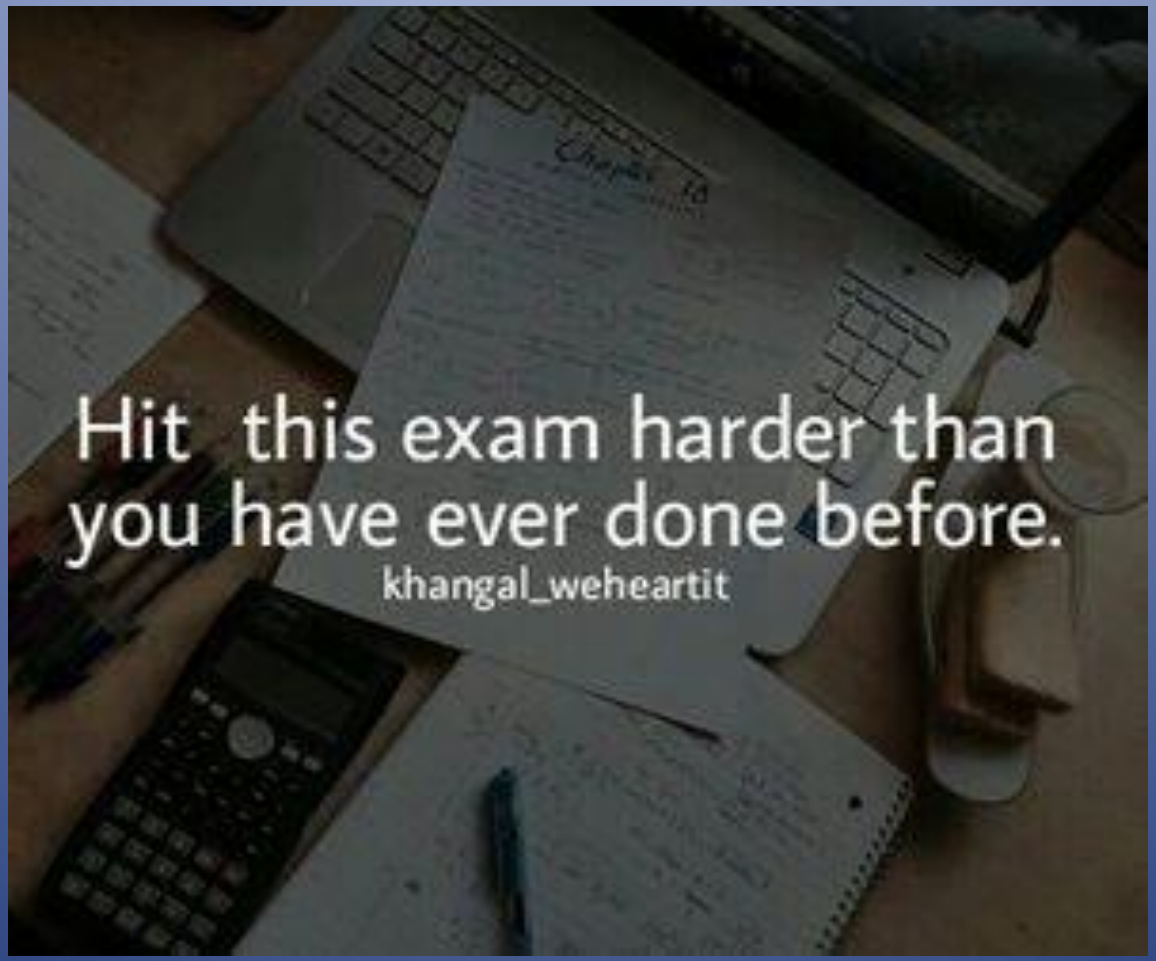
Pharmaceutical development of multisource (generic) finished pharmaceutical products – points to consider

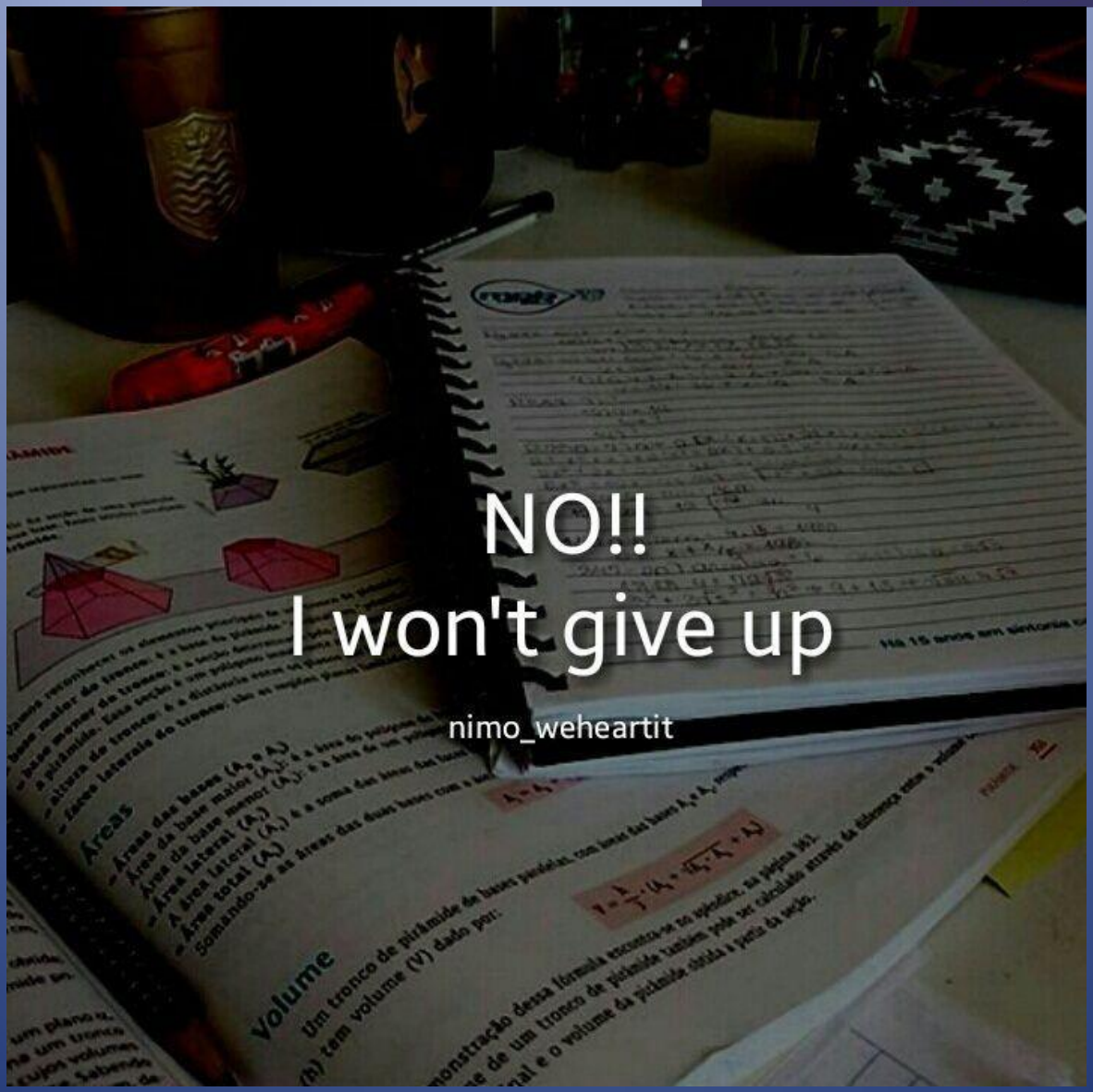
Guidance- Product Development

pharma mantra
Quality Advisory Consultancy

WHO TRS Annex3 970

Pharmaceutical development of multisource (generic) finished pharmaceutical products – points to consider


Hit this exam harder than
you have ever done before.
khangal_weheartit


NO!!
I won't give up
nimo_weheartit

Challenges – Scaling manufacturing to meet commercial requirements

Industry Perspective:

In recent years the pharmaceutical industry has faced declining R&D productivity, a rapidly changing healthcare landscape and fierce competition from generics resulting in lower growth and profit margins. Historically, drug development focused on clinical trials management and outcomes.

One meaningful and holistic approach to today's current challenges within the pharmaceutical industry is to focus on ***Product Lifecycle Management*** (PLM), which is a business transformation approach to manage products and related information across the enterprise. In recent years PLM has provided many pharmaceutical organizations with the ability to increase their ability to get products to market quicker, ensure greater regulatory compliance and efficiencies while reducing development costs.

Challenges – Scaling manufacturing to meet commercial requirements

Industry Perspective:

One meaningful and holistic approach to today's current challenges within the pharmaceutical industry is to focus on Product Lifecycle Management (PLM), which is a business transformation approach to manage products and related information across the enterprise.

In recent years PLM has provided many pharmaceutical organizations with the ability to increase their ability to get products to market quicker, ensure greater regulatory compliance and efficiencies while reducing development costs.

Challenges – Scaling manufacturing to meet commercial requirements

Industry Perspective:

Complex Drug Development Process

The drug development process is complex, consisting of many interrelated business activities and functional constituents participating in the *"Lab to Launch"* of any given product (Figure 1).

Figure 1 *"Lab to Launch"* Continuum

Challenges – Scaling manufacturing to meet commercial requirements

Industry Perspective:

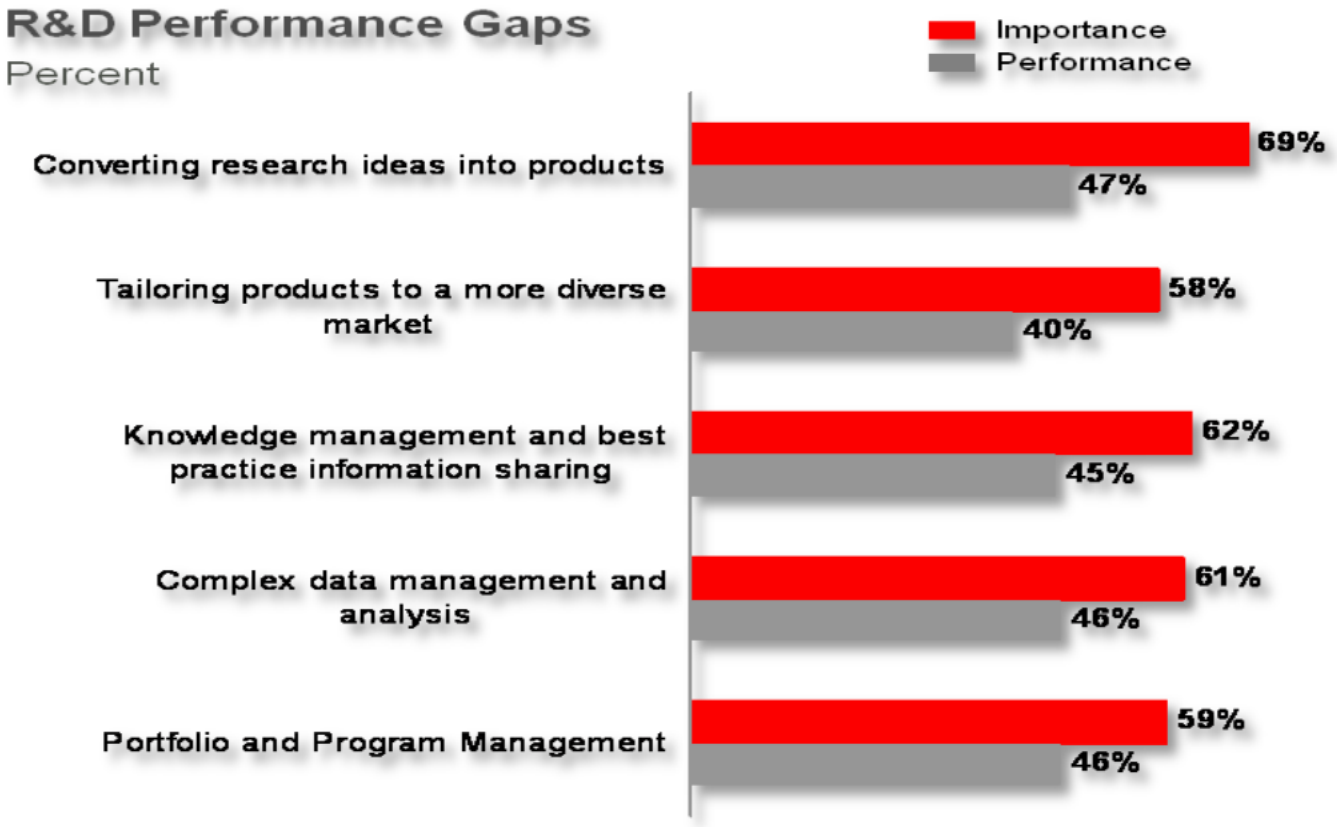
Large Gap Between R&D Operational Performance and Strategic Importance

To address the development process, the pharmaceutical industry has identified key R&D functions that are considered important in optimizing R&D pipeline effectiveness (AMR).

This research indicates significant gaps exist between R&D operational performance and strategic importance resulting in the industry operating at less than 50% effectiveness (Figure 2).


YMF
YOUNG WILD FREE
IF YOU CAN'T CONVINCE THEM, CONFUSE THEM.
@youngwild4free

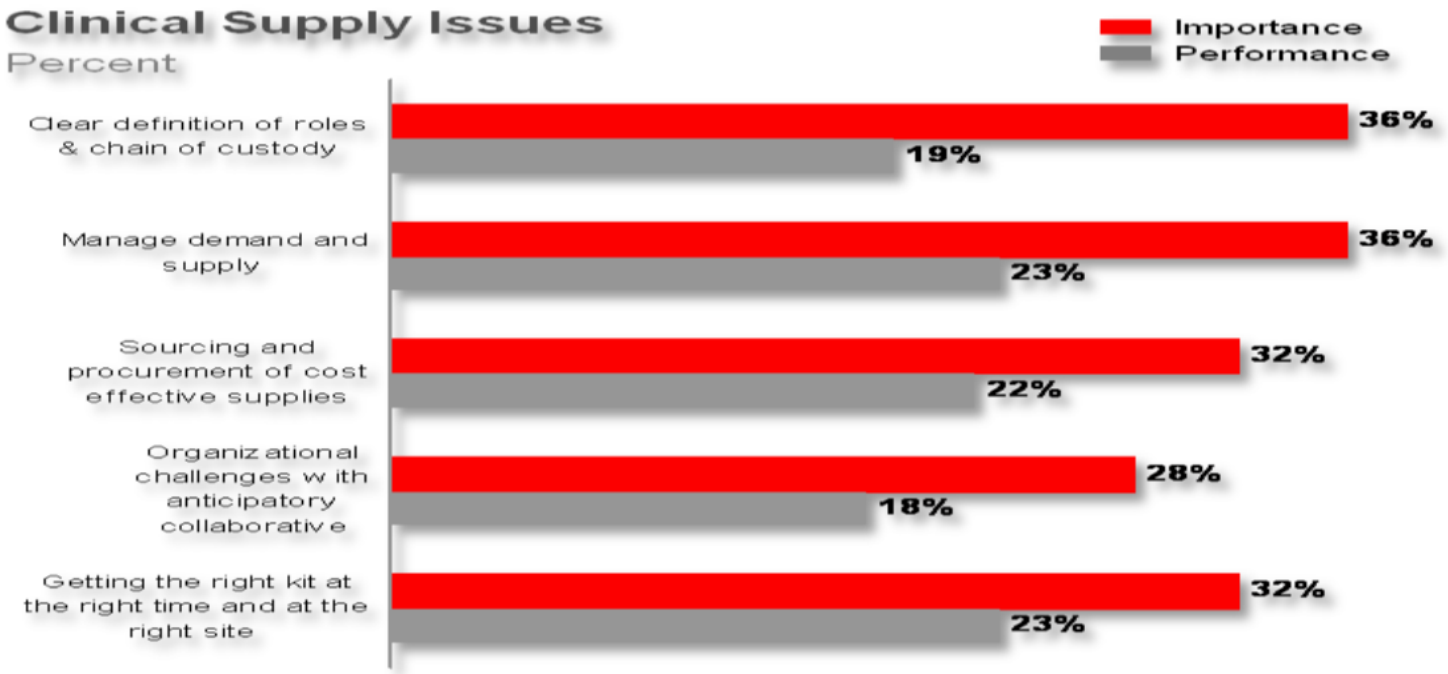
Challenges – Scaling manufacturing to meet commercial requirements



pharma mantra
Quality Advisory Consultancy

Challenges – Scaling manufacturing to meet commercial requirements

key clinical supplies metrics routinely result in less than 25% of their targeted performance objectives (Figure 3).



Challenges – Scaling manufacturing to meet commercial requirements

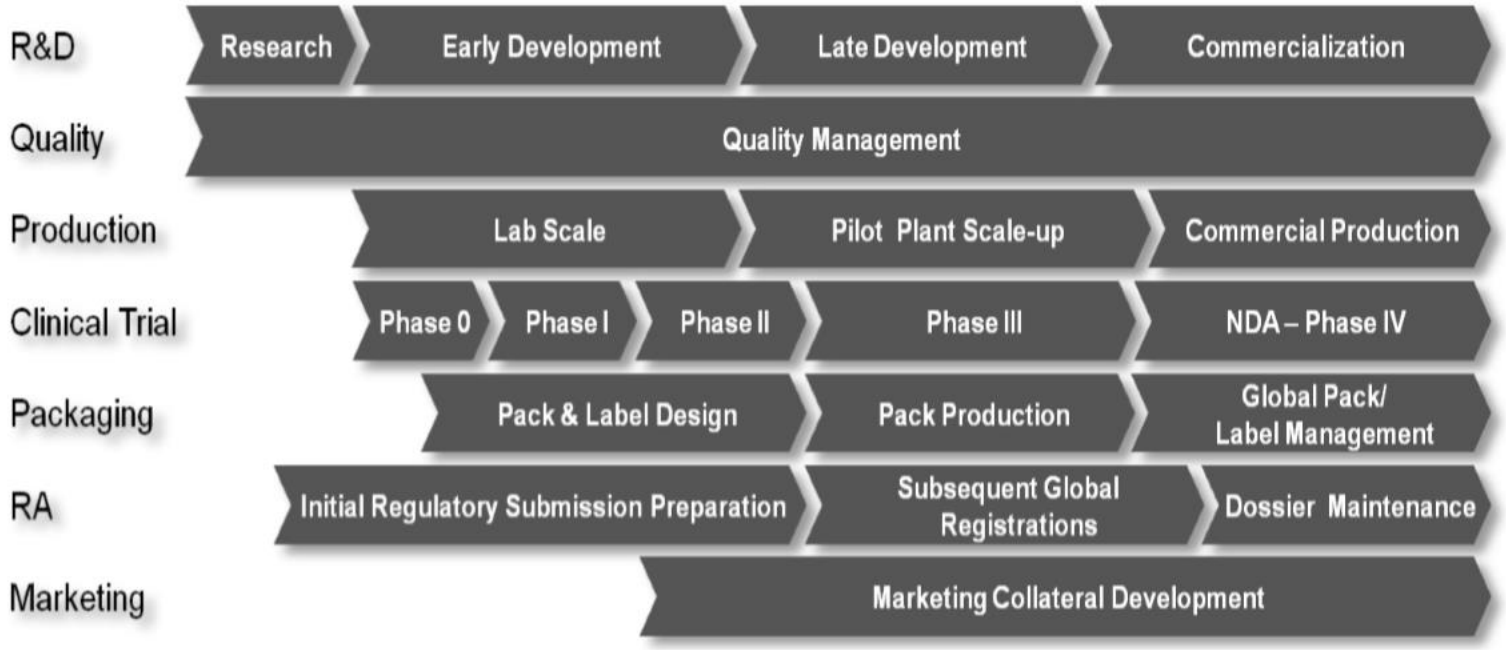
This combination of poor execution of the R&D pipeline and compromised production efficiency of the initial clinical supply process results in inadequate R&D results (AMR). Industry metrics based on project timeline performance, project cost, expected financial margin, and market share capture, show that approximately only 1 in 3 programs achieve their expected performance targets.


APOLOGIES
DON'T MEAN
ANYTHING
IF YOU KEEP
DOING WHAT
YOU'RE
SORRY
FOR.
My Dear Valentine

pharma mantra
Quality Advisory Consultancy

Challenges – Scaling manufacturing to meet commercial requirements

Understanding the functional requirements of each of the “swim lanes” and the inter-relationship across these constituents will define challenging areas to focus on for initiating this activity. A template of common drug development activities and constituents supporting this activity provides a starting point for many organizations beginning a business transformation process.



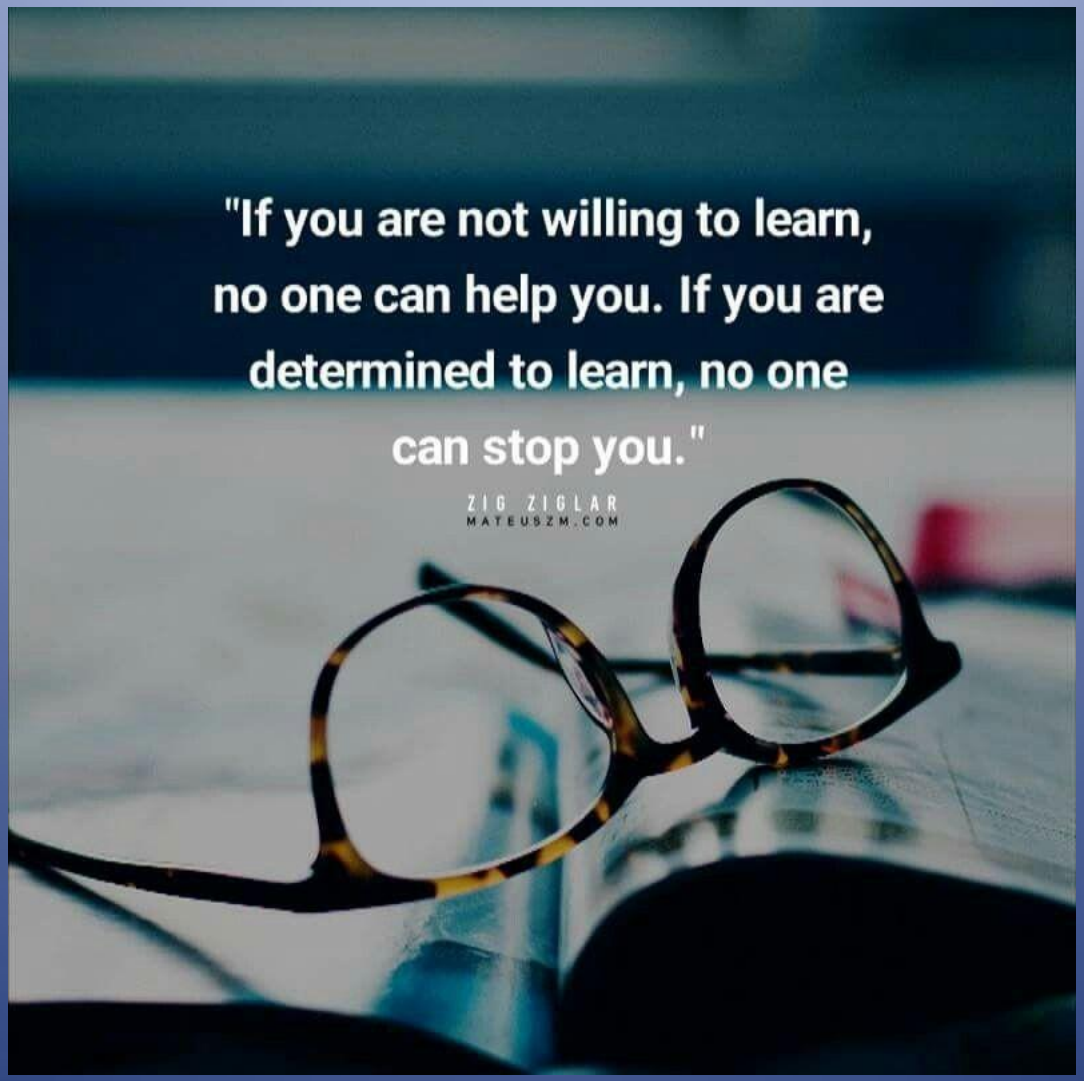
Challenges – Scaling manufacturing to meet commercial requirements

pharma mantra
Quality Advisory Consultancy

Industry Perspective:

Finally, some of the key influencers that have commonly impacted profitability, risk and growth can be traced back to three fundamental issues within the industry itself:

- Increasing internal and external complexity in managing the entire product lifecycle from product inception to phase out due to the simple fact that many pharmaceutical organizations suffer from silos of information across the different functional areas. In the case of R&D organizations this is typically based on therapeutic areas whereby cross-functional information flow is either lacking or non-existent.
- No single data source for products and related information due to a variety of different data sources and lack of collaboration across the organization. This often results in disparate, redundant and in worst cases inaccurate product information depending on functional area.
- Gap Between R&D and Commercialization: Historically R&D processes have been largely viewed as independent of product launch and subsequent commercialization efforts within the industry thus resulting in a fundamental gap for coordinated and transparent collaboration.


"If you are not willing to learn,
no one can help you. If you are
determined to learn, no one
can stop you."
ZIG ZIGLAR
MATEUSZM.COM

Challenges – Scaling manufacturing to meet commercial requirements

pharma mantra
Quality Advisory Consultancy

Industry Perspective:

7 Ways to Transform Business - Several companies are actively pursuing transformation initiates to address these challenges. Benchmarking of these initiatives helps identify common business processes required to enable this transformation. Based on input from 15 leading pharmaceutical companies; seven common enabling elements have been identified to support this transformation.

Challenges – Scaling manufacturing to meet commercial requirements

pharma mantra
Quality Advisory Consultancy

1. **Drug Development Portfolio Management**
   - Integrated project schedule & resources management with evidence creation
2. **Structured Electronic Drug Development Record (eDDR)**
   - Automated lab development archive & design dossier management
3. **Integrated Clinical Supply Development & Management**
   - CMO collaboration & material "chain-of-custody" management
4. **Technology Transfer & Collaboration**
   - Secure collaboration (int/ext) with evidence archive & knowledge re-use
5. **Integrated Quality & Risk Management**
   - Compliance & quality from development through commercialization enables QbD
6. **Comprehensive Packaging & Collateral Management**
   - Packaging/labeling & collateral content synchronized with registration
7. **Global Product Registration**
   - Product registration, strategy, submittal creation, eCTD management, & dossier maintenance

Figure 7 *Key transformation Elements*

An operational review of each of these elements can be used to determine what functional requirements need to be deployed to support the transformation roadmap.

Challenges – Scaling manufacturing to meet commercial requirements

Industry Perspective:

An operational review of each of these elements can be used to determine what functional requirements need to be deployed to support the transformation roadmap.

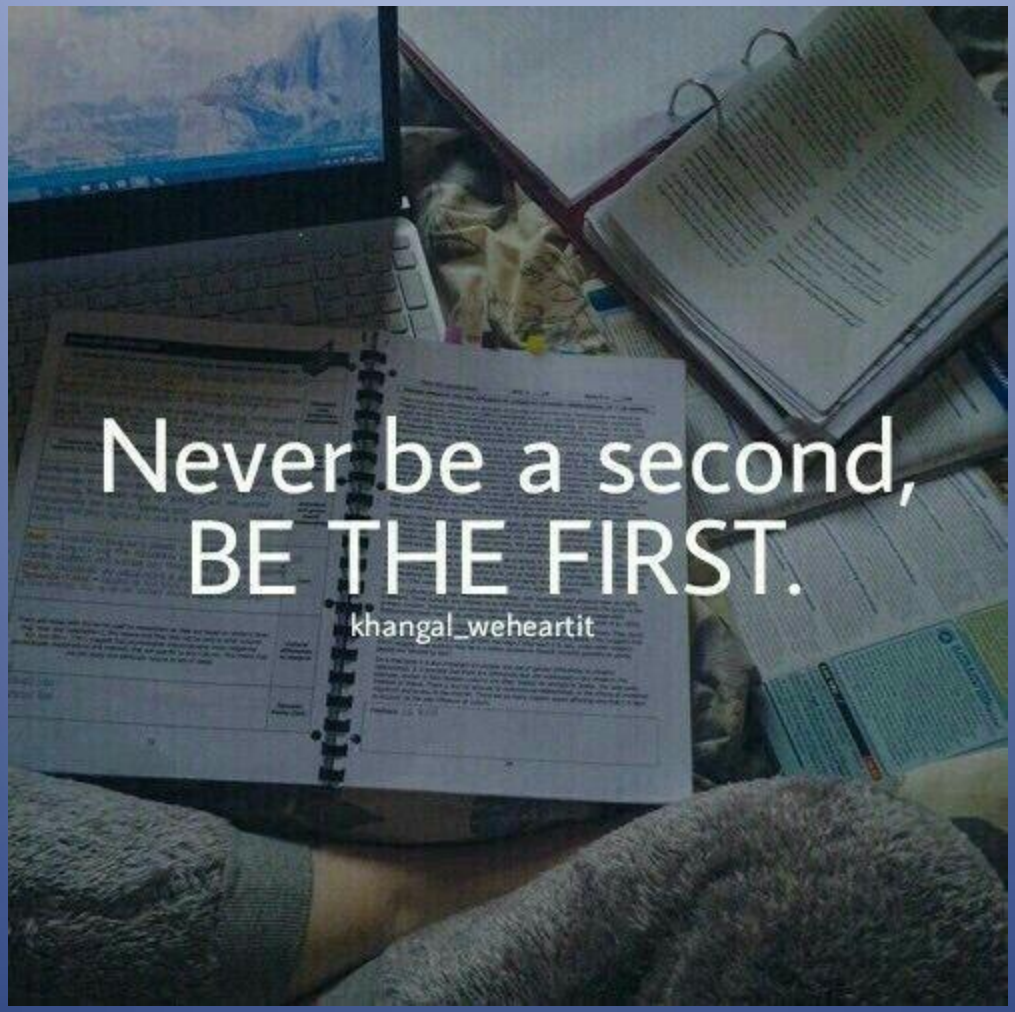
The complexity of individual drug development programs is further complicated as there are typically multiple programs occurring simultaneously in the R&D pipeline at any given time. Traditional drug development program management has focused on general program metrics such as schedule, and cost performance. To improve drug development execution, program management that synchronizes cross-functional collaboration and archiving of critical program deliverables is required. Integration of the decisions and approvals of these deliverables provide the regulatory evidence needed to confidently advance the drug development process through each phase. Management of each program and required deliverable evident in one system can also enable standardization of best practices to improve pipeline performance.

Challenges – Scaling manufacturing to meet commercial requirements

pharma mantra
Quality Advisory Consultancy

1. **Drug Development Portfolio Management**
   - Integrated project schedule & resources management with evidence creation
2. **Structured Electronic Drug Development Record (eDDR)**
   - Automated lab development archive & design dossier management

With the volume of program deliverables and regulatory evidence required in the development process ever increasing, a structured drug development archive is needed to effectively manage all of the associated content. This highly iterative development record must be automated to capture historical developmental information to support product claims and regulatory audits. Creating a structured archive for each individual design dossier in one unified system can also facilitate re-use of the Common Technical Documents (CTD).


Never be a second,
BE THE FIRST.
khangal_weheartit

Challenges – Scaling manufacturing to meet commercial requirements

Clinical trial management is a pivotal phase in the drug development process that has become more complicated with global and adaptive trials. As companies look for ways to reduce costs while significantly increasing profitability, externalization of clinical trials to CROs for example has become increasingly common and impacts everything from pre-clinical to post marketing research. The supply chain for clinical trials has also become increasing complex with multiple manufacturing sites and CMOs engaged in supporting the scale up for the required clinical inventory. For all supplies dispensed to each clinical site, a complete lot history of the campaigns producing the product must be archived. Synchronizing the approved manufacturing evidence of the clinical supplies with trial activity is required for clinical trial integrity to be maintained

Challenges – Scaling manufacturing to meet commercial requirements

pharma mantra
Quality Advisory Consultancy

The production of drug product is highly iterative and controls must be established for each lot from scale-up through commercialization of the final approved product. Effective scale-up of drug production requires collaboration across many interrelated activities and dependences. An enterprise solution that enables the analysis of the drug product value chain including suppliers, materials, equipment, and processes will not only provide individual lot control but also facilitate the scale-up to commercial drug production volumes.

Challenges – Scaling manufacturing to meet commercial requirements

pharma mantra
Quality Advisory Consultancy

6 Comprehensive Packaging & Collateral Management
- Packaging/labeling & collateral content synchronized with registration

7 Global Product Registration
- Product registration, strategy, submittal creation, eCTD management, & dossier maintenance

The integration of packaging, labeling and associated marketing collateral into the drug development process provides a significant business opportunity in the pharmaceutical industry. Often the creation of these assets is deferred until late in the drug development cycle creating delays in market launch and increased cost. This disconnect from the drug development evidence also creates the potential for misleading off-label claims that can be devastating for a product. Creation of a global repository for all packaging components, digital assets such as logos and artwork, and marketing collateral that references development evidence will improve the regulatory integrity of all the associated commercial content. Re-use of this commercial product content, and common translation services are just a few of the business benefits companies like GSK and Bayer have realized by the enterprise management of this critical asset.

Challenges – Scaling manufacturing to meet commercial requirements

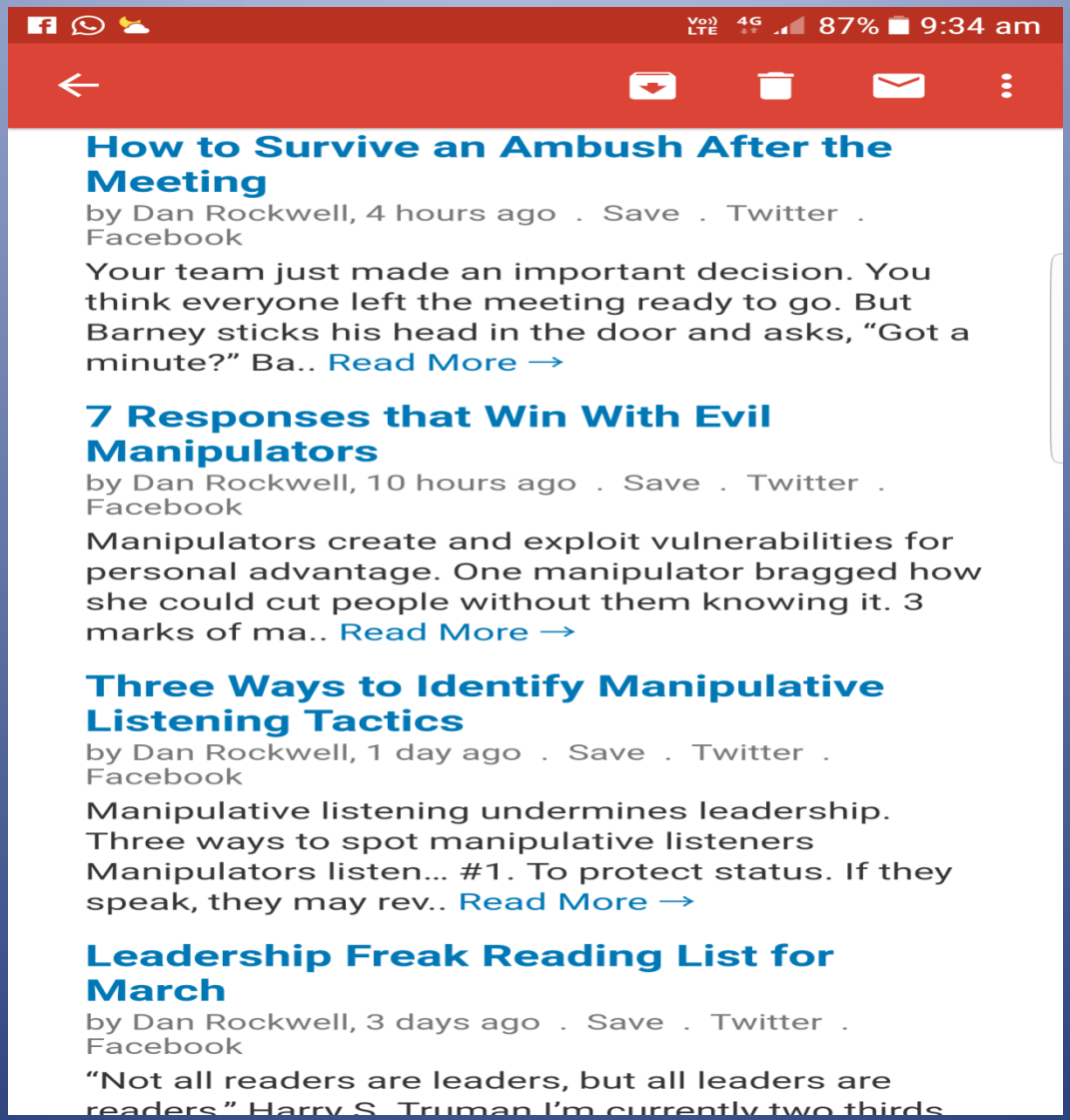
pharma mantra
Quality Advisory Consultancy

6 Comprehensive Packaging & Collateral Management
- Packaging/labeling & collateral content synchronized with registration

7 Global Product Registration
- Product registration, strategy, submittal creation, eCTD management, & dossier maintenance

The ultimate successful outcome of any drug development program is regulatory submission and approval for commercial distribution of the product. Global product registration is complex and constantly evolving, making registration management increasingly difficult. As a result, this creates delays in market launch and significantly impacts the anticipated product revenue. Leveraging the evidence captured in the previously described use cases provides the content to support regulatory submittal requirements. This content also can be used for on-going global product proliferation through re-use of this registration process significantly improving ROI for each new product developed.


A GROUP OF BABOONS IS CALLED A CONGRESS
VIA 9GAG.COM
IT'S ALL CLEAR TO ME NOW
MEMEFUL.COM


87% 9:34 am
How to Survive an Ambush After the Meeting
by Dan Rockwell, 4 hours ago . Save . Twitter . Facebook
Your team just made an important decision. You think everyone left the meeting ready to go. But Barney sticks his head in the door and asks, "Got a minute?" Ba.. Read More →
7 Responses that Win With Evil Manipulators
by Dan Rockwell, 10 hours ago . Save . Twitter . Facebook
Manipulators create and exploit vulnerabilities for personal advantage. One manipulator bragged how she could cut people without them knowing it. 3 marks of ma.. Read More →
Three Ways to Identify Manipulative Listening Tactics
by Dan Rockwell, 1 day ago . Save . Twitter . Facebook
Manipulative listening undermines leadership. Three ways to spot manipulative listeners Manipulators listen... #1. To protect status. If they speak, they may rev.. Read More →
Leadership Freak Reading List for March
by Dan Rockwell, 3 days ago . Save . Twitter . Facebook
"Not all readers are leaders, but all leaders are

Procedure - Investigation Plan

The team shall review the event to arrive at a detailed, precise, and unambiguous description of the event.

- The team shall develop a plan that defines tasks, responsibilities, resources, sequence and milestones.
- The investigation team shall take the following steps (this is not an all inclusive list) as applicable to understand the process that failed and collect data for investigation:
  - Interview involved people
  - Review procedures
  - Review training
  - Review trend analysis
  - Review R&D data
  - Review validation data
  - Observation
  - Other measures as applicable

Procedure - Investigation Plan

The Team shall have a Brainstorming session to analyze the collected data and based on outcome plan the Root Cause Analysis.

Investigation Methods

There is no single prescribed method of conducting Root Cause Analysis, following methods may be recommended :

- The **"5 Whys"** – used for simple investigations
- **Fishbone Diagrams**– used for more complex investigations

The investigation team shall select the appropriate method based on the event.

Head of affected department shall approve the investigation plan if satisfactory. Otherwise shall recommend for revision of the plan with comments.


DO IT OVER
AND OVER
AGAIN UNTIL
IT BECOMES
PART OF WHO
YOU ARE.
FCUK-MY-ACTUAL-LIFE.TUMBLR.COM

Procedure - Investigation Plan

pharma mantra
Quality Advisory Consultancy

Execution of investigation

- Investigation team under the guidance of team lead shall execute the investigation as per investigation plan.
- The investigation team shall identify the Root Cause of the event. In cases where root cause cannot be identified, the most Probable Cause shall be identified.
- The investigation team shall propose corrective actions to correct the problem and preventive actions to prevent it from recurring.


THEY TELL
YOU TO BE
YOURSELF &
THEN THEY
JUDGE YOU

Procedure - Investigation Plan

pharma mantra
Quality Advisory Consultancy

Investigation Report

- The key factor is that the investigation and any actions identified are documented in a manner that is clear and unambiguous to anyone reading the document.
- The report shall include documentation of all steps of investigation including techniques and methods used to identify the root cause/probable cause.
- All supporting documents shall be attached to the Investigation Report.
- Team lead shall verify the completeness of the Investigation Report and submit to Head of the affected department for review.
- Head of affected department shall submit this report to Head-QA for approval and closure.

Procedure - Investigation Plan

pharma mantra
Quality Advisory Consultancy

Closure of Investigation

- Head-QA shall review the investigation for its adequacy, analysis and identification of root cause/probable cause.
- Head-QA shall approve the investigation if satisfactory. Otherwise shall recommend for re-investigation with comments to explain justification.
- Investigation shall be closed within 30 days from the reporting date of the event.
- If needed, with the approval of Head of affected department and Head -QA this can be extended based on justification.

Procedure - Investigation Plan

pharma mantra
Quality Advisory Consultancy

Corrective and Preventive Action (CAPA)

- Based on root cause/probable cause CAPA shall be proposed and taken
- CAPA reference shall be documented in Investigation Report.

ALCOA

Although the **cGMPs** articulate a number of the expectations for data quality, the **GLP** regulations, , are the first FDA regulations which bring the ALCOA elements of data quality together in a comprehensive fashion.

For this reason, the GLP requirements pertaining to **data quality elements**, particularly **21 CFR 58.130(e)** which articulates virtually all the **elements of ALCOA**.

This acronym stands for :

1. **A**ttributable,
2. **L**egible,
3. **C**ontemporaneous,
4. **O**riginal and
5. **A**ccurate.

pharma mantra
Quality Advisory Consultancy

ALCOA

The first "A" in ALCOA stands for Attributable.

Simply put, FDA expects data to be linked to its **source**. It should be attributable to the **individual** who observed and recorded the data, as well as **traceable** to the source of the data itself. (e.g. study, test system, analytical run, etc.) The applicable GLP requirements pertaining to attribution of data are found in 21 CFR 58.130 (c) and (e).

The requirement for attribution of data to the individual who collected it is found in 58. 130(e). According to the regulation,

"All data entries shall be dated on the date of entry and signed or initialed by the person entering the data". The same is true for automated data. The regulation states, ***". . . In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input. . ."*** Not only does this concept of attribution apply to the collection of original data but also to any changes made to the data. ***Changes made to data must be signed and dated by the individual making the changes***.

An example of a requirement for attribution of data to its source, is illustrated by 21 CFR 58.130(c) which requires study specimens to be identified by test system, study, nature, and date of collection.

ALCOA

The "L" in ALCOA stands for Legible.

Quality data must also be **legible** if it is to be considered fit for use. The concept of legibility means that data **are readable**. This of course implies that data must be **recorded permanently** in a durable medium (e.g. pen and ink on paper). 21 CFR 58.130(e) addresses this directly by requiring that, ***"data shall be recorded directly, promptly, and legibly in ink"***. The concept of legibility of data also extends to changes made to data. For example, 58.130(e) requires that ***changes be made so as not to obscure the original entry***, thereby maintaining its legibility.

The requirements for legibility of electronic data may present technical challenges and take on new meaning, with respect to recording data permanently on a durable medium. However, the underlying concept of legibility/readability is the same.

If one consults FDA's Electronic Record; Electronic Signature rule (21 CFR 11), many of the traditional ALCOA data quality elements are addressed. For example, with respect to legibility of data, 21 CFR 11.10 (b) requires that compliant electronic systems have, ***"The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency."*** This requirement clearly establishes the expectation that electronic data must be readable (i.e. legible).

pharma mantra
Quality Advisory Consultancy

ALCOA

The "C" in ALCOA stands for Contemporaneous.

This element of data quality refers to the **timing of data collection** with respect to the time the observation is made. In short, the more promptly an observation is recorded, the better the quality. Data should be recorded **at the time** the observation is made (i.e. contemporaneously). The GLPs address this at 21 CFR 58.130(e) as discussed above. Specifically the regulation at 21 CFR 130(e) states, **". . . data shall be recorded directly, promptly, and legibly. . ."**

The requirement that data be contemporaneous is also implied in the regulations that require the date of data entry to be recorded. For example, 21 CFR 58.130 (e) also requires **"All data entries shall be dated on the date of entry and signed or initialed by the person entering the data".** The longstanding and virtually universal requirement in FDA regulations for dating record entries is intended to assure, or at least document, the extent to which data is recorded contemporaneously with the observation being made.

pharma mantra
Quality Advisory Consultancy

ALCOA

The "O" in ALCOA stands for Original.

Original data is generally considered to be **the first** and therefore **the most accurate** and **reliable recording** of data. The terms **source data or raw data** embody this concept of the first recording of data, and are sometimes used interchangeably. Source data is the term generally used in the context of Good Clinical Practices (GCP), while GLP enthusiast use the term raw data as it is officially defined in the GLP regulations at 21 CFR 58.3 (k). The term source data, although defined in guidance, is nowhere to be found in FDA regulations. On the other hand, the GLPs were the first and only place the concept of raw or source data is actually put explicitly into FDA regulations. Indeed, the GLP definition of raw data is the foundation upon which the term source data is defined in a number of FDA guidance documents on GCPs.1 The definition at 21 CFR 58.3 (k) states in part **"Raw data means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study. . ."** Although the GLPs and GCP do provide for the substitution of certified copies of source/raw data in lieu of the original record, the concept that the original recorded data is of the highest quality is retained. The concept of originality being an element of data quality is further reinforced in 58.130(e) which states **". . . data shall be recorded directly. . ."**

ALCOA

The last "A" in ALCOA stands for Accurate.

Accuracy is an implied element of data quality under the GLP regulations. The Merriam-Webster Dictionary- defines accurate as 1: **free from error** especially as the result of care 2: **conforming exactly to truth** or to a standard: EXACT 3: able to give an accurate result **synonym see CORRECT** .

Accuracy is probably the most intuitive element of data quality. The most direct reference in the GLPs to the expectation of accuracy is found in 58.35 (b) which requires the QAU to assure the **final report accurately describes the study conduct and that the reported results accurately reflect the raw data**.

Case Studies

pharma mantra
Quality Advisory Consultancy

Analytical Method –

During AMT of the assay for Injectable product ,unknown impurity at the tailing of principal peak has been observed , which is not separated properly (i.e. base to base separation is not there).

During analytical method validation/ development , same pattern was not observed as this impurity might have merged in the principal peak.

This may give high assay result or false positive assay result . As per the specificity parameter for test like assay, Dissolution, CU etc. there should not be any interference / impurity at the retention time of principal peak and the peak marking should be base to base .

Case Studies

pharma mantra
Quality Advisory Consultancy

Manufacturing Process –

After taking exhibit batch of the one of the Injectable product ,the assay results found out of specification i.e. very high ,in the range of 125% against limit of 95% to 105% for all the validation samples.

After investigation it was concluded that the standard weighing needs to be done on the balance kept in glove box as material was highly hygroscopic in nature. Thus absorbs moisture during weighing resulting into less weight & subsequent less area during HPLC run & proving high results for assay test.

However same was remained unidentified during Method development & subsequent validation hence same was not part of the specification /procedure .

Finally batch was rejected.

Summary –
2 sides of a coin Opportunity & Challenges

pharma mantra
Quality Advisory Consultancy

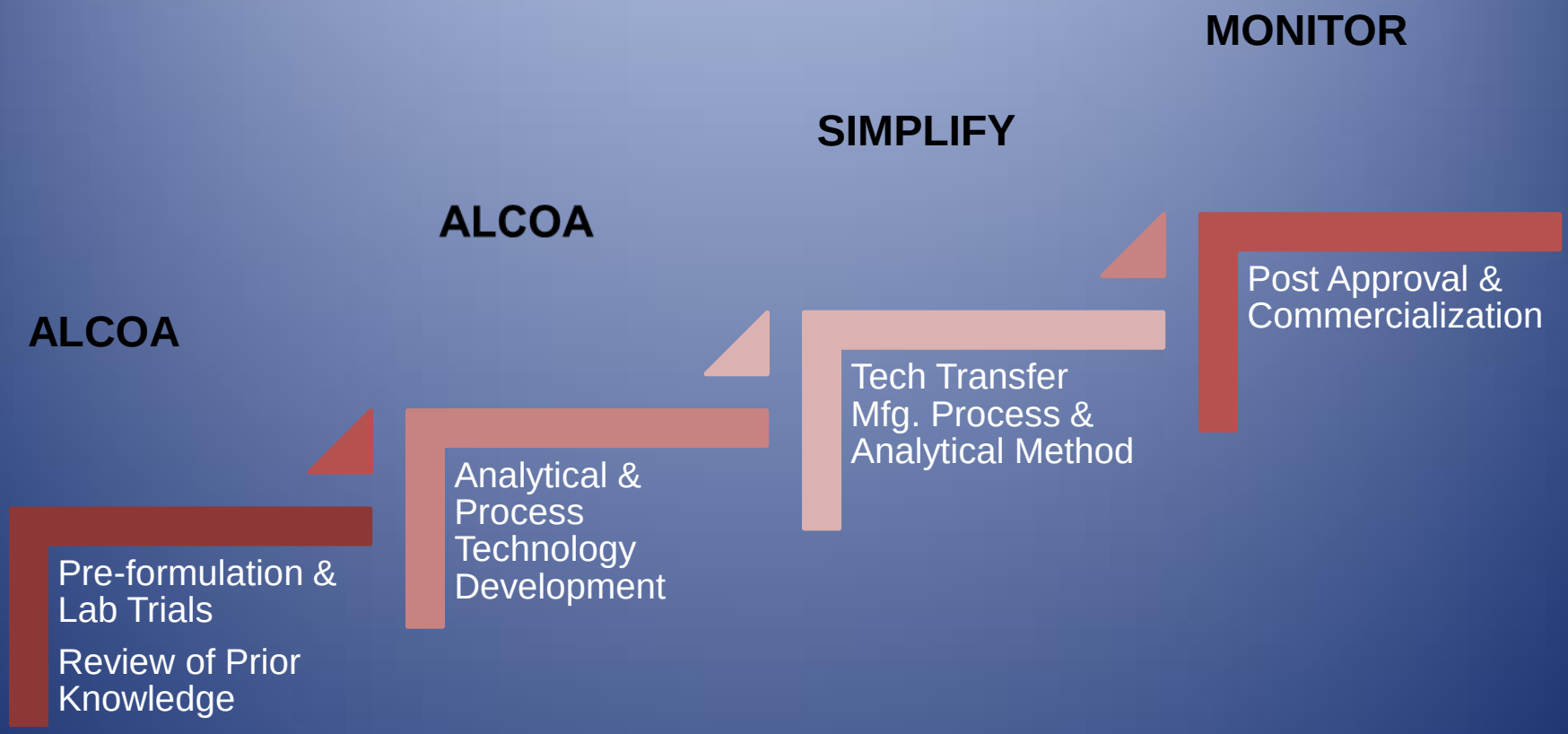
New Product development

Technology Transfer & scale-up

Post Approval & Commercialization

Learning……Challenges – Documents…..Records…

pharma mantra
Quality Advisory Consultancy



Learning……Challenges – Unlearning…..No Repeats….mistakes

pharma mantra
Quality Advisory Consultancy

New Product development

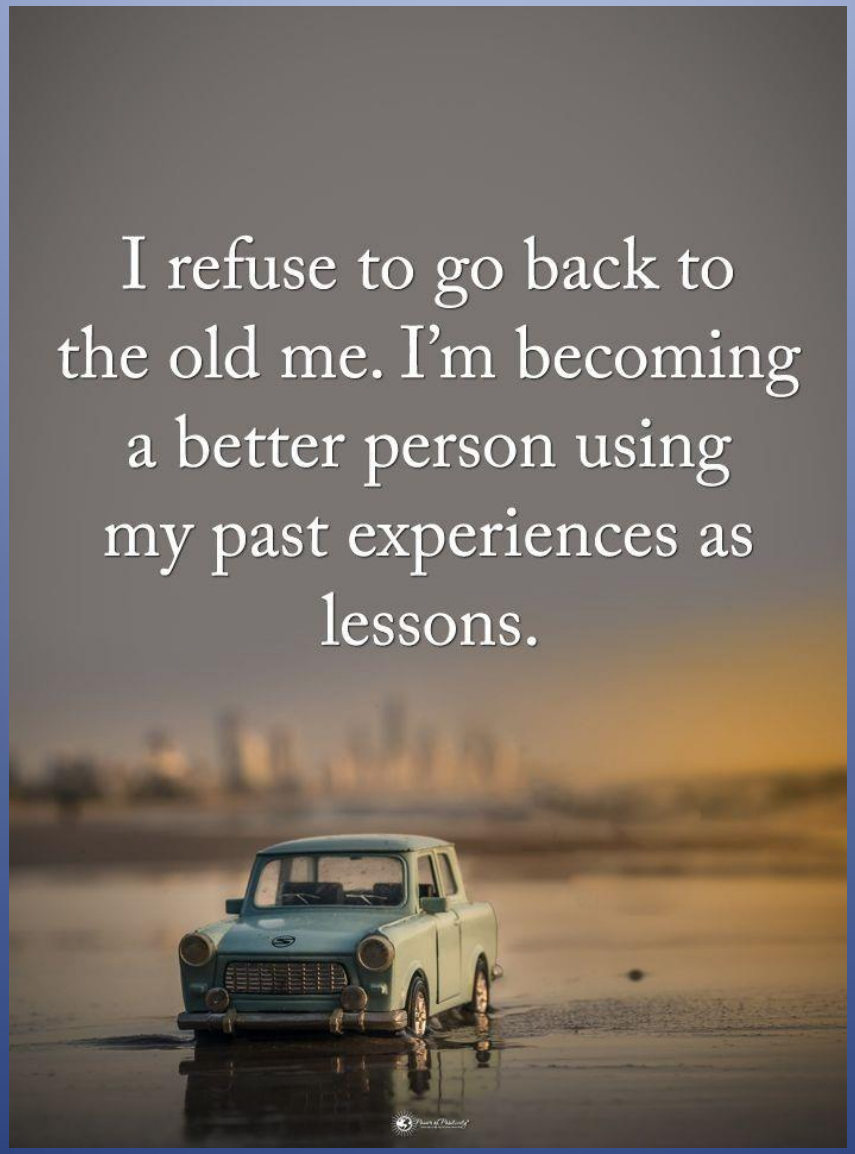
- Identification of Candidate – Business Case
- Develop – Dosage, Prototype Process, Method (innovator)
- Bio-batches, Clinical, BA/ BE studies
- Investigations of Failure - Learning

Technology Transfer & scale-up

- Scale-up of Batch Process, Method of Analysis, Specifications,
- Validation, Reproducibility, Process Capability
- Investigations of Failure – Process Optimisation

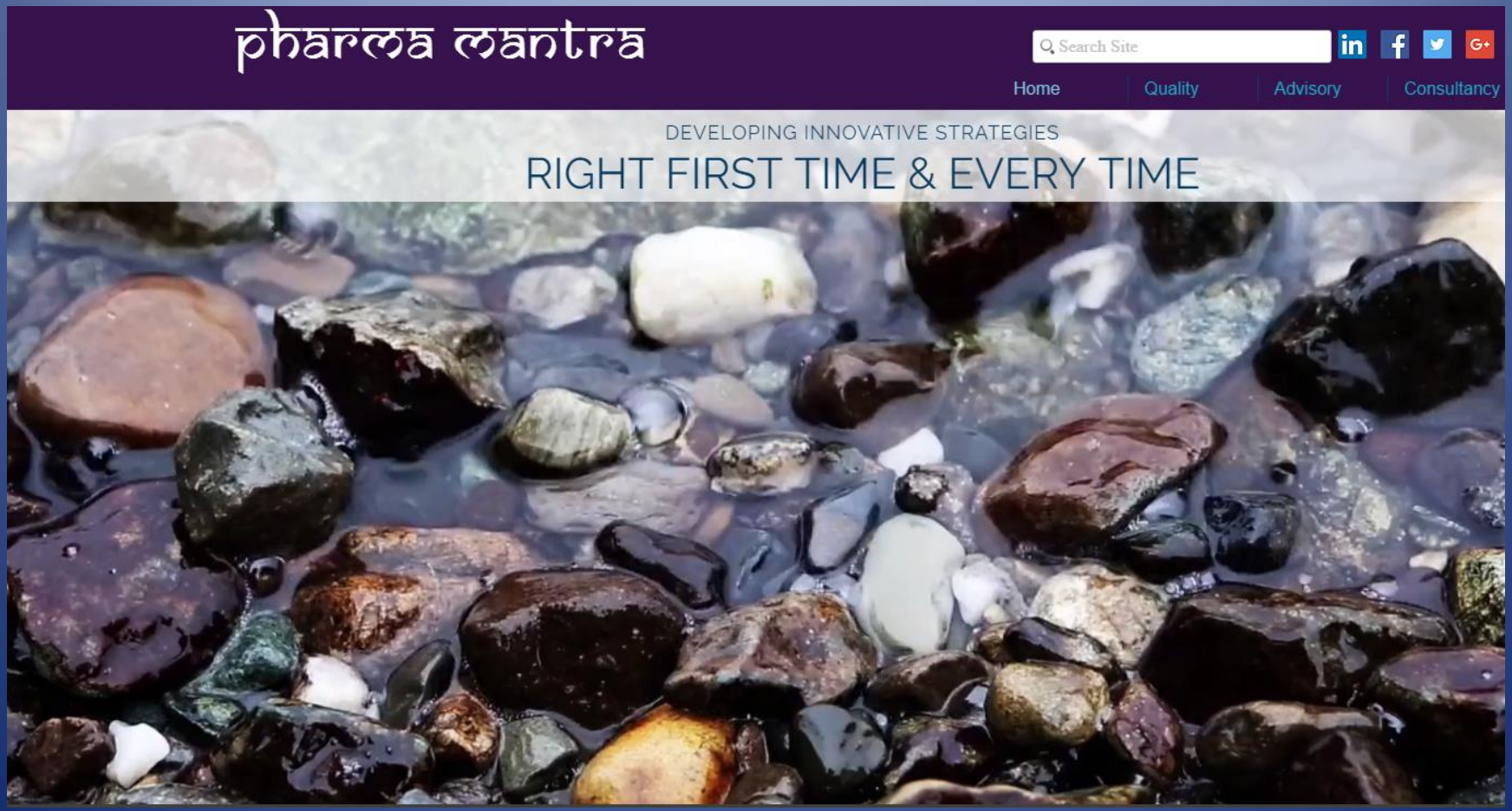
Post Approval & Commercialization

- Change Control - Batch Process, Method of Analysis, Specifications,
- Investigations of Failure - Trend
- CPV, Monitoring the Process Capability
- PLM (lifecycle management)


I refuse to go back to
the old me. I'm becoming
a better person using
my past experiences as
lessons.

pharma mantra
Quality Advisory Consultancy

Our Website: Home



pharma mantra
Quality Advisory Consultancy

Our Website: Services

pharma mantra

Search Site

Home | Quality | Advisory | Consultancy

SERVICES WE OFFER

Delivering strategic and transformational Quality leadership drive for imparting Culture of Pharmaceutical Quality to provide successful international growth initiative in Pharmaceutical & healthcare industry

Provide effective leadership for Quality Assurance of Pharmaceutical (API & DF), Biosililars, Drug- Device combination products in Manufacturing and R&D operations

Steering organization through complex Quality & Regulatory challenges, remediation, transitions & building an empowered Quality Operations Team which is capable and empowered to deliver results within highly competitive products and regulatory environment.

QUALITY

- Training - GxP compliance
- Audits - GxP
- Pre-approval inspection (PAI) readiness
- Operational readiness and sustainability programs (mentoring)
- Formulation of CAP – corrective action plan
- Assistance during regulatory inspections & post-inspection correspondence and meetings
- Assistance to legal counsel in FDA enforcement matters
- Due diligence of product and facility acquisitions

More Info

ADVISORY

- New Project Management
- Quality & Compliance Strategy
- QMS Initiation, Implementation, Review
- Imbibe the Culture of Quality

More Info

CONSULTANCY

- Quality Management
- Regulatory submission and site readiness
- Resource Management for SOC (state of control)
- Remediation Program
- GxP Compliance Strategies

More Info

pharma mantra
Quality Advisory Consultancy

Our Website: Contact

pharma mantra

Search Site

Home | Quality | Advisory | Consultancy

CONTACT US

Udaykumar Rakibe

Mobile: +917756848484

Email: pharmantra.expert@gmail.com

Name

Email

Subject

Message

Send

Our Website: About us

pharma mantra

Search Site

Home | Quality | Advisory | Consultancy

Udaykumar K. Rakibe

Founder

M.Pharmacy & MBA from Pune University – was mandated and given the task to execute and spearhead the proactive remediation in 2006 by Ranbaxy Lab. Ltd. In late 2011 he was recruited by Intas Pharma. to create a self-sustaining quality management system and enhance inspection readiness. Further, in 2013 he was hand-picked & recruited by Wockhardt Ltd., as Senior Vice President – Quality, to turn around the Quality Management, lead and manage the remediation of Quality initiatives.

Udaykumar is a quality professional with a dynamic career steering organizations through complex Quality & Regulatory challenges, transitions, building an empowered and talented workforce in the cross-cultural environment within highly competitive products and regulatory environment.

He began his career in Quality function in the Executive in-process QA with Glenmark Pharma Ltd. and then moved to different levels and organization spanning 26 plus years of hands-on and hardcore experience in the pharmaceutical regulatory environment. He has gained the domain experience in Quality by working 20 years' in Quality operations- out of twenty years last 11 years focusing and leading the Quality & Regulatory remediation. He has 7 years experience in Corporate Quality functions, overseeing the Developmental & filing of - Clinical, Analytical, Formulation, Devices. Has setup the Global Quality organization for the Contact Manufacturing in regulated and semi-regulated markets He has worked as a senior member of the Quality Team with Ranbaxy Labs Ltd., Dabur Pharma Ltd., Gland Pharma Ltd., IntasPharma Ltd., and Wockhardt Ltd.