5th INDIA PHARMACEUTICAL FORUM 2020

Indian Pharmaceutical Alliance
IPA
Innovation, Quality and Global Reach

QUALITY BY DESIGN FOR ROBUST PRODUCT

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Quality by Design Learning from other Industries

Toyota Corolla recalled to replace entire gearbox

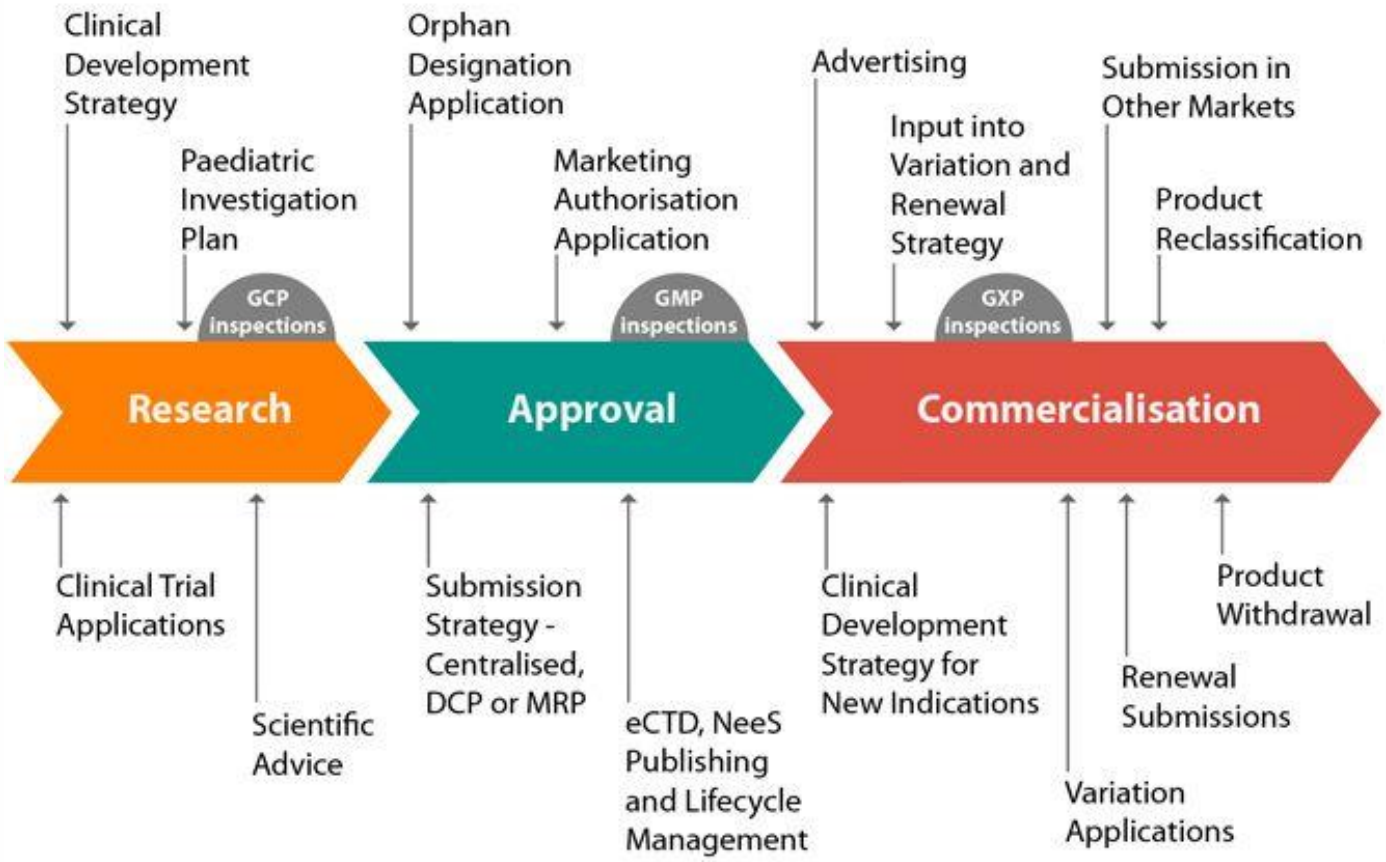
- Serious issue with the car's **Continuously Variable Transmission (CVT) gearbox** that can cause a loss of power at high speeds
- **Design error** impacted in manufacturing of torque converter in the **CVT** assembly
- Design was **improved by QbD** and replaced the CVT

The explosion of TWA Flight 800, Boeing 747

- Boeing 747 that had just taken off from JFK bound for Paris, killed all 230 people.
- **Short circuit** in a wire bundle led to a spark in the fuel gauge sensor.
- **Developed** a **fuel-inerting system** that injects nitrogen gas into fuel tanks to **reduce** the chance of explosions.

Designing the Product

Quality by Design (QbD) provides not only scientific, risk based, holistic, proactive approach to enhanced product development/understanding (product formulation, process, and device) but also ensure consistent desired product quality including performance over the product life-cycle, including continual improvement.



Designing the Product

QUALITY BY DESIGN

Continuous improvement is a hallmark of quality by design

- G. Taguchi on Robust Design: design changes during manufacture can result in the last product produced being different from the first product

In pharmaceutical manufacturing, we don't want this – patients and physicians must count on each batch of drug working just like the batches that came before

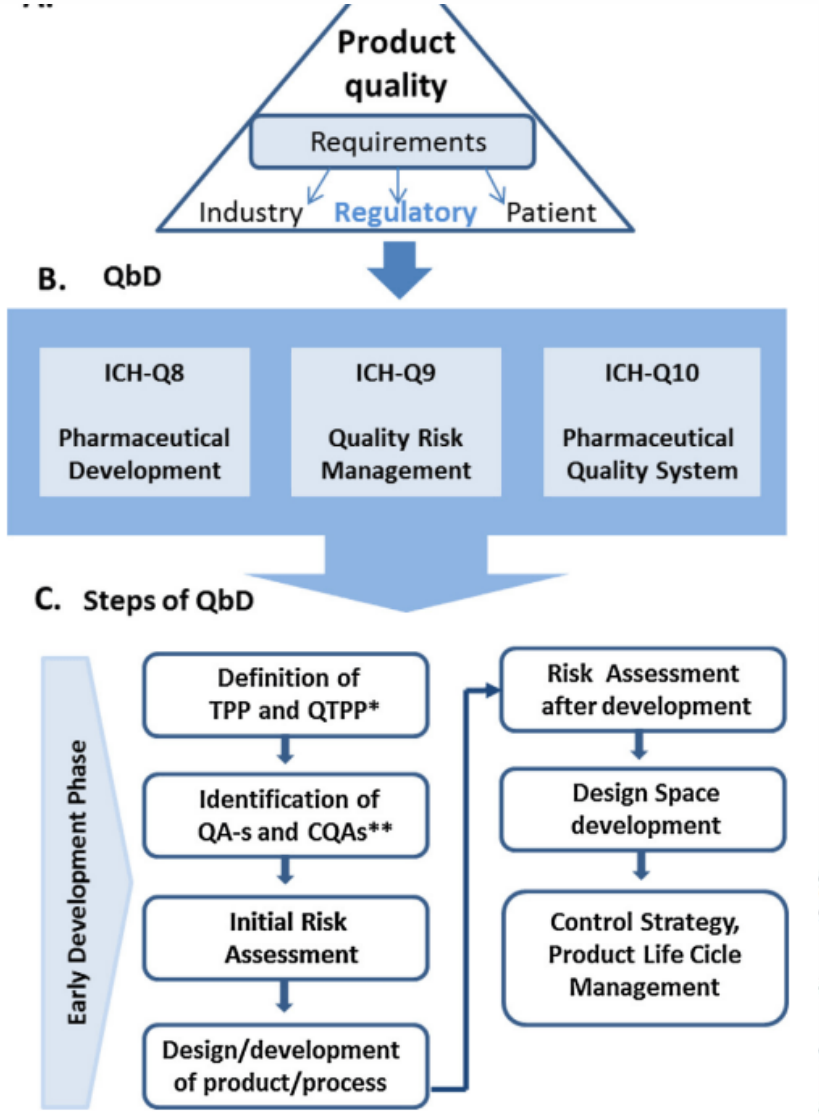
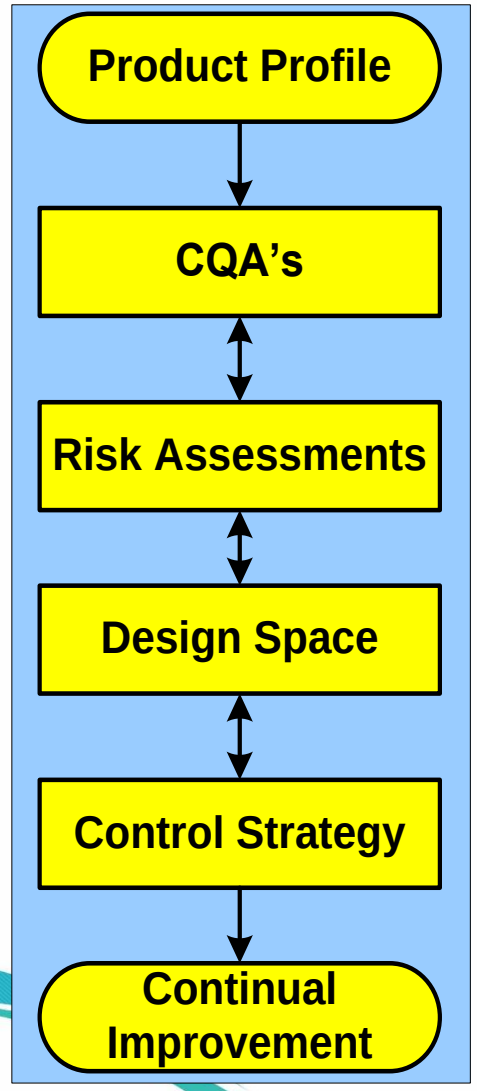


Fig. 5. Quality requirements and elements with the steps and roadmap of the

QbD APPROACH



Quality Target Product Profile (QTPP)

Determine "potential" critical quality attributes (CQAs)

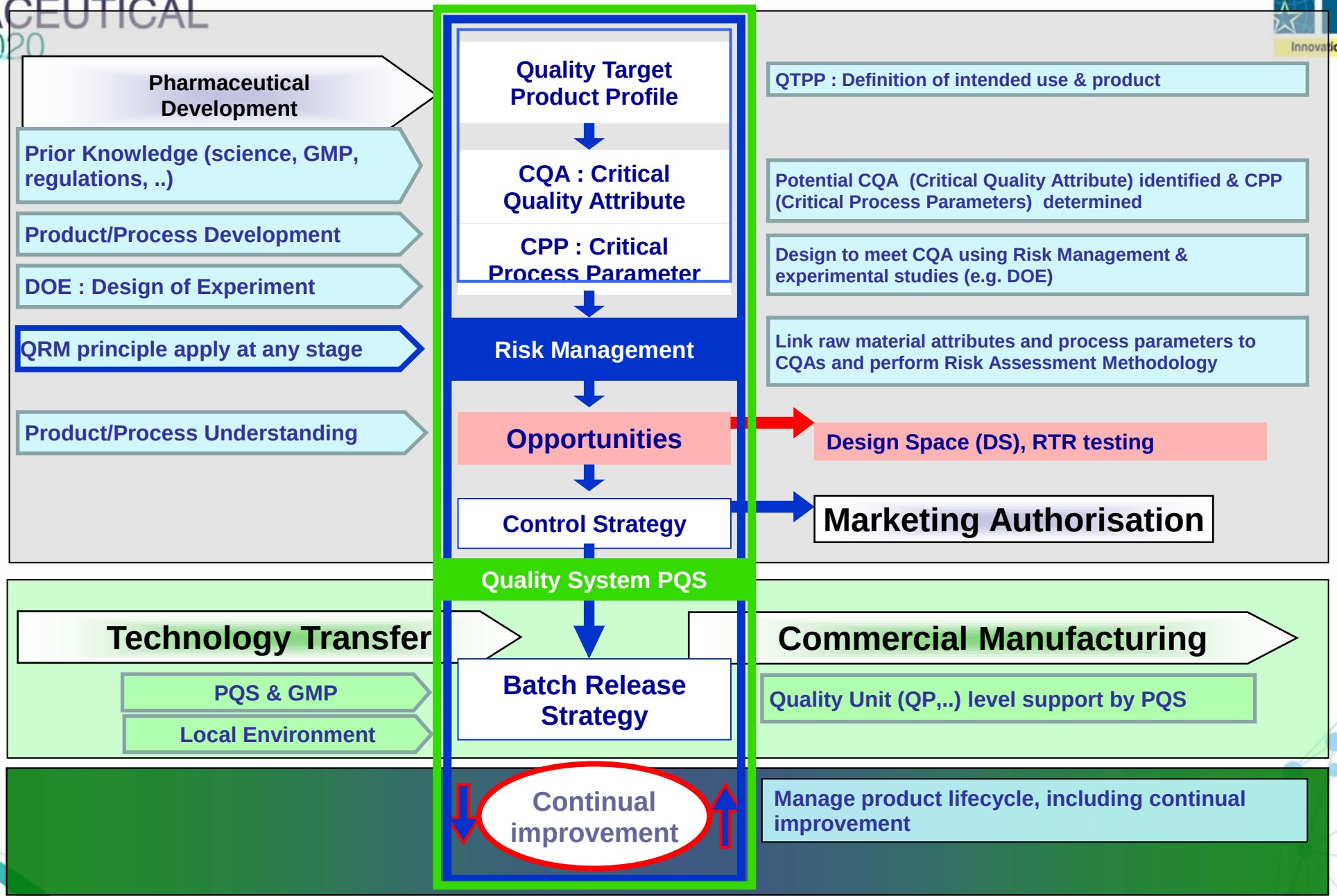
Link raw material attributes and process parameters to CQAs and perform risk assessment

Develop a design space

Design and implement a control strategy

Manage product lifecycle, including continual improvement

Key Steps for a product under Quality by QbD



QTPP TO CQ TO CMA TO CPP

The Quality Target Product Profile (QTPP) describes the design criteria for the product, and should therefore form the basis for development of the CQAs, CPPs, and control strategy.

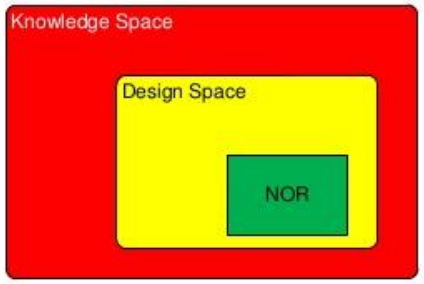
Critical Quality Attributes (CQA) A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8)

Critical Process Parameter (CPP) A process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8)

- **Critical Material Attribute (CMA)* A physical, chemical, biological or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired quality of output material.**

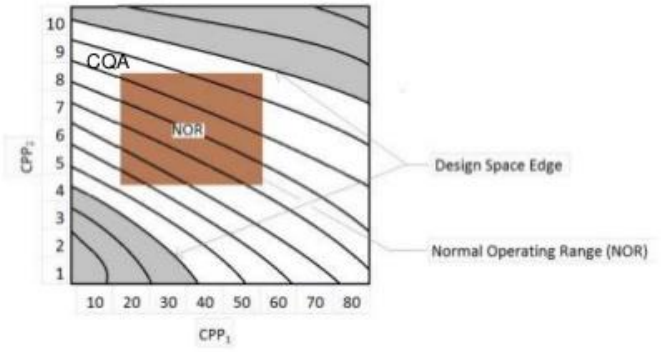
Designing the Product

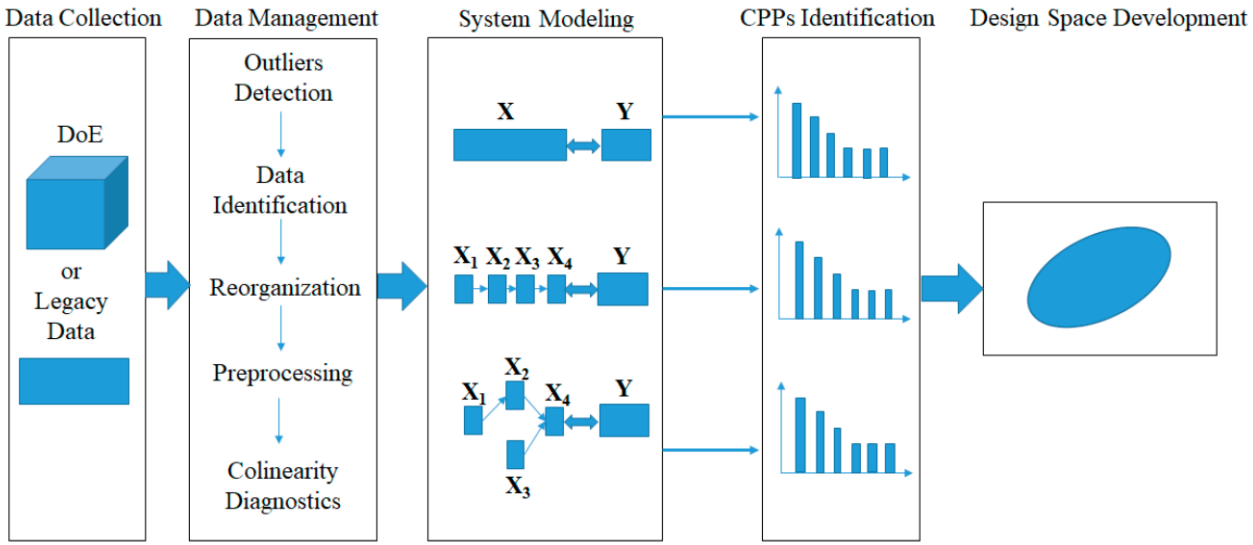
A Design Space



Design Space: "Multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality."

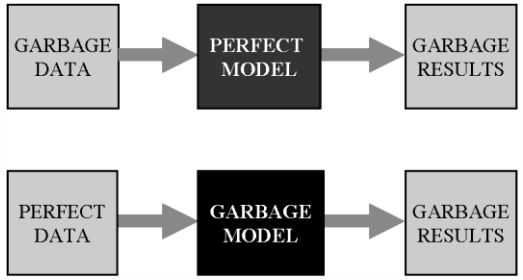
Knowledge Space: "A summary of all process knowledge obtained during product development."

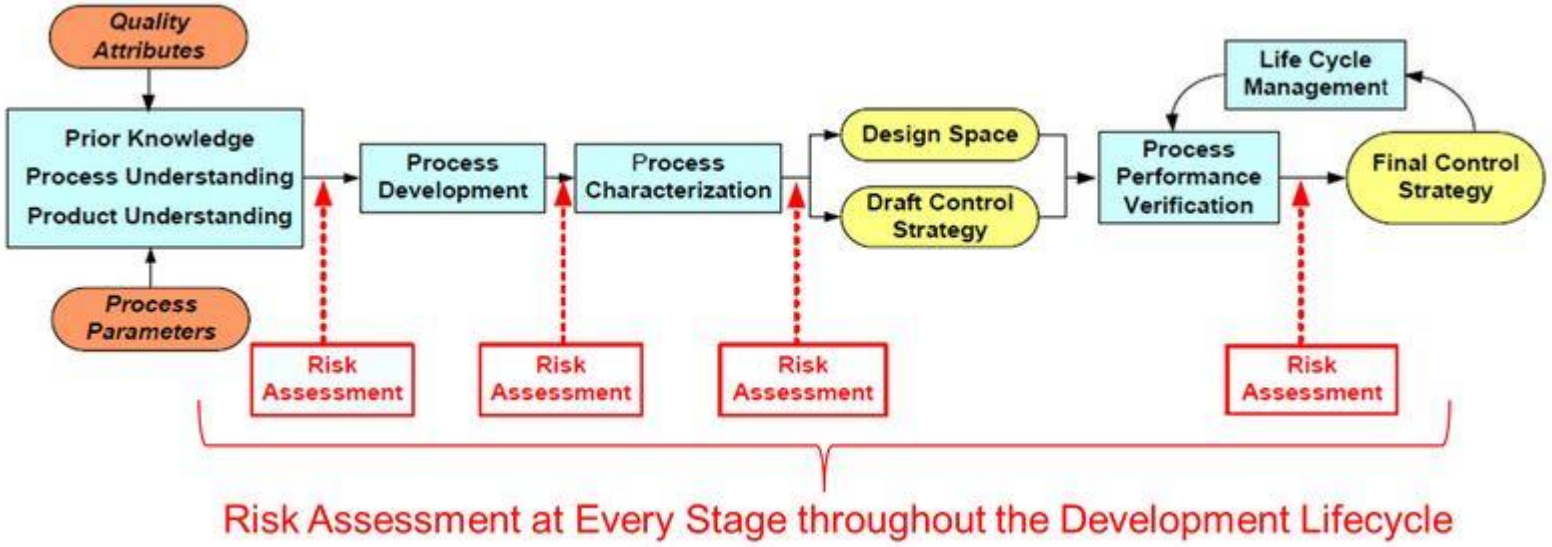




Risk management and QbD

MODEL CALCULATIONS
"Garbage In-garbage Out" Paradigm





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QbD CASE STUDIES : QTPP

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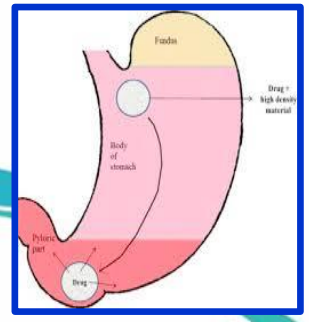
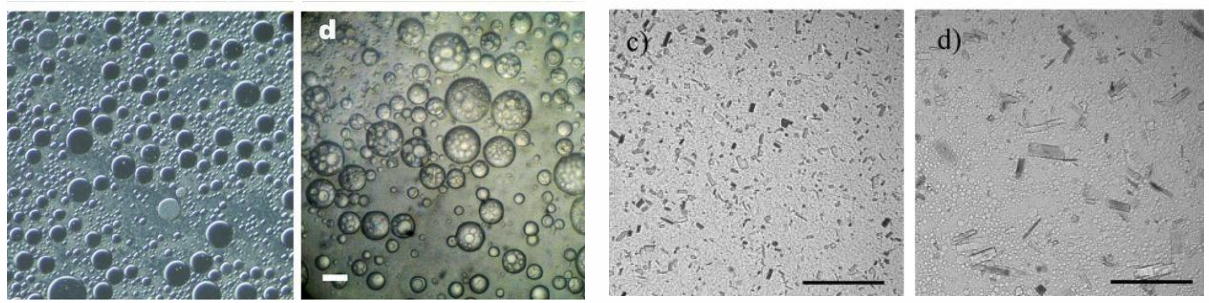
DOSAGE FORM	CASE STUDY
 IR/DR Tablet or Capsules	In-vitro suspension stability study to support RLD PI dosage and administration section. in vitro NG tube and/or G tube studies to support RLD PI dosage and administration section. Size and Shape comparison of Tablet/Capsules/tablet within Capsules/beads size etc.
 IR/ER Tablets	Quadrisect split tablets study data
 ER Tablets	Test product's slow dissolution in acidic media and observed difference in the lag time as compared to BE may lead to a conclusion that product is not therapeutic equivalent (Reformulation and repeat BE)
 ER Tablet (Gastroretentive)	Comparative swelling data between test and RLD to ensure gastric retention, total floating time and floating lag time (Protocol based studies; Reformulation)
Nasal Sprays / Inhalers	Drug product PSD in nasal spray and inhalers.

QbD CASE STUDIES : QTPP

	DOSAGE FORM	CASE STUDY
	ODT Tablets	Shipment study (Also for drug products having deep score line) Palatability study or taste masking study (If API is bitter in taste) (Reformulation and or additional studies)
	Topical Ointment	Thermal cycling and freeze-thaw stability study (Compliance to CQAs is a challenge)
	Complex Injection/TDS/ Topicals	Comparative analysis of safety and performance attributes of the Test and RLD products using multiple lots of different ages and also Threshold analysis report (Labeling, performance/Task analysis and physical comparison of device component parts) (Time, cost, resources and uncertainty of availability of RLD lots of different Ages)

QbD CASE STUDIES : CQA

DOSAGE FORM	CASE STUDY
IR Tablet	DT test in the FP specification (Acid Stage): HPMC phthalate was used in the film coating part of the tablet to prevent API degradation in the acidic environment as 'Polymer' in-line with RLD PI.
Topical Cream (O/Water emulsion)	Control of Globule Size and API PSD (if remains insoluble in the final product/tends to recrystallize) in the FP specification and proposing specific limit comparable to RLD data.
Topical Spray	Control of Penetration enhancer (Assay) in the FP Specification
Almost all dosage forms	Evaluation/Control of undesired polymorphic forms in the FP (one time study / routine control)



QbD CASE STUDIES : CMA

DOSAGE FORM	CASE STUDY
IR Capsules	Supplier change of corn start to be notified as a supplement. Provide optimization trials using low and higher level of corn starch with different LOD values.
ER Tablet (Matrix)	Magnesium stearate surface area test in API specification. RM CQA and Input material control: Uniform distribution of three different grades of HPMC 2910 in the final blend to avoid dissolution variability. Tabular comparison of physical properties such as particle size distribution and bulk density of the intra-granules (not the final blend) and the three grades of extragranular hypromellose.
Soft Gel Capsule	API PSD and % crystallinity content are critical to the DP Dissolution and there by Bioequivalence (Optimization studies with higher and lower API PSD and %crystallinity and Pilot Bio)

QbD CASE STUDIES : CMA

DOSAGE FORM	CASE STUDY
Trasdermal Systems	Adhesive as a raw material's CMA like Rheological property, Mole weight, polydispersity, residual monomers/dimers/solvents/heavy metals/catalyst etc. to be addressed and assessed during product development (Impact on Peel, Tack, Shear, Release force, Cold flow to be studied).

QbD CASE STUDIES : CPP

DOSAGE FORM	CASE STUDY
IR Tablet	**Commercial BMR revision for better % Yield:** Addition of agitator in the bin at Compression stage base on low yield observed in the EB batch [Required generation of Scale up batch data and CPP optimization (i.e., Agitation speed)]. **Environmental Condition:** 60% RH leads to smear formation on the tip of punch surface due to use of approx. 12% Sodium Citrate dehydrate (hygroscopic material). **Evaluation of leachable due to use of strong organic Solvents in the DP mfg process:** Use of methylene chloride as the granulating fluid for the wet granulation process and transferring it through tubing and vessel, filter bags, and gaskets in RMG and FBE.
ER Tablet	Functional **coating process parameters optimization** and range determination based on **DoE** (pan speed, inlet air temperature, atomization air pressure, peristaltic pump speed, and spray rate during pan coating; inlet air temperature, bed temperature, and air velocity during drying).

QbD CASE STUDIES : CONTROL STRATEGY

DOSAGE FORM	CASE STUDY
IR/DR/ER Tablets or Capsules	**Tightening of CQA limits supported by the development batches data, EB data, scale-up data** - Set Dissolution specification limit based on BE batch profile data at the time of BE study - Tightened the impurity limits beyond ICH / USP monograph as supported by EB and development batches data - Water content limit Vs. Actual Stability data trend - Add control of Leachable observed above AET (Analytical Evaluation Threshold) - Shelf life specification Assay should be within 5% of the BE batch **Discrimination power of the Dissolution Method** for your proposed test formulation although it is OGD method or USP monograph method **Control of Maillard Reaction Products, Geotoxic sulfonate esters impurities (alcohols +** sulfonate/Mesylate Compound/Tosylate Compound/methane sulphonic acid/p-toluene sulfonic acid/Methyl sulfonyl chloride)
Nasal Spray	**Proposed limit of DSD (Droplet Size Distribution) and Plume geometry differences** between Test and RLD product may lead to different therapeutic outcomes.

QbD CASE STUDIES

An Extended–Release (ER) Capsule

➢**API: 100 mg highly soluble, excellent chemical stability, no polymorphism**

➢**Manufacturing Process: Seal-coated sugar sphere core**
API coated pellets
ER polymer coated pellets
Encapsulation and packing

➢**Dissolution is a high risk CQA**

One-factor-at-a-time (OFAT) approach

- Polymer- quantity
- Polymer- viscosity
- ER layer coating weight gain

➢Applicant's conclusion: No impact on dissolution; hence, these factors are not critical

➢Agency's comments: Any interaction? How's the range justified? Coating process variability?

Don't use insufficiently powered studies to force a favorable conclusion of non-criticality. The narrow range of 'non-critical process parameter' is still potentially critical.

QbD CASE STUDIES

Oral IR tablet: 2.5 mg and 5 mg Drug substance:

BCS high solubility, non-hygroscopic, only one crystalline form known, excellent chemical stability

- **API loading: 2.4%**
- **Diluents: microcrystalline cellulose (~40%) and lactose monohydrate (~50%) Other excipients: disintegrant, wetting agent, and lubricant**
- **Manufacturing Process: blending, screening, lubrication, roller compaction, milling, blending and lubrication, compression, and film-coating**

- **Content Uniformity is a high risk CQA**

Process understanding and control strategy

In-line NIR method to determine BU and blending endpoint

- **At-line NIR method for tablet Assay and CU (Large N)**
- **Other traditional in-process controls: ribbon density, ribbon thickness, core tablet weight & hardness**

QbD CASE STUDIES : PACKAGING COMPONENTS AND PROCESS

DOSAGE FORM	CASE STUDY
IR Tablet	RLD: 2 Tablets in CRC HDPER Bottle Proposed Test product: 2 Tablets in Non CRC Blister/Carton Finally packed 2 Tablets non CRC Blister in the CRC Bottle
DR Capsules	Capsule Brittleness due to inclusion of the desiccant in the HDPE bottle
Topical, Opthalmic, PFS Injections, Transdermal etc.	Selection of the device components for the Topical Dosage Forms with drug delivery device: Evaluation of the Threshold Analysis and Comparative Human Factory Study (If required)

QbD in Packaging Development

QbD in Packaging Development

Applying Quality by Design to packaging development

QTPP

- Define quality target profile for PPM and dosing devices based on route of administration for safety and efficacy of drug product
- Focus on chemical and functional aspects
- List out quality characteristics required considering
  - Reliable and accurate
  - Stable and dimensionally consistent
  - Mechanically robust
  - Protection of formulation
  - Patient friendly (variable and rugged use)

CQA

- Define physical, chemical and functional properties within acceptable range each in relation to packing operations, machinability and drug product characteristics
- Share requirements with PPM vendors, consult and make agreement to specifications
- Study impact of PM attributes, packaging process parameters on CQAs of the drug product

QbD in Packaging Development

Applying Quality by Design to packaging development

Risk Assess-ment

- Conduct risk assessment by linking variability in chemical, physical and functional properties of each packaging component , packaging process parameters and impact on product quality and performance
- Consider handling and storage at plant, transportation and storage at warehouses till retailers
- Evaluate qualitative and quantitative profiles of plastic and elastomeric packaging components from vendors and assess effect on product quality
- Develop risk mitigation strategies

Design Space

- Define physical, chemical and functional properties within acceptable range each in relation to packing parameters, machinability and drug product characteristics
- List and perform design of experiments (DoE) on functional aspects of packaging component
- Change in vendor site, and vendor to be critically assessed
- Change in materials of construction by vendor to be studies specific to formulation

QbD in Packaging Development

Applying Quality by Design to packaging development

Control Strategy

- Define set of controls of that ensure package performance
  - Attributes of packaging components
  - Packaging process parameters
  - Challenge tests and in-process controls on packaging lines
- Establish control strategy with combined efforts of packaging development, engineering, production and in-process quality assurance
- Make agreement with vendors on specification

Continual Improve-ment

- Develop program of interaction with logistics, marketing personnel, physicians and nurses, users for the feedback on CCS
- Review of inputs and incorporating changes within design space
- Proactive approach on possible effects and preventive measures
- Trend analysis of packaging components and packaging

Quality by Design by Facility upgradation

Sterility Assurance

- Installation of isolator for aseptic operations in new facilities
- Reduction in number of open door interventions during aseptic filling
- Use of advanced aseptic processing technologies e.g. Rubber stopper loading for aseptic filling

Real time monitoring

- Real time monitoring of non-viable particle count in grade A and B area
- Real time monitoring of differential pressure in clean room along with RABS and dynamic passbox
- Real time monitoring of air velocity measurement of the filling and sealing RABS

Process improvement

- To enhance cleaning efficiency and reduce cross contamination, spray ball system installation for duct cleaning of FBD

Digitization

❑ BENEFITS

- ✓ Paperless Documentation
- ✓ Automated document routing (Review/ Approve)
- ✓ Eliminate time consuming manual process
- ✓ Automated enforcement and Audit trail
- ✓ On time retrieval
- ✓ No storage / Space required
- ✓ Integrate with other systems like ERP, LIMS and QMS

Add Master data → Create Project → Build Project Document → Assign workflow for sign → Review, Approve / Reject

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PAT Utilization - Use of NIR Technique (Real Time Release Testing)

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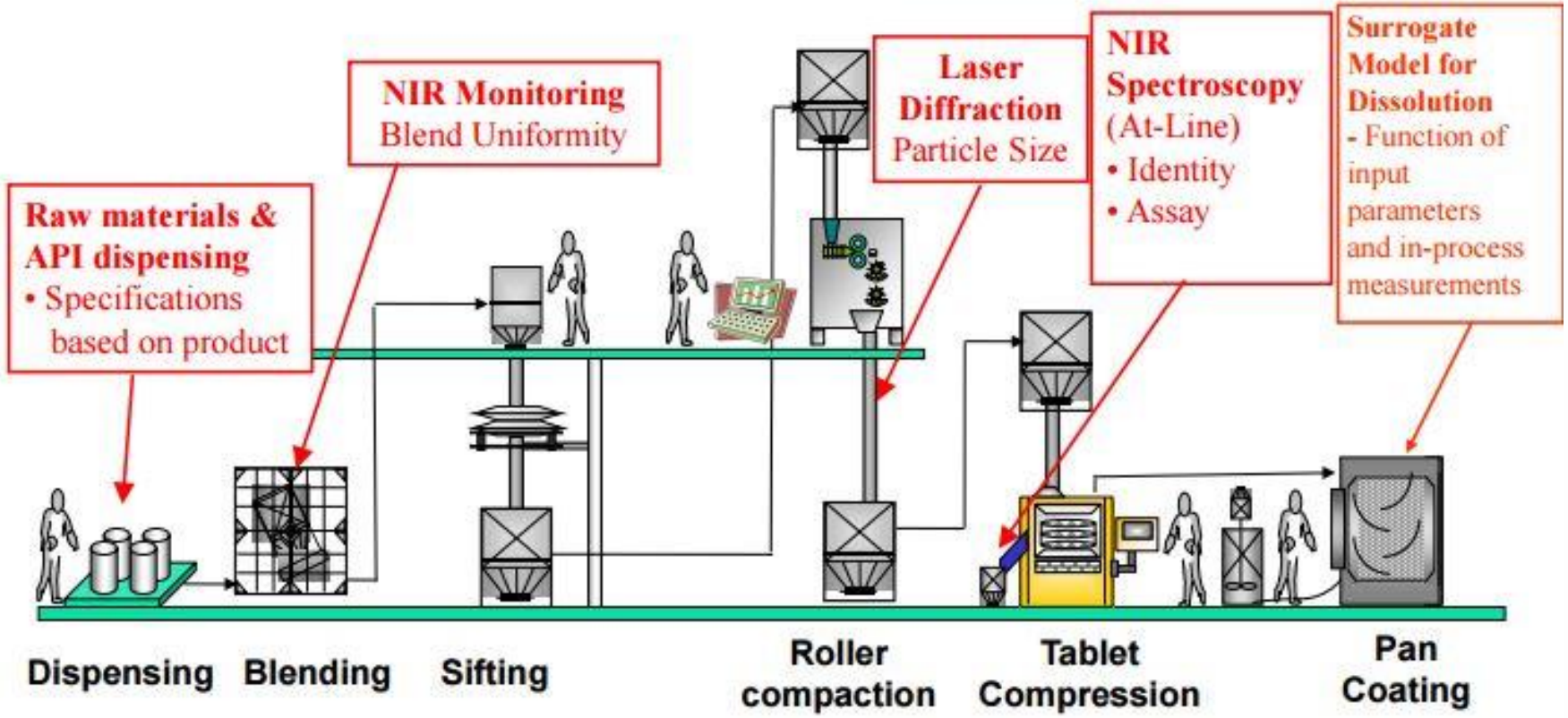
Aspects	Traditional approach	Enhanced QbD approach
Pharmaceutical Development	Empirical, Random, Focus on optimization	Systematic, Multivariate experiments, Focus on control strategy and robustness
Manufacturing Process	Fixed	Adjustable within design space, managed by company's quality systems
Process Control	Some in-process testing	PAT utilized, Process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy , real-time release possible

In process core tablet stratified CU (by HPLC)

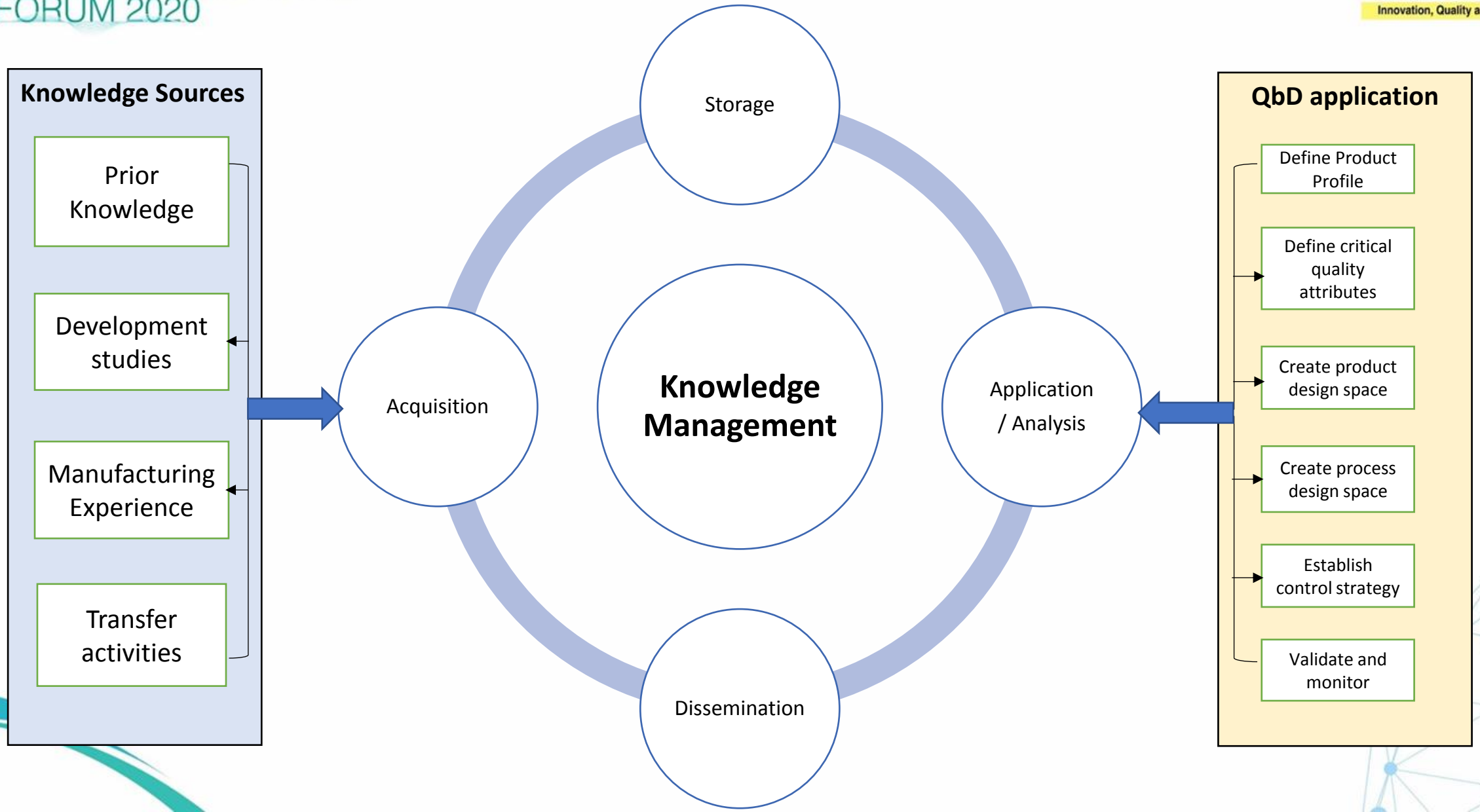
Real time release using NIR validated and equivalent chemometric model.

Advantages: Saving of Time, Money, reduces human imparted variability / analytical errors.

Example Comprehensive RTRT Approach



QbD: KNOWLEDGE MANAGEMENT



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Agency's new upcoming initiative for Robust Product - KASA

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- **KASA Program lead by OPQ Director Dr. Michael Kopcha**
- **A.k.a NextGen ANDA Assessment Tool / Knowledge**

What is KASA?

Modernized Tool (Computer aided analysis) for Quality Assessment of the ANDA based on the Risk Identification, Risk Mitigation and control strategy performed by Structured IT framework.

Why KASA?

X Avoid Unstructured text based written narrative

√ To reduce the Assessor's inconsistency

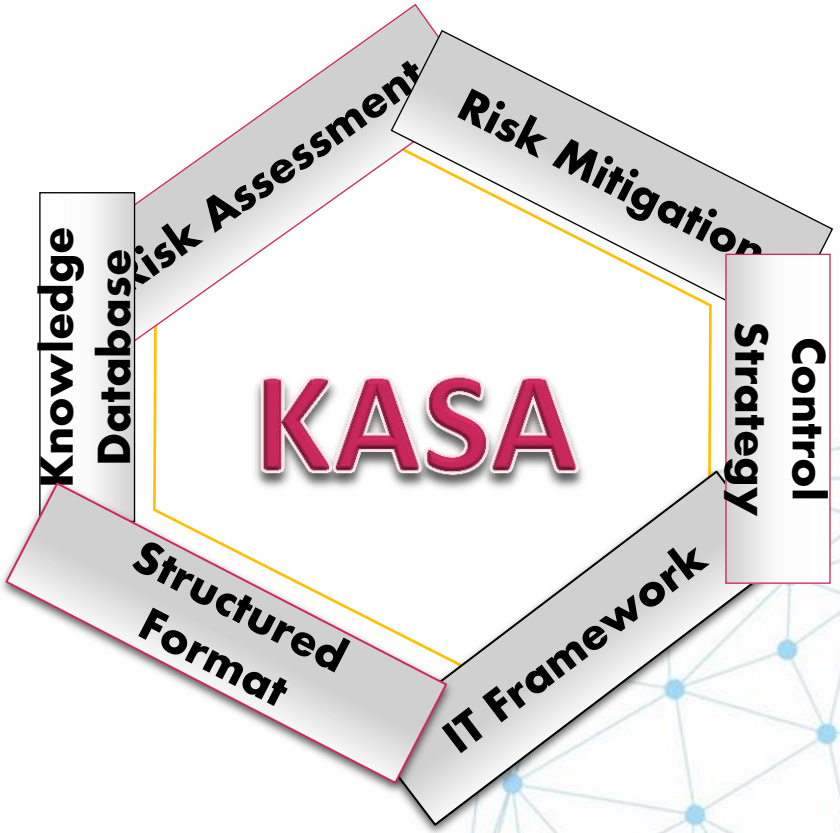
√ To compare the Approved and under review application's relative Quality and Risk

√ To promote issue-based quality assessment

√ To reduce the drug shortage and quality failures

√ To establish the acceptance criteria based on desired clinical performance instead of process capabilities or manufacturing process control.

√ To eliminate administrative tasks for the assessor and improve the assessment efficiency by allowing assessors to focus on high risk areas.



KASA (Knowledge-aided Assessment and Structured Application)

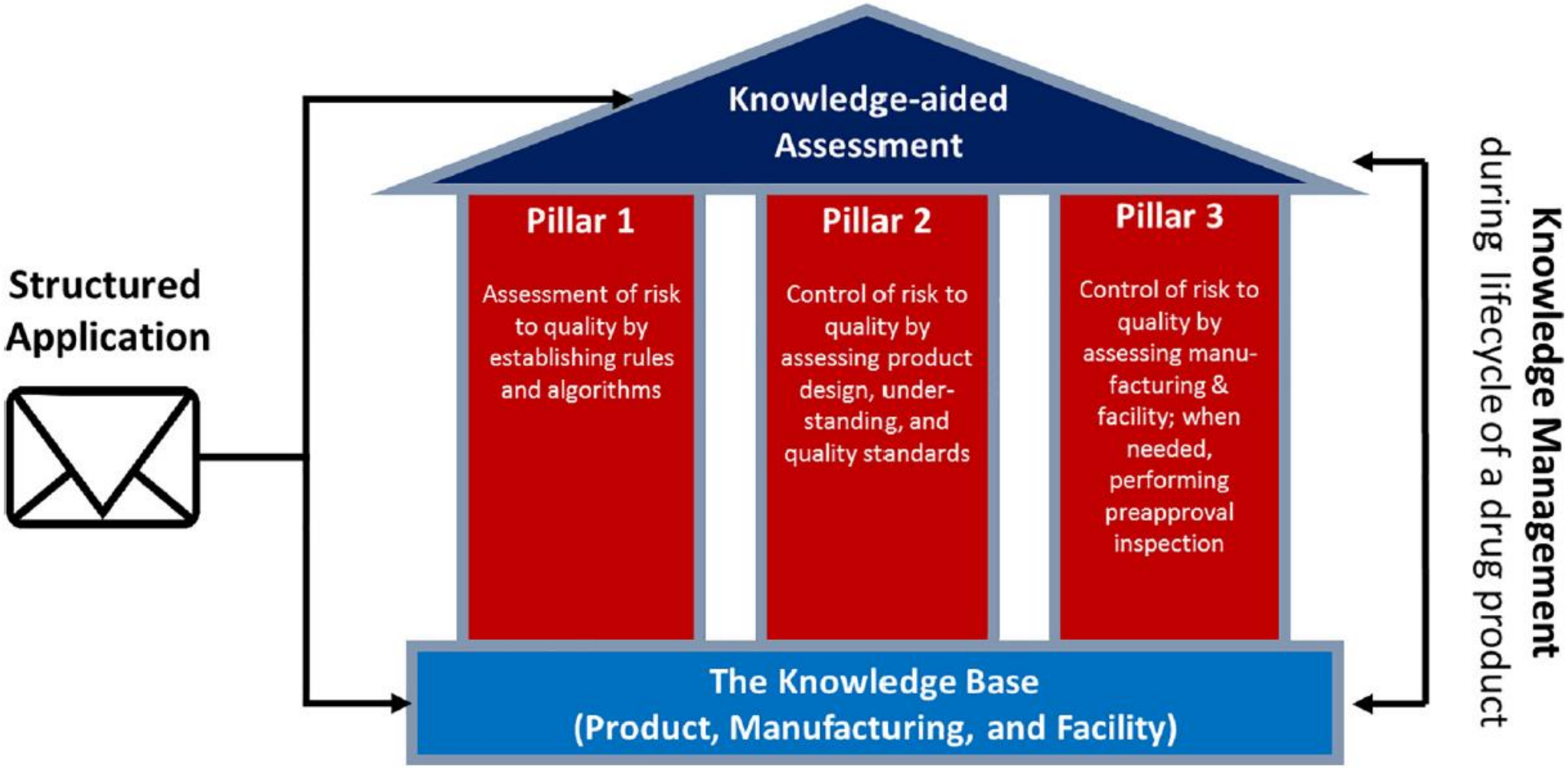


Fig. 1. Knowledge-aided Assessment & Structured Application (KASA) system.

OUTCOME OF QbD

Quality cannot be tested into products. Quality should be built in by DESIGN.

- Systematic approach to development
- Begins with predefined objective
- Use Quality Risk Management Proactively
- Better process knowledge
- Fewer batch failures, scale up issues and stability recalls
- Fewer review cycles, Faster review approval
- Pharmaceutical Industry Viability and Culture Change

Ultimately benefits patients

CULTURE EATS STRATEGY INTO BREAKFAST