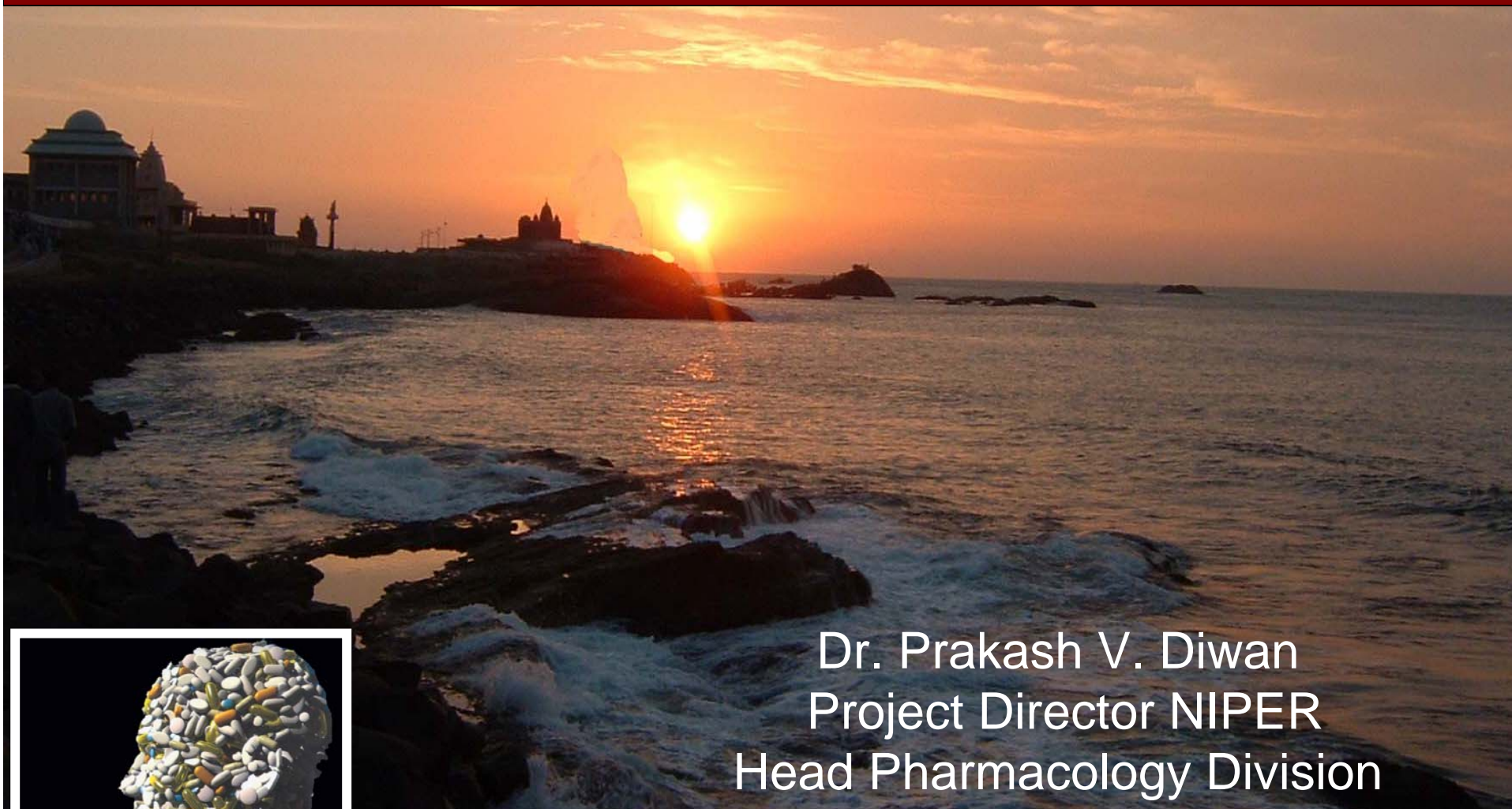


# Qualification of Impurities and Toxicity Testing.



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# “ One size fits all approach” not valid

- ICH guidelines only apply to standard impurities which do not exhibit unusually high toxicity
- For highly toxic impurities
  - identification is required even at very low level of threshold
  - However it is a paradox
- How does one know the toxicity potential if structure is unknown?
- A different approach is required to cut this **Gordian knot**

## \* What Does “Reasonably Practicable” Mean

\* Are you convinced that you can defend your position [not to do it] **as being reasonable to the regulatory agency?**”

## *Role of National and International regulatory authorities in genotoxicity testing*

\* The current differences in protocol design and practices between different regulatory authorities hinder the drug discovery process and delay.

- Guidelines only mention about test but not details.....
- **SOPs are must for better application**

# Genotoxic impurities:-

## Why do we need guidance?

- Existing Q3 guidelines not clear on how to handle genotoxic impurities
- Standard threshold not applicable to Genotoxic impurities
- ICH Q3 A (R) – No need to identify structure below (0.1%) 1000 ppm. (If dose is >29/day)
- Genotoxicity assays **too insensitive** to detect effects on impurity at 0.1%.
  - Very few compounds will be detected for genotoxicity
- Unidentified impurities below 0.1%

**How would its potential toxicity be known or suspected ????**

# Genotoxicity testing procedures used in regulatory toxicity

## Genotoxicity studies – Pharmaceutical products

- ❖ Not applicable for active components of biotechnology product
- ❖ Alternative relevant models required to be developed
- ❖ These products should be tested cautiously

# Genotoxicity studies

- Time consuming
- Resource intensive processes
- Need a large number of animals for experimentation.
- The guidelines are inadequate to draw a definite conclusion ,

Choice of specific test system and test protocols

– No details available

## Each specified identification Of impurity;

Any unspecified impurity with an acceptance criterion of not more than ( $\leq$ ) the identification threshold

- Total impurities.
- ... degradation product ...

Maximum Daily Dose	Reporting Threshold	Identification Threshold	Qualification Threshold
$\leq 2$ g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
$> 2$ g/day	0.03%	0.05%	0.05%

How do we justify ??

## Importance of Genotoxicity:-

Most commonly, genotoxic impurities are tested and considered qualified based on genotoxicity assays.

(Battery of tests) Highly potent mutagens can be detected in genotoxicity assays

- Mutagenic potency to methyl methane sulfonate would only be detected when present in the drug substance at levels of 0.33% or higher.
- Slightly higher levels could be acceptable!!!

**Who has to decide?**

## Ame's tests

- Suitable for identifying the genotoxic potential of impurity
- For structural alert it may not be the most appropriate choice
- **Criteria of acceptability –ppm require justification**
- Threshold Toxicological concerned [TTC]-Approach-altering structure in relation to genotoxic carcinogenic, such as aflatoxin-like, azoxy, and Nnitroso-compounds.

# Genotoxicity Biologics Vs. Small Molecules

- Genotoxicity assays typically not performed
- Not expected that proteins would interact with DNA
- Presence of organic impurities or organic linkers might warrant genotoxicity testing

## Phototoxicity testing Replacement:

- ✓ *In vitro* 3T3 NRU PT to replace animal phototoxicity test
- ✓ Formal validation process mainly driven by non-pharma sectors: OECD TG 432
- ✓ EU Photosafety Guideline for Pharmaceuticals (2002) clearly recommends use of *in vitro* model
- ✓ No ICH regulations (yet)

# Regulatory acceptance of 3R methods for pharmaceutical testing

- No clearly defined process of acceptance / implementation of 3R methods
- Multiple and flexible approaches possible to adapt to specific purposes and requirements
- Implementation via ICH process most promising

## Limitations in genetic toxicity tests in different models.

Processes/ Properties	Microbial	Mammalian ( <i>in vitro</i> )	Mammalian ( <i>In vivo</i> )
<b>1. Sensitivity</b>	<b>1. Strain specific responses</b>	<b>1. Cell in specific responses</b>	<b>1. Tissue specific responses</b>
<b>2. Cytotoxicity</b>	<b>2. Extreme cytotoxicity can interfere in test result</b>	<b>2. Extreme Cytotoxicity can interfere test result</b>	<b>2. Uptake, metabolism and distribution of the test compound can alter the target organ toxicity</b>
<b>3. Metabolism</b>	<b>3. Different sources of S9 and conditions of incubation can lead to qualitative and quantitative differences</b>	<b>3. Different sources of S9 and conditions of incubation can lead to qualitative and quantitative differences</b>	<b>3. Varies among strains/species/sexes/tissues of the animal</b>
<b>4. DNA repair/cell proliferation</b>	<b>4. Lack of DNA repair system exaggerated genotoxicity</b>	<b>4. Selective cell proliferation by some chemicals increases DNA lesion by forming DNA adducts</b>	<b>4. Some selective chemicals disturb DNA replication and delay in cell cycle; hence interfere in the end point evaluation</b>

## Limitations in genetic toxicity tests in different models.

<b>5.Physiological differences</b>	<b>5. Prokaryotes cannot mimic the network and delicate intracellular biochemical pathways</b>	<b>5. Limited enzymatic capabilities and viability</b>	<b>5. In some cases, drug levels cannot reach the target organ because of distribution</b>
<b>6.Cytogenetic end points</b>	<b>6. Only gene mutation can be detected in a single cell system</b>	<b>6. Both gene as well as chromosomal changes in a single cell line</b>	<b>6. Both gene as well as chromosomal evaluation in different tissues</b>
<b>7.Dose/Conc. Limitations</b>	<b>7. Test compounds solubility in culture medium is a limitation factor</b>	<b>7. Chemical solubility in culture medium is a limitation factor.</b>	<b>7.Varies among species/sexes/tissues of the animal</b>

**IN SUCH SITUATION CAN WE  
DEPEND ON THIS TEST ???**

# Drawbacks of current genotoxicity tests

- Mechanism of action by which impurity caused genotoxicity is not known
- No validated test system for detecting induced genome mutation (aneuploidy) in germ cells
- Both rats and mice are valid for *in vivo* detection of genotoxins
- The compounds, which produce negative results in the standard genotoxic battery of tests but having structural alerts, need to be subjected to further additional tests with modified protocols.

- ✓ A sound, scientific appraisal of chemical reactions involved in the synthesis and likely degradation pathways.
- ✓ Alerting structures should include the API itself as well as starting materials, reagents, and intermediates in the synthetic process and potential degradation products.
- ✓ SAR databases like *DEREK* could be used to identify potentially hazardous compounds among the listed impurities.
- ✓ However, it was considered not sufficient and inappropriate to rely solely on a screening by such databases
- ✓ Because such screens for alerting structures and properties of chemical substances often result in a high number of potential

**“Decision Tree for Safety Studies” should be consulted.**

The artificial **sweetener saccharin** may cause tumors in experimental animals after large dose (10 g causes a 50% change of tumors) versus aflatoxin B (1  $\mu\text{g}$  causes of 50% chance of tumors)

**Forgotten art?!**

- certainly for the analysis of sulphonate esters
  - derivatisation with NaSCN to give alkyl thiocyanate
  - derivatisation using 2,3,4,5,6 Pentafluorothiophenol

**Not assured by Science (up till now)**

- TTC based on analysis of 730 carcinogens
- Highly sensitive analytical methods are needed to quantify
- Essential tool to monitor process optimization and purification steps.
- Any level below this limit (eg, 1.5  $\mu\text{g}/\text{day}$  TTC limit) does not represent a safety concern

# Scientific:

## Analytical Comparability: Key Questions

- Are analytical methods robust enough to compare critical parameters of safety & efficacy across multiple manufacturers?
- Can physico-chemical data – even when correlated to SAR – still allow for expedited development based on demonstrated comparability across manufacturers?
- Can SAR help address observed differences in microheterogeneity and impurities in lieu of full comparative (safety & efficacy) clinical trials?
- All things being equal, can SAR reduce or eliminate the need for preclinical testing and some clinical testing?
- Can SAR be used to facilitate comparisons even with large manufacturing differences?

## Key SAR considerations to include in FDA Guidance on Follow-on Biologics:

- ✓ Perform side-by-side physico-chemical profile of innovator and comparator product:
- ✓ Evaluate bioassay activity of innovator and comparator products
- ✓ Summarize SAR links to manufacturing, stability, PK/PD, or clinical endpoints as much as possible.
- ✓ Identify critical process steps with SAR impact and controls.

- o QSAR programs may be used for prediction of toxicity, ... the results are not generally considered conclusive for qualification purposes
- o Development of more strict criteria currently not planned (not desirable?)
- o Guideline also does not address the regulation of products used during the clinical research stages of development

# Limitations of SAR

- ❑ Complexity of structure:
- ❑ Impurities:
- ❑ Pleiotropic mechanisms of action:
- ❑ Method limitations:
- ❑ Mechanisms of action may not be well understood:

## ➤ Products not covered

- Biological/biotechnological products
- Peptides
- Oligonucleotides
- Radiopharmaceuticals
- Fermentation and semi-synthetic products
- Herbal products
- Crude products of animal or plant origin are not covered may still be used if a correction factor is applied or the degradation products
- These new degradation products should be identified and/or qualified.

- **Process Analytical Testing (PAT)**

Impact on genotoxicity testing? Based on PAT the material is released.

- **How do we justify this?**

No test is required for OTC products

Process

**How do we control?**

Excipients

Heavy metal contaminations

Eg. Starch – produced in India is highest and supplied to garment industry and same is given to pharmaceuticals, which is only 1% total production.

Does this firm comply with pharma regulations?

**May not be but still we use it!!!**

-

- Impurities in multiple crop batches for drugs
  - Paracetamol – snow white to pink. Last can be used in syrup
  - to mask the colour. But what about quality?
- **Is this batch tested for carcinogenicity**

**How do we control?**

## Difficult task ahead

- Portable water used for final washing – Throughout globe

### Is it safe ?

- Are there any reference standards available for the comparison of **new impurities?**

We have to satisfy with our working standards??

- How do we test unstable impurities?
- Impurities – Impossible to synthesize
- Limitation of detection levels with analytical tools – is a crucial point

# Conclusions & Need attention

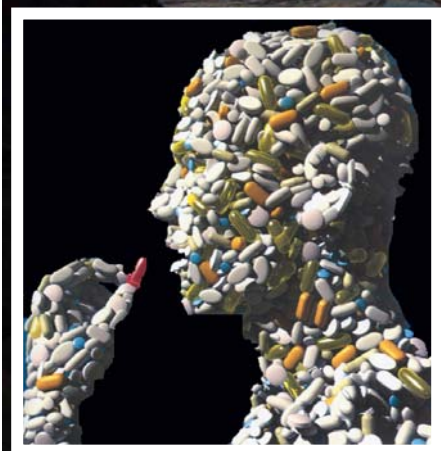
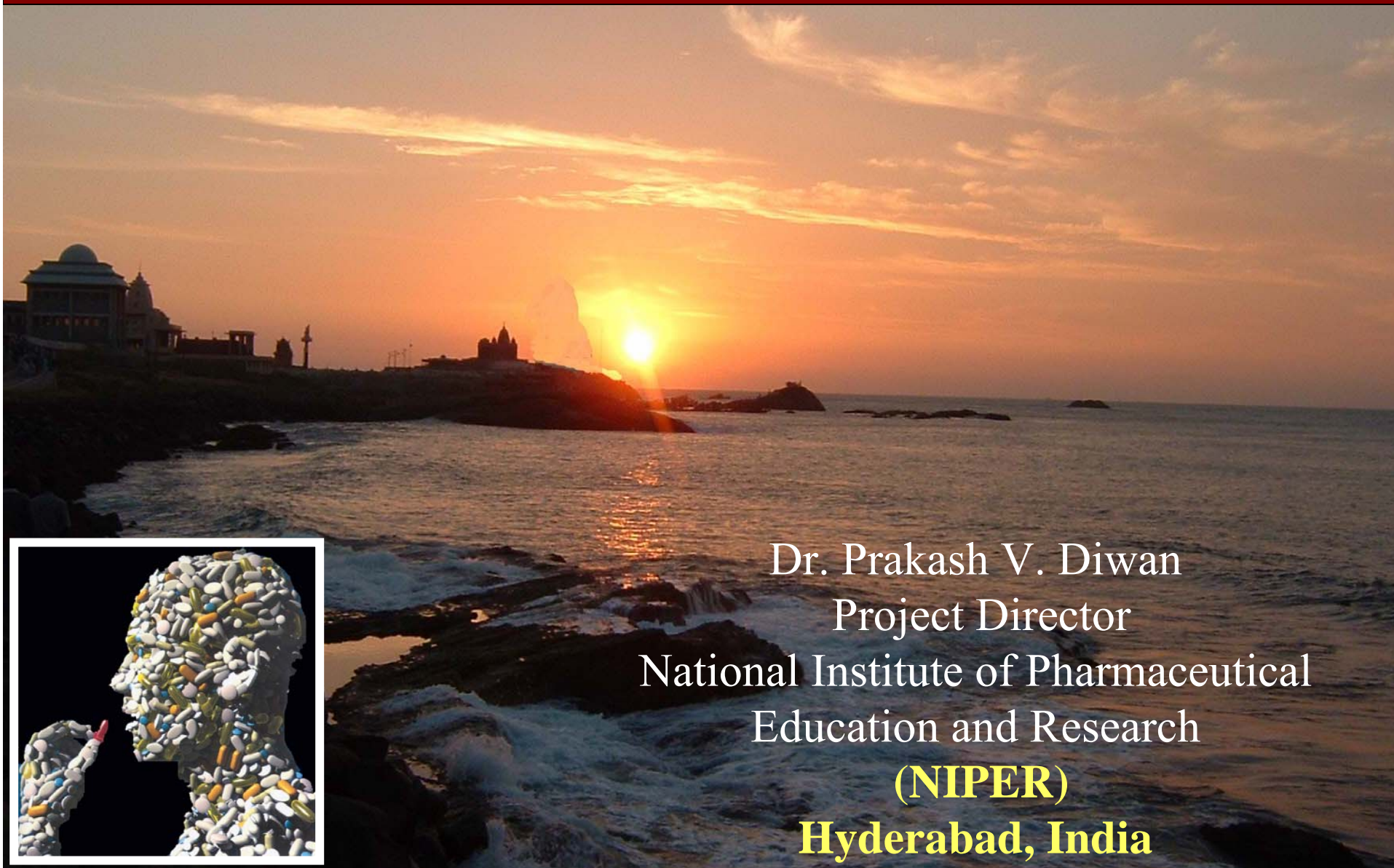
## Scientific/Compendial Areas:

- Create high quality monographs for biotech products
- Harmonize monographs across different compendial bodies with testing algorithms for differences
- Weave SAR insight into testing and general chapters on product classes
- Publish adverse event information associated with certain physico-chemical features
- Create decision trees for immunogenicity testing and incorporate into guidance documents (FDA, ICH, etc.)



**NIPER HYDERABAD**

# Biopharmaceutics and Toxicity Input into QBR Responses



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# “Desired State”

- Science
- Risk
- Predictability
- Consistency

- **Process Analytical Testing (PAT)**

Based on PAT the material is released.

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- Paracetamol – snow white to pink. Last can be used in syrup to mask the colour. **But what about quality?**

-

# Requirement of Right Assessment

- Regulatory Science Training Series

  - **Workshops**

    - Polymorphism, Controlled Release, Injectable Drug Products, Aerosols and Sprays, Impurities, Excipients, and Manufacturing

  - **Future training workshops**

    - Preformulation, Biopharmaceutics, Dissolution
    - Process Identification, Simulation, Monitoring, and Control

# Review Process - Needs Difference

- The level of scientific understanding ?
  - All products (simple and complex) use the same approach
  - All products are subject to the same post-approval supplements

# ANDAs Under QbR

- Quality
  - Eliminate unnecessary fact finding of information such as composition, specification, and manufacturing process, etc.

# ANDAs

- The 1999 Guidance for Industry  
“Organization of an ANDA”
  - Does not include Quality by Design principles
  - Does not provide for a QoS
  - Is no longer current for the OGD Question-based Review

# ANDAs Under QbR

- Explanation of Product Development is a must
  - Drug substance and formulation variables affect the performance of the drug product
  - The critical manufacturing steps,
  - determines operating parameters,
  - selects in-process tests to control the process,
  - scales up the manufacturing process

# Invivo and Invitro

- A difficult proposal
- Most of the time the result do not tally
- Invitro can only add to make conclusions
- Therefore more stress is needed on Invivo
- Pharmacokinetic parameters are studied in normal conditions but accounting the bioavailability for diseased conditions ?
- Are we justified in conducting studies for normal animals
- Method development for NCE needs expertise

# Toxicity studies

- A difficult task
- Regulation differ drastically
- Time consuming and justification for use of animals makes it difficult.
- A short term study does not justify the safety
- Does it corelate with humans ???

# Do we have any alternate???

- Can the study be done in diseased individual or animals to assess its activity
- Can we use transgenic animals to correlate the studies
- How do we assess the targeted and novel drug delivery systems
- The guidelines mention the regulatory requirement but not what procedure to be used
- Hence an SOP is ideal for procedure which promises harmonization of test
- Most of the time we have pure compounds for study but what do we account for excipients and other interactions
- How do we account for drugs crossing blood brain barrier

# Benefits

- Quality by design and performance-based specifications assure product quality
- Risk assessment facilitates continuous improvement and reduces CMC supplements
- Standardized review enhances the quality of CMC evaluation

# QbR Helps to Industry

- Industry
  - Accelerated approval of applications
  - Reduced supplements
- Public
  - Availability of low cost and high quality generic products

# Details required for a drug substance

- Description and Characterization
- Control of Drug Substance
  - Appearance and Identification
  - Assay
  - Impurities and Residual Solvents

# QBR: Drug Product

- **Description and Composition**

- What are the components and composition of the final product?  
What is the function of each excipient?
- Do any excipients exceed IIG limits in the context of maximum daily dose and route of administration?
- If product is an NTI drug or a non-simple dosage form
  - Are there significant differences between this formulation and the RLD that present potential concerns with respect to product performance?

- **Control of Excipients**

- What are the specifications for the inactive ingredients and
- are they appropriate per their intended function?

Simple Dosage Form: Either a solution or an IR solid oral dosage form

# QBR: Drug Product (Continued)

- **Reference Standard**
  - **Are there a qualification report and COA provided for the reference standard or is this material purchased from an appropriate source?**
- Drug Product Stability
  - Data
    - What stability data has been submitted? Has the sponsor provided stability data for the drug product packaged in the proposed container/closure?
  - Acceptance limits
    - Are all attributes that could change over time evaluated in the stability tests?
    - What are the acceptable limits on these attributes?
  - Shelf-life recommendation
    - What is the justification of shelf life?
    - Is the post-approval stability protocol acceptable?

# Complex Dosage Forms and NTI Drugs

- Drug Substance
  - Which properties or physical chemical characteristics of the drug substance affect drug product performance?
- **Excipients**
  - **Is there any evidence of incompatibility between the excipients and drug substance?**
- Formulation
  - **What is the formulation intended to do?**
  - **What mechanism does it use to accomplish this?**
  - **Were any other formulation alternatives investigated and how did these perform?**
  - **Were any formulation optimization or sensitivity studies carried out for variations in composition around the final formulation? Were these studies sufficient to establish a design space for formulation composition?**
  - **Is the formulation design consistent with the dosage form classification in the label?**
- Drug Product
  - What are the critical quality attributes that ensure the product will perform as labeled?

# Drug Substance Properties

- Current Practice
  - Significance often not recognized
  - Example of deficiency
    - The polymorphism for drug
    - Which properties of the drug substance affect drug product performance?

# Formulation Design

- Current Practice
  - Reasons for design decisions not fully explained
  - Example of deficiency
    - “Spray dried lactose is used as a diluent in the formulation. Potential drug-excipient interaction.” ?

# Manufacturing Process

- **Current Practice**
  - **Limited information submitted**

Risk Assessment Facilitates Continuous  
Improvement and Can Reduce  
Supplements

Report Justify the fast review

# Industry Expectations

- Predictable
- Consistent, science and risk-based assessment
- Accelerated approval of applications
- Reduced supplement



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A close-up photograph of a vibrant red rose against a black background. The petals are in sharp focus, showing their texture and the way they curve. The lighting highlights the edges of the petals, creating a sense of depth. In the lower right quadrant, the words "Thank you" are written in a yellow, cursive font with a subtle drop shadow.

*Thank you*