

Scientific and Regulatory challenges in Quality by Design (QbD) submissions

Krishnan R. Tirunellai, Ph. D.
Bureau of Pharmaceutical Sciences
TPD, Health Canada
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Information and opinions provided in this presentation are scientific in nature and not the official position of Health Canada.

Perception of Quality - a Paradigm Shift

- Health Canada's Progressive Licensing initiative to modernize the Food and Drugs Act incorporates drug's life cycle management.
- Drug Life-Cycle begins with the early stage of discovery followed by the development stages, regulatory review, market authorization, and post-market activities, until it is no longer on the market.
- Important elements throughout the drug life cycle are:
 - **Safety & Efficacy:** Therapeutic Effectiveness, and Pharmacovigilance.
 - **Quality:** Innovation, Improvement, and Post Approval Changes.

New Opportunities and Challenges

***“risk-based”
concepts and
principles of ICH***

Q8

***Pharmaceutical
Development***

Q9

***Risk
Management***

Q10

***Quality
Systems***

Ref: ICH

Future Vision Is Driven by ICH Q9

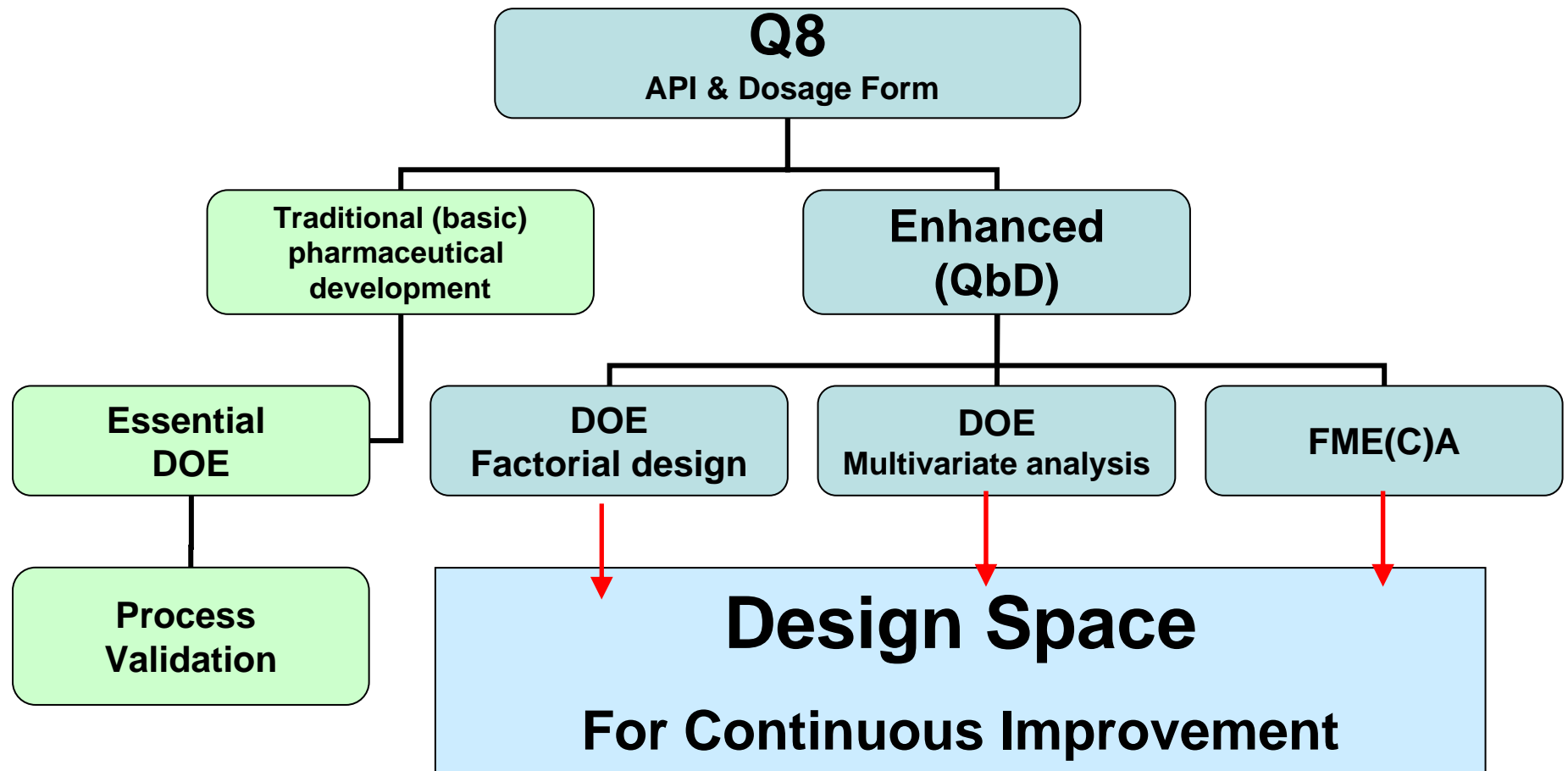
- **Manage risk to patient, based on science:**
 - **Product, process and facility**
 - **Robustness of Quality System**
 - **Relevant controls to assess & mitigate risk**
- **Level of oversight required commensurate with the level of risk to patient and the depth of product/process understanding for:**
 - **Marketing authorization applications**
 - **Post-approval change review**
 - **GMP inspections**

Quality Risk Management

- ***Quality:*** Degree to which a set of inherent properties of a product, system or process fulfills requirements.
- ***Risk:*** defined as the combination of the ***probability of occurrence*** of harm and the ***severity*** of that harm.
- ***Management:*** Systematic process for the **assessment, control, communication and review of risks** to the quality of the drug (medicinal) product across the **product lifecycle**.

Pharmaceutical Development Paths

Q8 is not yet finalized by ICH



Rest of the presentation will focus on dosage form

QbD- a Well Known Concept of the 50's

Ref: Out of Crisis (1986): W. Edwards Deming

- Depending on inspection is like treating a symptom while the disease is killing you. The need for inspection results from **excessive variability** in the process. The disease is the variability. Ceasing dependence on inspection means you must **understand your processes** so well that you can **predict the quality** of their output from upstream activities and measurements. To accomplish this you must have a thorough **understanding of the sources of variation** in your processes and then **work toward reducing the variation**. Ceasing dependence on inspection forces you to reduce variability.

Ref: <http://deming.eng.clemson.edu/pub/den/files/varman.txt>
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Pharmaceuticals and Quality Risk Management

- **In Canada, industries that have adopted structured risk management in the quality area are:**
 - Medical devices: ISO 14971
 - Food: HACCP (Hazard Analysis Critical Control Point).
- **Pharmaceuticals use quality risk management but its implementation is patchy, and there is ample scope for improvement.**

Where are TPD & Canadian Companies on Product Development?

- Many non-sterile products are approved based on information on smaller size lots (1/10th or 100, 000 tablets).
 - Information on commercial scale batches is not a requirement for approval.
 - Process validation test results on commercial lots are not required, only a protocol and commitment is necessary.
- Many industries conduct PD studies but do not share all important information with TPD.


Where are TPD & Canadian Companies on Product Development? (Cont'd)

- ✓ TPD has had the product development (PD) requirement for several years.
- ✓ QbD is an extension of PD and many companies have started stepping up their efforts because it makes good scientific and business sense.
- ✓ Process Parametric Release for terminally sterilised products:
 - ✓ efficiently managing risk with in-depth process understanding which is the QbD approach.
 - ✓ needs a lot of work by the company upfront to enjoy the benefits later.

Traditional PD *versus* QbD

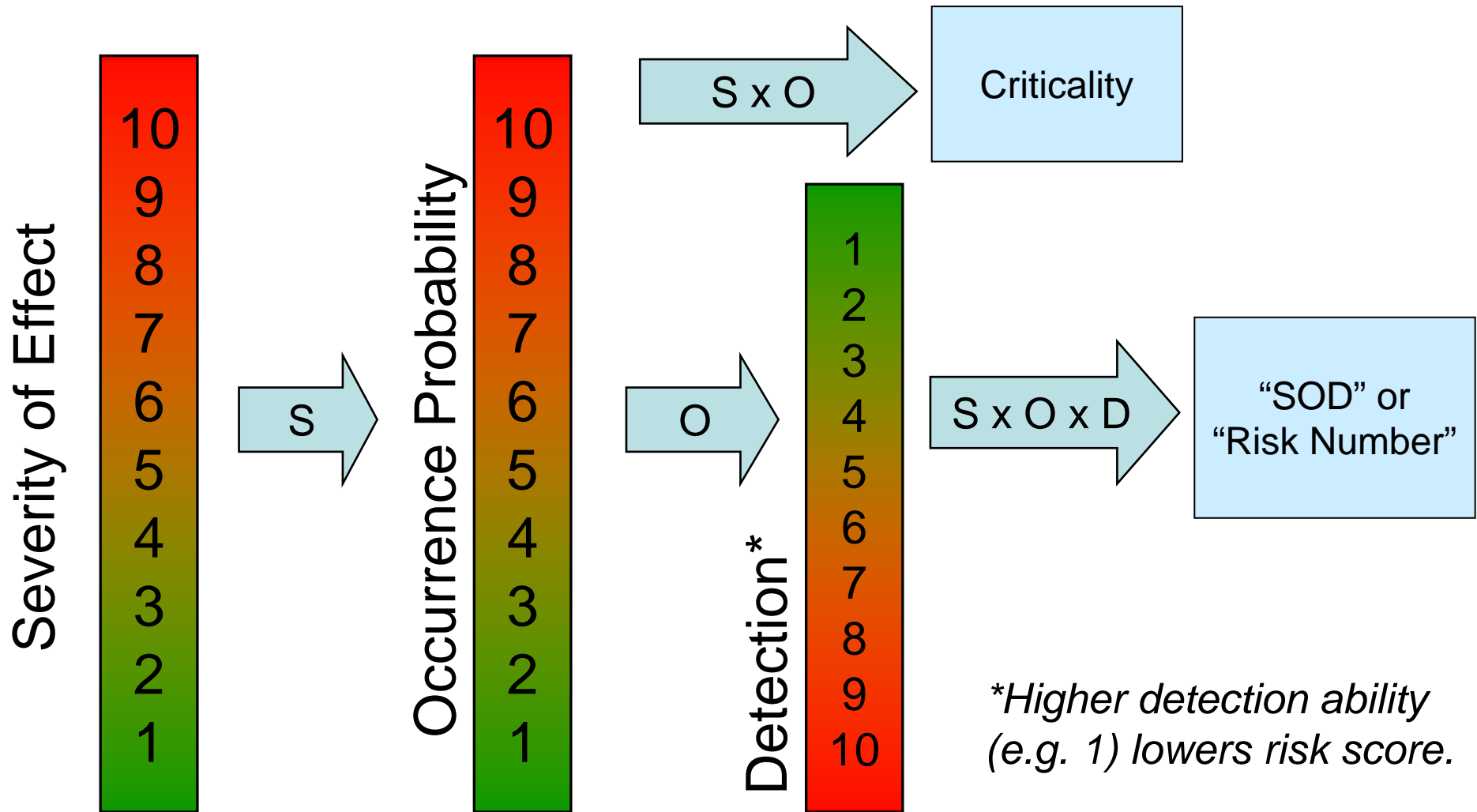
- **Traditional Product Development:**
 - Limited development and scale-up work.
 - Final confirmation by validation of 3 batches
 - 'Worst-case' scenarios supposed to be included.
 - Market recalls and underutilization of capacity indicate this approach has had limited success.
- **QbD:**
 - Complete understanding of process and monitoring of all critical steps. Corrective actions are taken to prevent product failure.
 - Acceptable quality of the product is ensured - no recalls
 - Innovation encouraged
 - Maximized utilization of capacity

Essential Elements of QbD

1. Complete **understanding** of product development and manufacturing processes.
2. Identification of critical factors (e.g., FMEA), and use of control tools (e.g., PAT) to monitor, and **control critical** factors to **reduce variability & avoid failure**.
3. Develop **design space** based on **DOE** (design of experiment).
4. **Operate within a design space** which could be independent of:
 - a) Batch size.
 - b) Equipment (size etc.).
 - c) Manufacturing site. E.g. of NC (notifiable change)
5. **Design space** created would determine the degree of regulatory **flexibility** that could be obtained.

Failure Mode Effects (Control) Analysis

FME(C)A

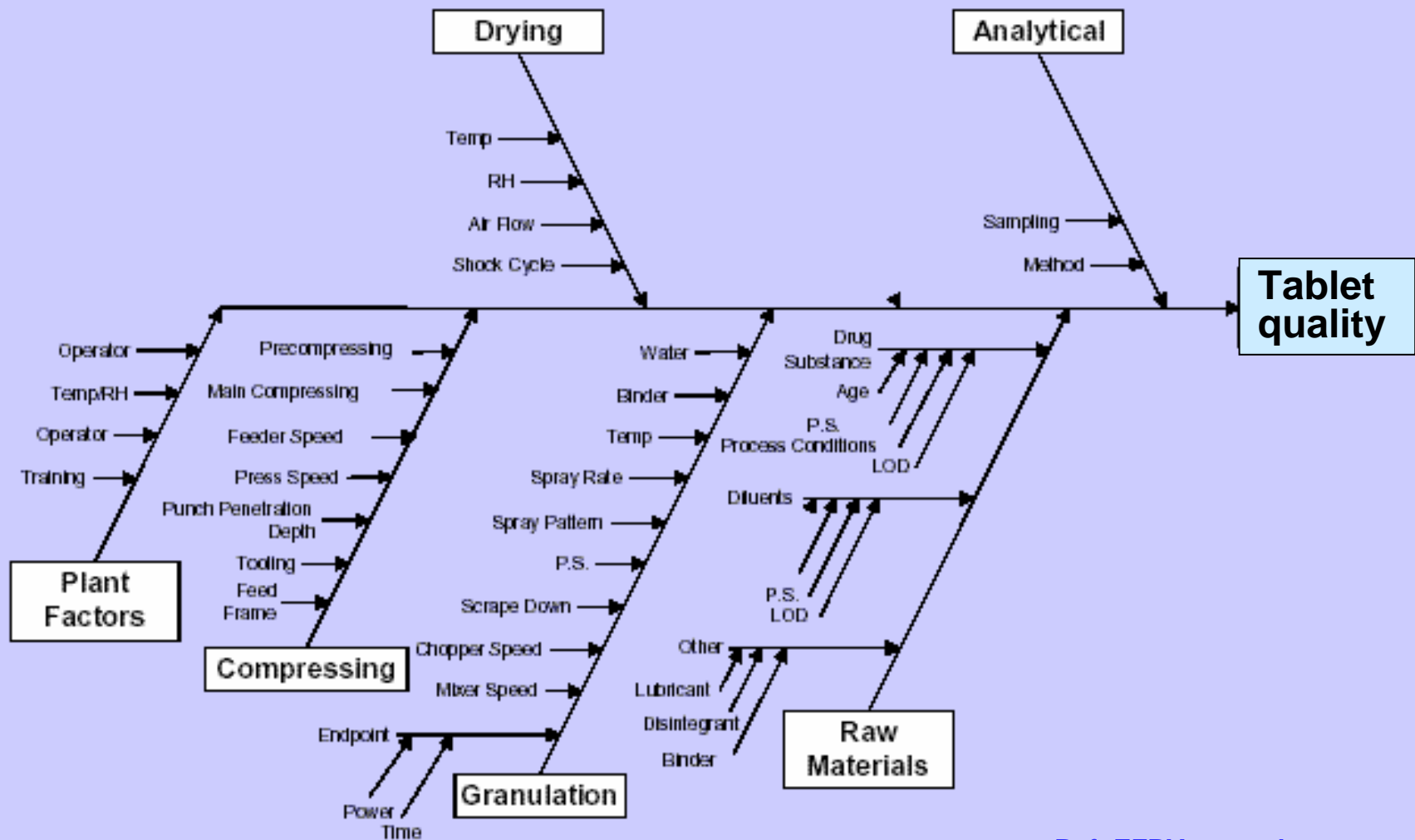


E.g., FME(C)A Chart

Traditional											
ID #	Process step	Equipment	Cause for failure	Potential effect	Effect on entire system	Severity	Occurance Probability	Criticality	Detection	SOD	Control
1	DS Milling	Jet Mill	Overloading	Large particle size	Dissolution failure	9	5	45	2	90	Particle size
2	Dry blending	High shear	Excipient quality	Homogeniety	Content U failure	8	3	24	5	120	Blend Homo
3	Wet massing	Hign Shear	Excipient quality	Over/under gran.	Tableting problem	8	8	64	8	512	Time
4	Lubrication	V Blender	Load	Flow/Dissolution	Content U, dissolution	9	4	36	8	288	Time
5	Compression	Tablet Press	Speed	Weight, hardness	Variations	8	6	48	8	384	Release test
QbD approach											
ID #	Process step	Equipment	Cause for failure	Potential effect	Effect on entire system	Severity	Occurance Probability	Criticality	Detection	SOD	Control
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3	Wet massing	Hign Shear	Excipient quality	Over/under gran.	Tableting problem	8	8	64	3	192	Time, Power
4	Lubrication	V Blender	Load	Flow/Dissolution	Content U, dissolution	9	4	36	2	72	NIR
5	Compression	Tablet Press	Speed	Weight, hardness	Variations	8	6	48	4	192	Statistical in-process

Cause & Effect Diagram

(a basis for DOE)



Process Robustness

A key factor in increased process understanding

- **Robustness** is the ability of a process to demonstrate acceptable quality and performance while tolerating variability in inputs.
- It should be demonstrated in:
 - Formulation design:
 - qualitative & quantitative,
 - API & excipients
 - Process design: manufacturing variables

Process Robustness

- Its important elements are:
 - Critical Quality attributes and
 - Critical Process parameters
- Robustness should be established during:
 - development,
 - **scale-up**,
 - commercialization and
 - post-approval stages.

Scale-up

- Scale-up studies are referred to as one of the **primary sources** of data and information needed to understand the **multifactorial** relationships among various **critical** formulation and process **factors** and for developing **effective risk mitigation** strategies (e.g., product specification, process controls etc.).
- Industry has many examples where approved products could not be launched because they could not be scaled-up!

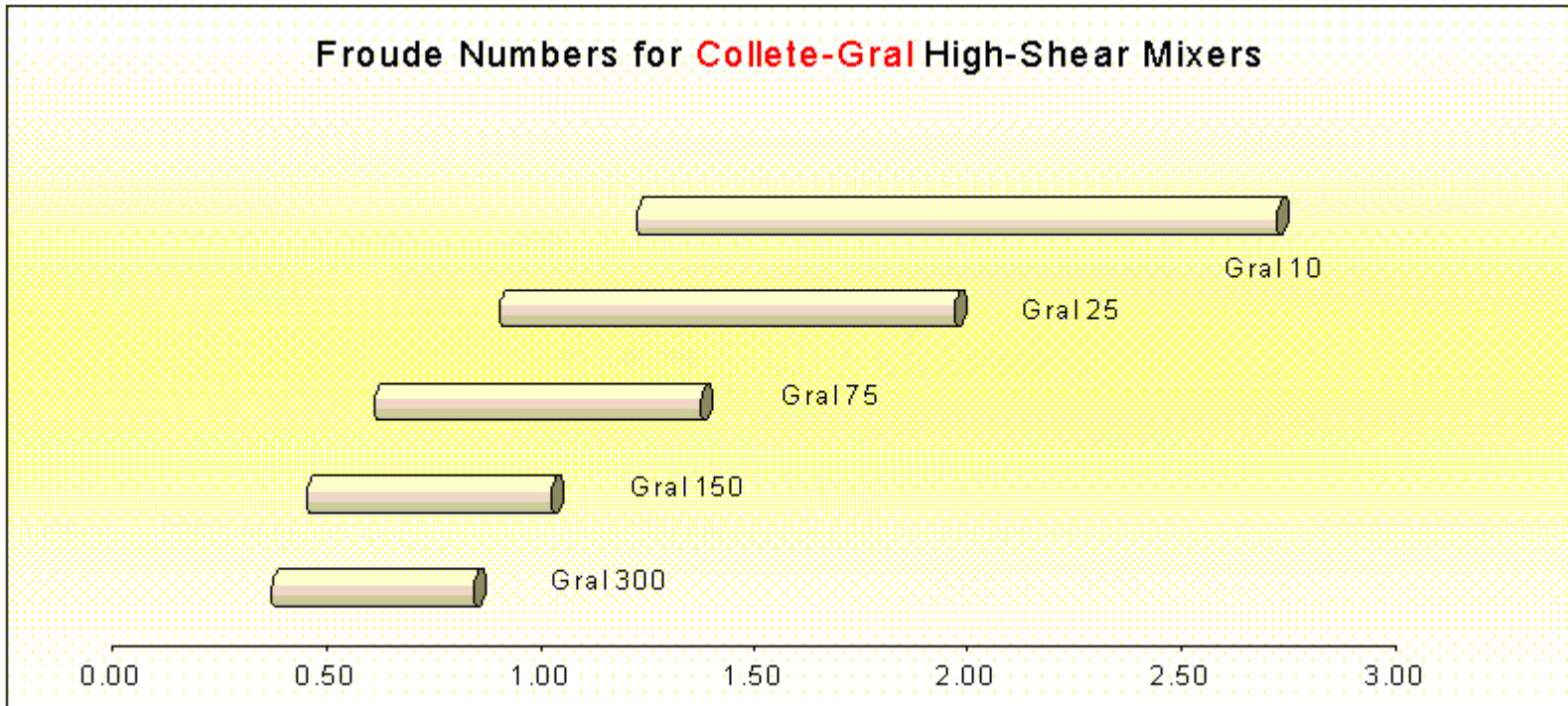
Challenges in *Complete* Process Understanding During Drug Life Cycle

Illustrations on Tablets

Why tablets?

- *Most popular dosage form*
- *Most challenging due to non-homogenous system*

E.g., 1: Challenges in Scale-up Granulation & Equipment Size



- Scale-up needs to be **gradual, and carefully planned.**
- **Smaller scale mixers** tend to produce high-shear (intense) agglomeration. With such mixers processing at lower speeds should be attempted.

Reference: M Levin, Granulation end point determination and scale-up

Compression: Facts (i)

- **Compression force**

- **Increased force** leads to reduced porosity - may influence dissolution and stability (plastic material, such as, Aspirin, Avicel, certain types of lactose).
- **Punch tip geometry:** increased curvature requires larger force to achieve same porosity (deep concave ➤ concave ➤ bevelled ➤ flat).
- **Punch & die size:** larger tablets are less affected than smaller tablets at different compression forces.

Compression: Facts (ii)

- **Increased compression speed**
 - **Reduces hardness** for many tablets (e.g., ibuprofen, acetaminophen tablets; plastic material such as MCC).
 - **Increases capping & lamination** tendencies.
- **In-process specifications** include tablet weight, diameter, thickness and hardness, but **not force and speed** which determine the degree of tablet expansion, and porosity.
These influence tablet dissolution.

Tablet dissolution: Facts (iii)

- Tablet dissolution test is only as good as it is developed for.
- A well developed test can be a valuable tool to discriminate between good and bad batches.
- Poorly developed dissolution method could give a false positive or false negative result.
- At the very least it could be used as a good QC test to ensure batch reproducibility.

E.g., 2: Challenges in Scale-up Compression

- **Compression by *trial and error*** is still widely practiced to produce tablets of a specified weight and hardness at the maximum possible speed.
- **Clinical lots versus commercial lots**
 - Most clinical lots are made with slower presses.
 - Granule / tablet characteristics **change dramatically** at commercial scale, **especially at higher speed.**
 - Often the tablet shape is changed.

E.g., 3: Challenges in Scale-up Compression

- Tablets are compressed without a force-feeder at the R&D facility (in one country - often this is the case).
- Scale-up and commercial lots are made (in another country) using force-feeder.
- In such instances target hardness may not be achieved due to lubricant over mixing on the tablet press – **anticipate dissolution problem.**

E.g., 4: Challenges in Scale-up

API (50% of tablet), X 60 mg (crystalline, mean ϕ 180 μm), Y 4 mg (amorphous, mean ϕ 120 μm) + MCC + lactose + disintegrant + lubricant - Mill, screen, blend & compress (**Direct Compression**)

8 kg lot

16 quart V-blender, acceptable blend uniformity,
16-stn.gravity-feed press
CU : excellent; Assay 96% & 106%, RSD <2

65 kg lot

5 cu ft blender, acceptable blend uniformity,
30-stn. gravity- feed press
CU : excellent; Assay 97% & 105%, RSD <2

200 kg lot

16 cu ft blender, acceptable blend uniformity,
30-stn. **force-feed press**
CU : failed; Assay 80% & 122%, RSD >9

Cause

Segregation at overhead feeding system –
difference in cohesion/adhesion between actives,
& length/angle of feeding system caused segregation

Solution

Modify blending process and **modify feeding system**

E.g., 5: Challenges in Scale-up

Chewable antibiotic for children, API granulated with a sucrose base in FBD. Blended with additional sucrose, flavour, colour & other excipients	
5 kg lot	Single station press, kid/fun shaped tablet Met all specification requirements
Scale-up lot	High speed rotary press Die crack was noticed
Cause	As speed was increased, the dwell time decreased, thereby increasing the peak force required for compaction
Solution	Adjust the amount of dry binder Adjust moisture specification Redesign tooling

E.g., 6a: Post-approval Challenge: Recalls (post-approval stage)

- Enteric coated capsule & tablets—
dissolution failure – too soon or too late –
during stability.
- Particulate (metallic) matter in lyophilized
injectable - poor change control & process
validation.

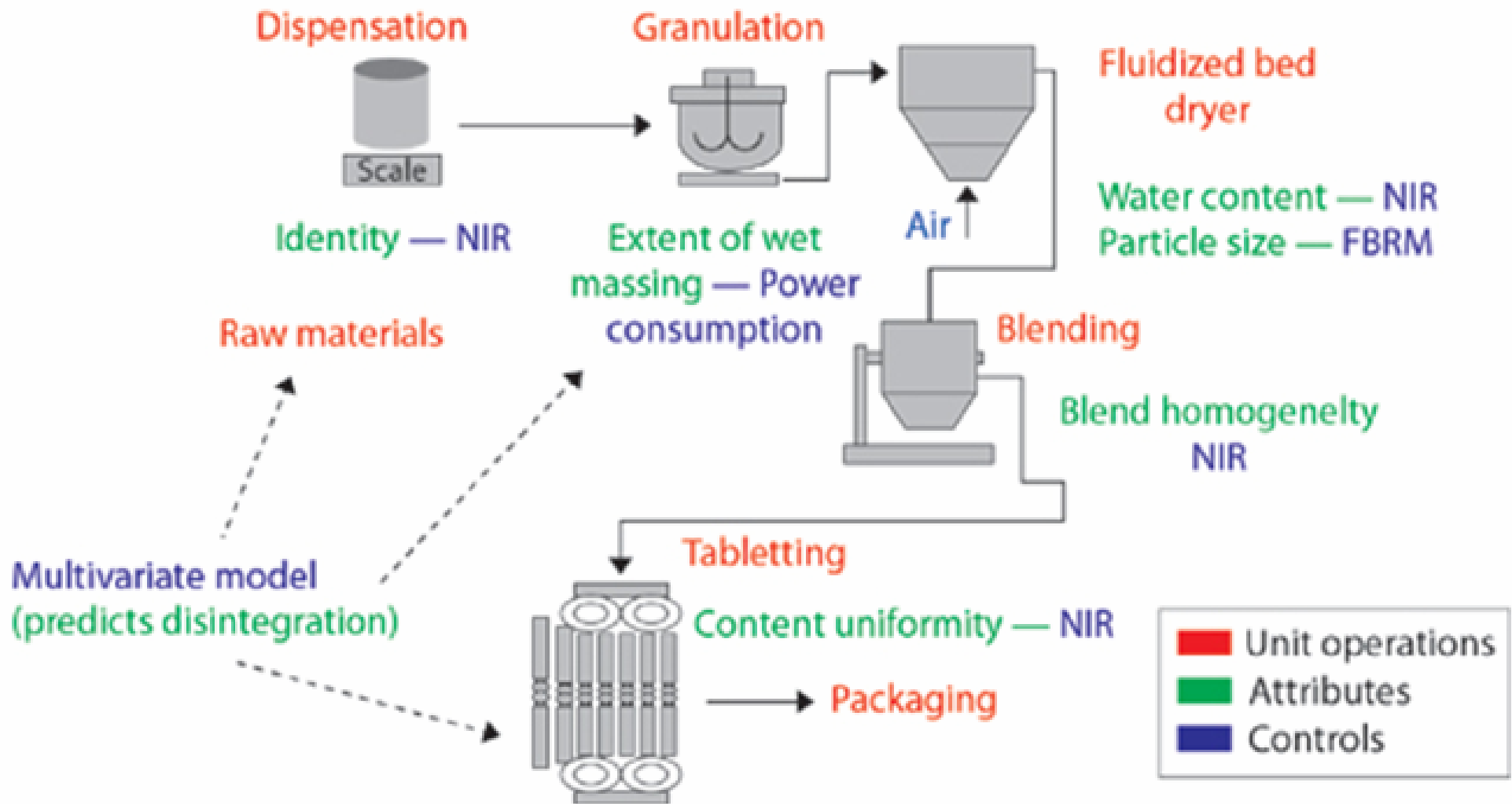
E.g., 6b: Post-approval Challenge: Recalls (post-approval stage)

- Modified release tablet failing release specification – mainly due to poor pharmaceutical development:
 - Moisture uptake during storage – prevented by use of desiccant – a temporary measure!
– what is the assurance during patient use?
 - Change in excipient supplier (e.g., magnesium stearate) caused dissolution failure
 - poor formulation
 - poor control (e.g., excipient functional test not performed).

Mitigating Risk of Failure in the QbD Approach

- All critical process parameters should be monitored using meaningful in-process tests (PAT tools - NIR etc.).
- Corrective actions should be taken to prevent batch failure (e.g., real time monitoring of critical steps) at all times.
- The information should be shared with regulatory authorities.

Example of a QbD Process



Conclusions

- QbD based approach require extra effort from all players to make it work.
- Companies that have QbD type information should share them with regulators to benefit from it.
- For *traditionally* developed products at least the most critical parameters should be identified and controlled to ensure patient safety and to avoid expensive market recalls.
- Industry and regulators have made phenomenal progress in bringing better quality products to the public in the last two decades. We are in this journey together!