What is necessary for conducting RTR approach in Japan ?
--Effective use of nondestructive analysis in pharmaceutical production--
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Agenda

- **Using QbD and PAT is the key to create enhanced quality assurance system**
- **Effective use of PAT tool is the key to adopt Real Time Release Testing (RTRT)**
- **Importance of discussion with authorities and cooperation with relative departments**
- **Summary**

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Current quality assurance system is sufficient ?

『Is the Potato Chip Industry More Hi-Tech than Pharmaceuticals ?』

・Feedback control of pepper amount, salt amount and roll pressure etc. has been conducted in manufacturing process of potato chip in order to keep good taste and good crunchiness

From Powlex seminar held on July 22th 2009 : Senior Technical Director in GSK Dr. Theodora Kourti

Current release test in pharmaceutical production (Destructive analysis)

- **Assay : 20 tablets (Averaged value) / million tablets**
- **Relative substance : 10 tablets / million tablets**
- **Content uniformity : 10 tablets / million tablets**
- **Dissolution : 6 tablets / million tablets**
- **Microbial test : small amount of tablets**

It is impossible to use lots of tablets if test method is destructive analysis.

PAT is the key technology to create an enhanced quality assurance system

『From FDA PAT guidance』

Continuous improvement is an essential element in a modern quality system and it aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. In the current system continuous improvement is difficult, if not impossible. Reducing variability provides a "win-win" opportunity from both public health and industry perspectives, therefore continuous improvement needs to be facilitated.

If nondestructive PAT tools are used for quality monitoring in pharmaceutical production, advanced quality assurance system can be launched.

"QbD" approach links to RTR

An enhanced, QbD approach to product development would additionally include the following elements:

•A Systematic evaluation, understanding and refining of the formulation and mfg process, including:

Identifying the material attributes and process parameters that can have an effect on product CQAs

Determining the functional relationships that link material attributes and process parameters to product CQAs

• Enhanced Process Understanding + Quality Risk Management = Appropriate Control Strategy, which can, for example, include a proposal for design space(s) and/or real time release

ICH Q8 (R1)

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NIRS is one typical nondestructive PAT tool

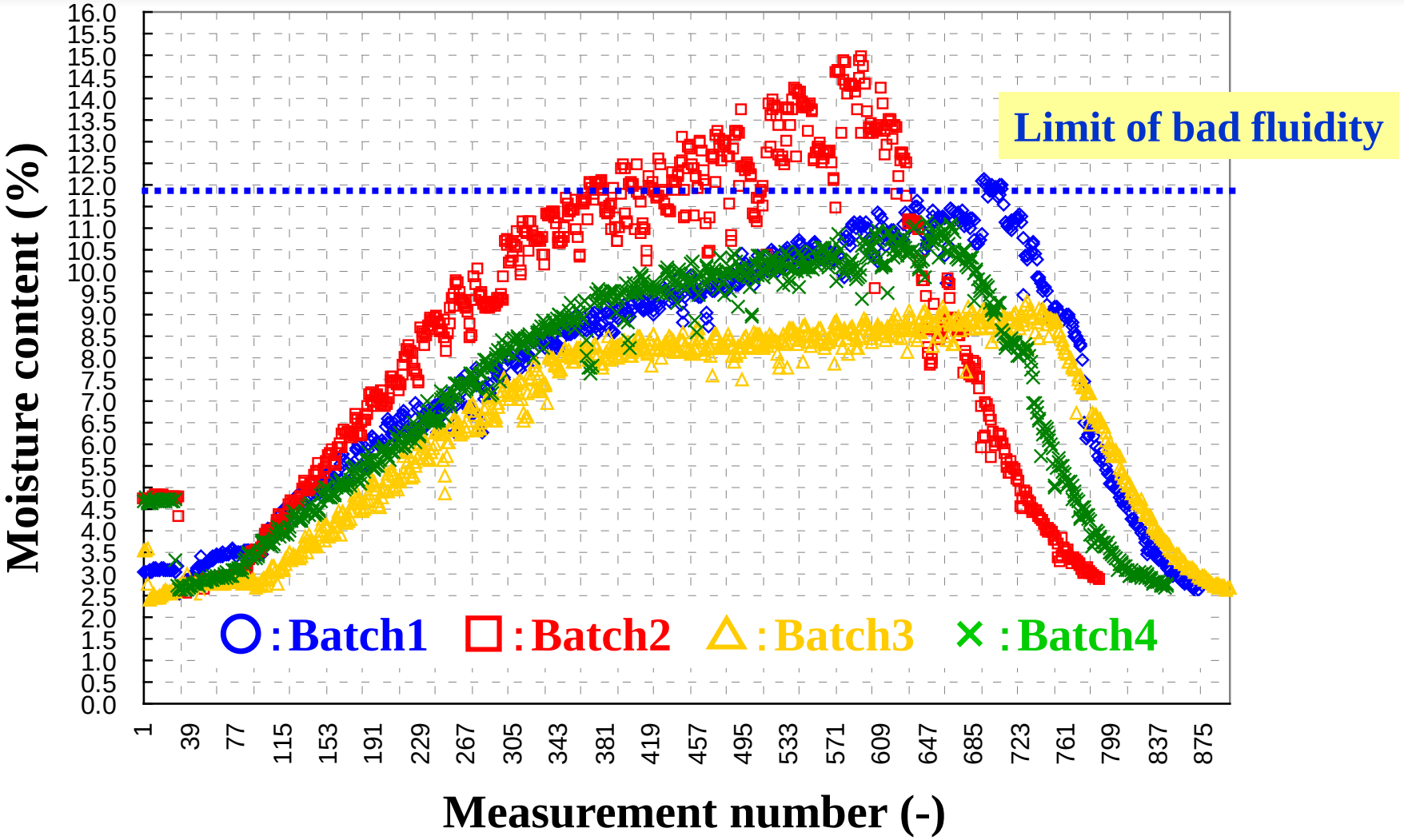
・NIRS has lots of achievements to be applied in pharmaceutical production in the world.

・There are lots of nondestructive analysis tools except NIRS.
（Raman, Terahertz etc.）

Merits of using NIRS
①High transmittance
②Low damage to sample (Low energy)
③Quick measurement（usually <10sec）
④Appropriate absorbance. Preparation before measurement is not needed.
⑤Easy operation

⇒NIRS is suitable for PAT（On-line, In-line）analysis.

NIRS is used for in-line moisture monitoring during wet granulation



- Ideal moisture profile for reduction of fine granules
- Detection of bad fluidity

NIRS is used for in-line blend monitoring

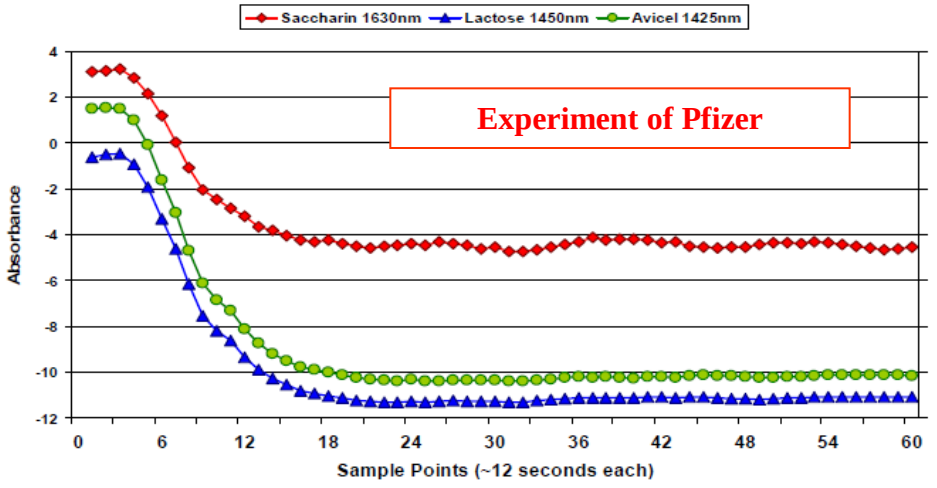
（Application examples of in-line blend monitoring）

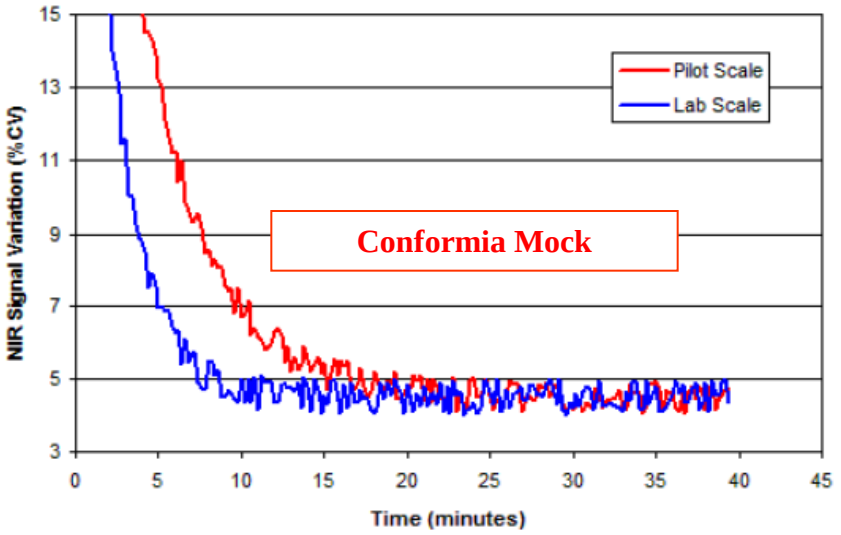
・Every product includes different batches of active ingredients and excipients, so adequate blending time can't be estimated even if blending time was set at validation.

・Segregation is occurred during sampling of powder.

・At the scale-up from pilot scale to commercial one, adequate blending time can't be estimated.

・At the site transfer, adequate blending time can't be estimated.





Model-free method is easy to be used for estimation of blend homogeneity

Example of RTRT (Assay and Content uniformity)

Now

Blend uniformity of API

Blender

- End-point is defined by blending time (constant time)

Content uniformity of API

Compression machine

- Tablet weight check

Release after film coating

- Content uniformity and assay check（Destructive test）
30 tablets/ Million tablets

Future

- Blend homogeneity is monitored by in-line NIRS data (Nondestructive monitoring)

- Tablet weight check
- Content uniformity and assay check by at-line NIRS data (Nondestructive monitoring)

Release after film Coating

- Content uniformity and assay check is skipped

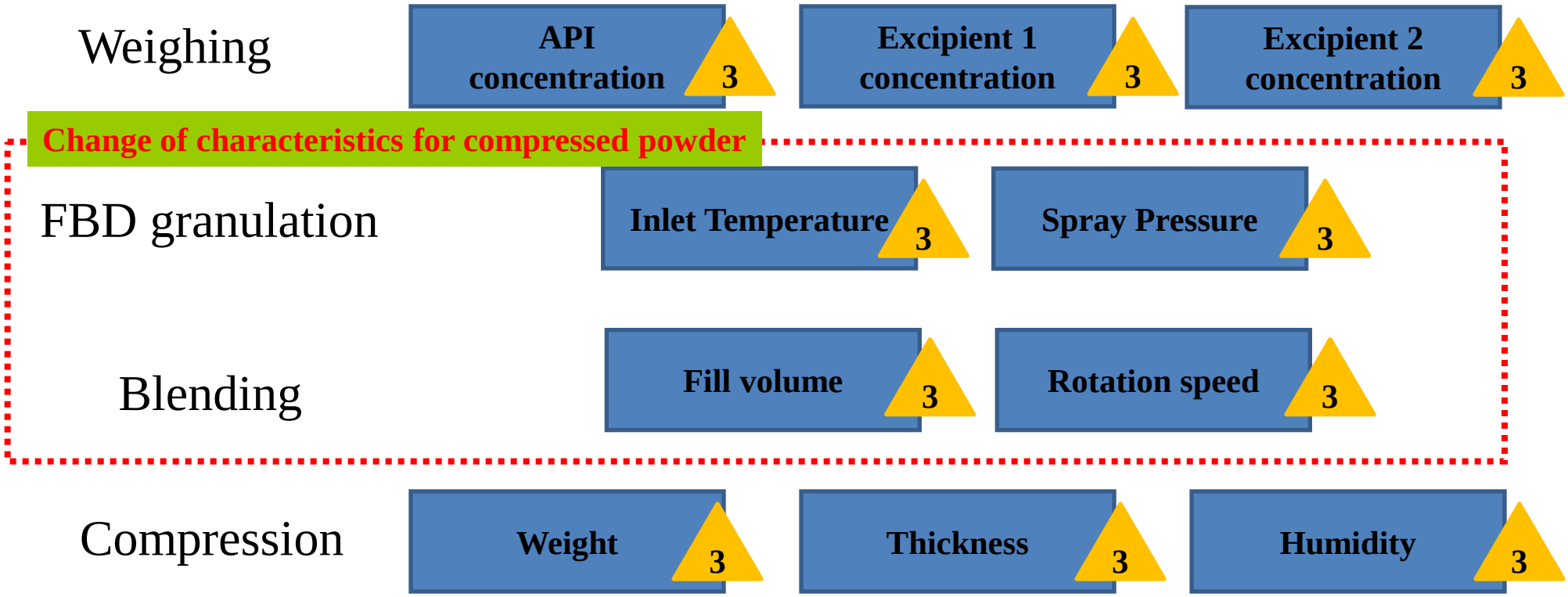
Quality level UP + Cost merit by reducing QC man power

Why is content uniformity check at compression process important for conducting RTRT (Assay and Content uniformity)?

- **Compression is important process that time-series quality can be measured.**
- **Preparation of assay prediction model using compressed tablet is easier than that using blended powder.**
- **Even if assay prediction model using blended powder can be prepared for, segregation during compression process can't be detected.**

- **Nondestructive monitoring of assay and C.U. is very important because large number of samples can be used for quality check.**
- **Assay prediction model is used for quality check in plant, so it must be prepared by including lots of factors which affect content uniformity.**

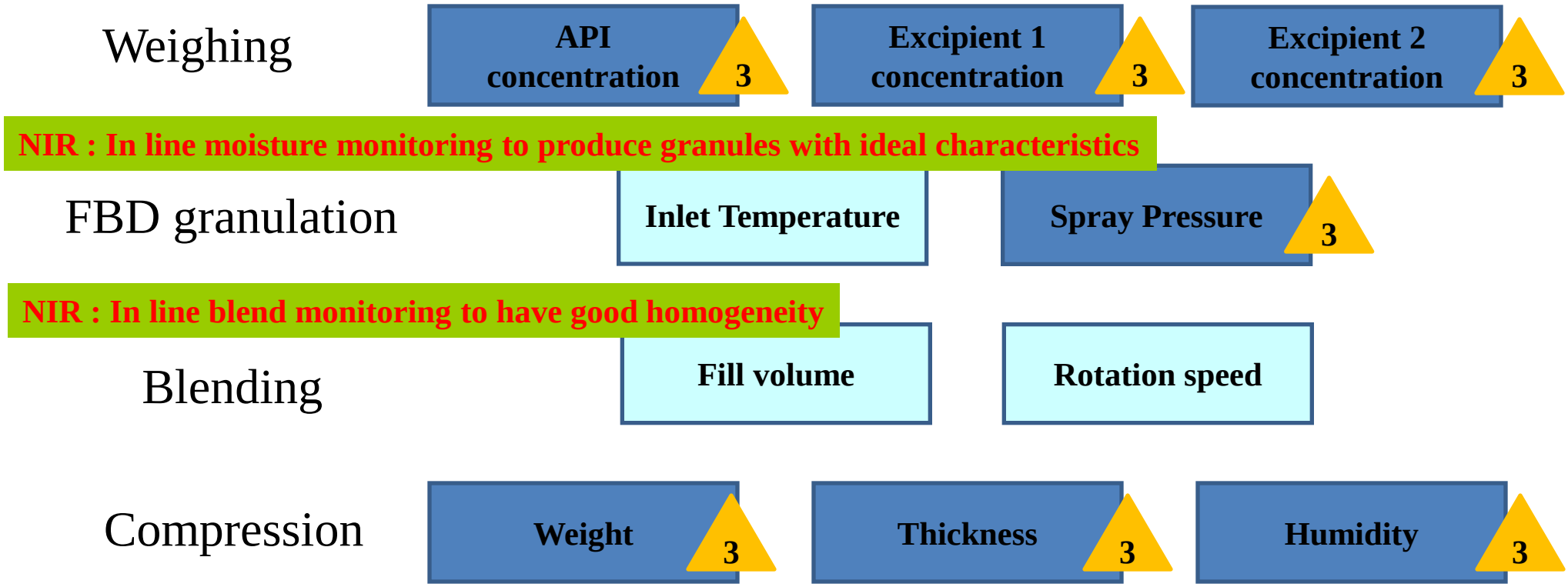
Well balanced DOE and chemo metrics are very important to prepare for robust assay prediction model



Full : 3^{10} = 59049 experiments ⇒ Risk analysis and DOE are necessary

- **Well balanced DOE has to be used for preparation of assay prediction model**

Well balanced DOE and chemo metrics are very important to prepare for robust assay prediction model



- Reduction of factor number by using risk analysis and technical tool is important

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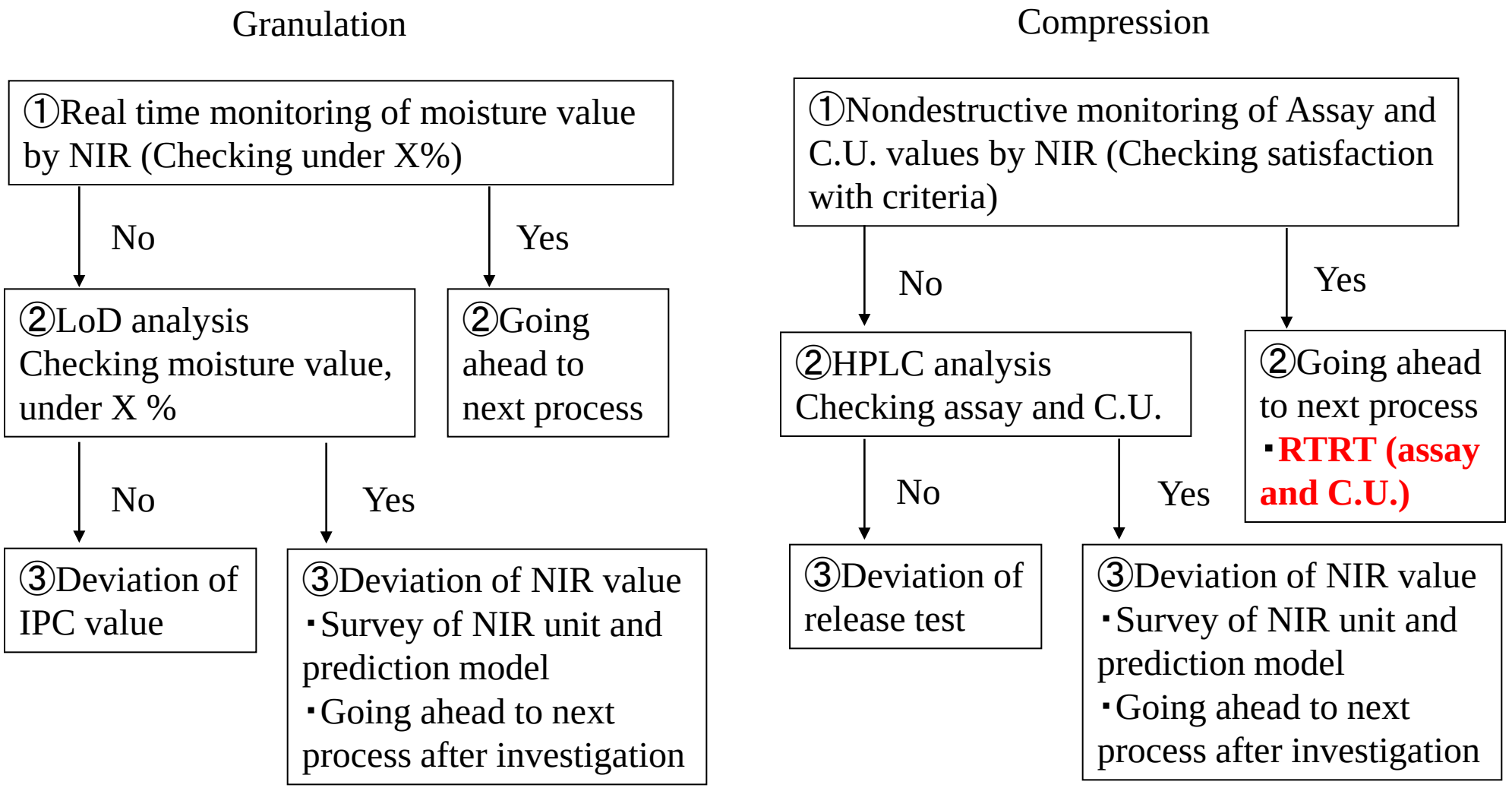
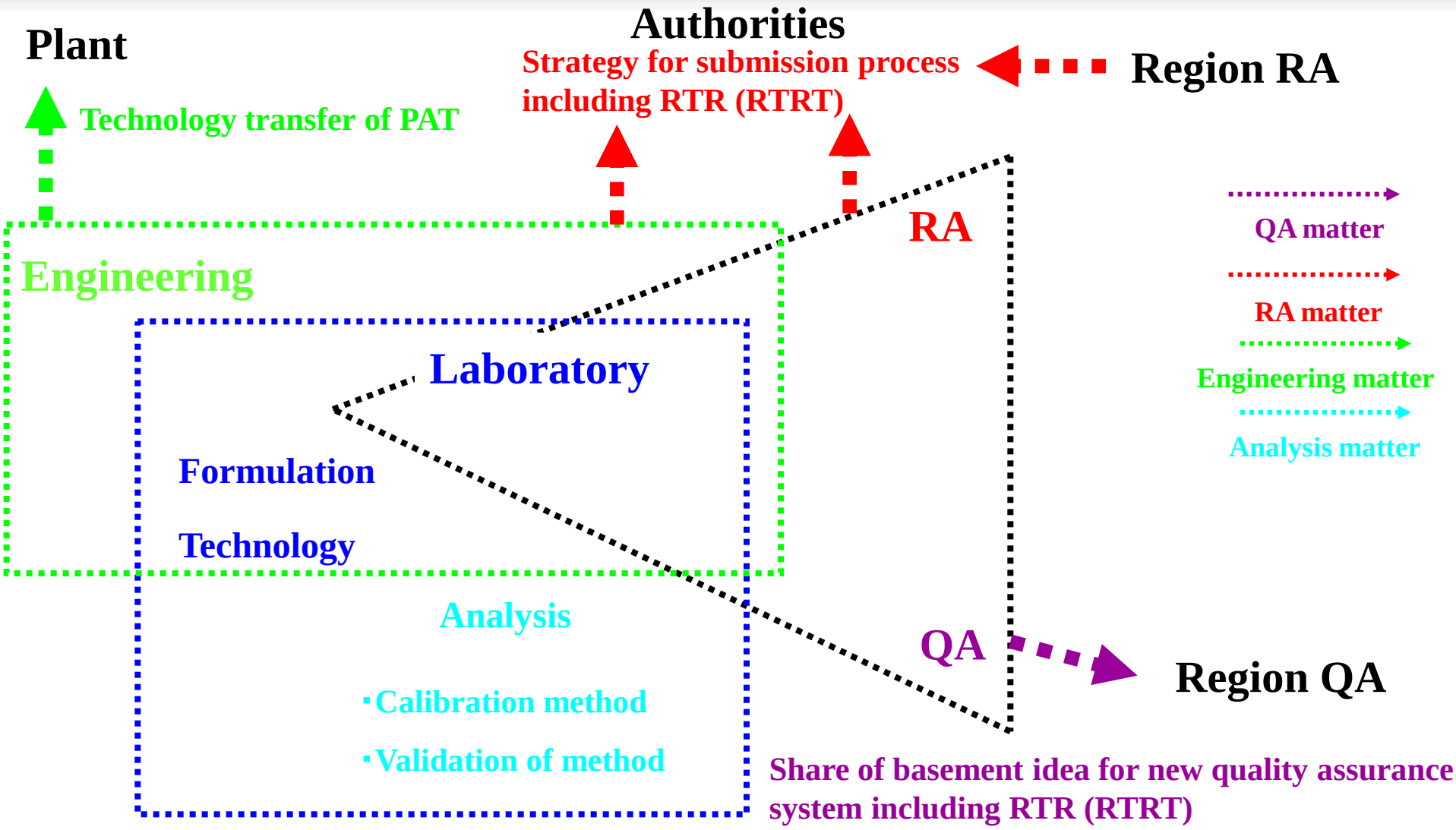
It is necessary to discuss RTRT strategy including deviation flow with authorities



・In preparation for deviation, setting alternative test method is necessary

It is necessary to have common understanding among relative departments about RTR (RTRT)



Summary

What is necessary for conducting RTR approach in Japan ?

・Discussion with authorities deeply about effective and appropriate use of PAT

・Common understanding among relative departments including RA, QA and Engineering etc

・Technology and analytical development of nondestructive PAT tools deeply

・Using nondestructive PAT tools for QbD studies at development stage and for continuous improvement at commercial production

Changing tomorrow is difficult independently, so whole pharmaceutical industry has to move in the same direction

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