Risk mitigation →
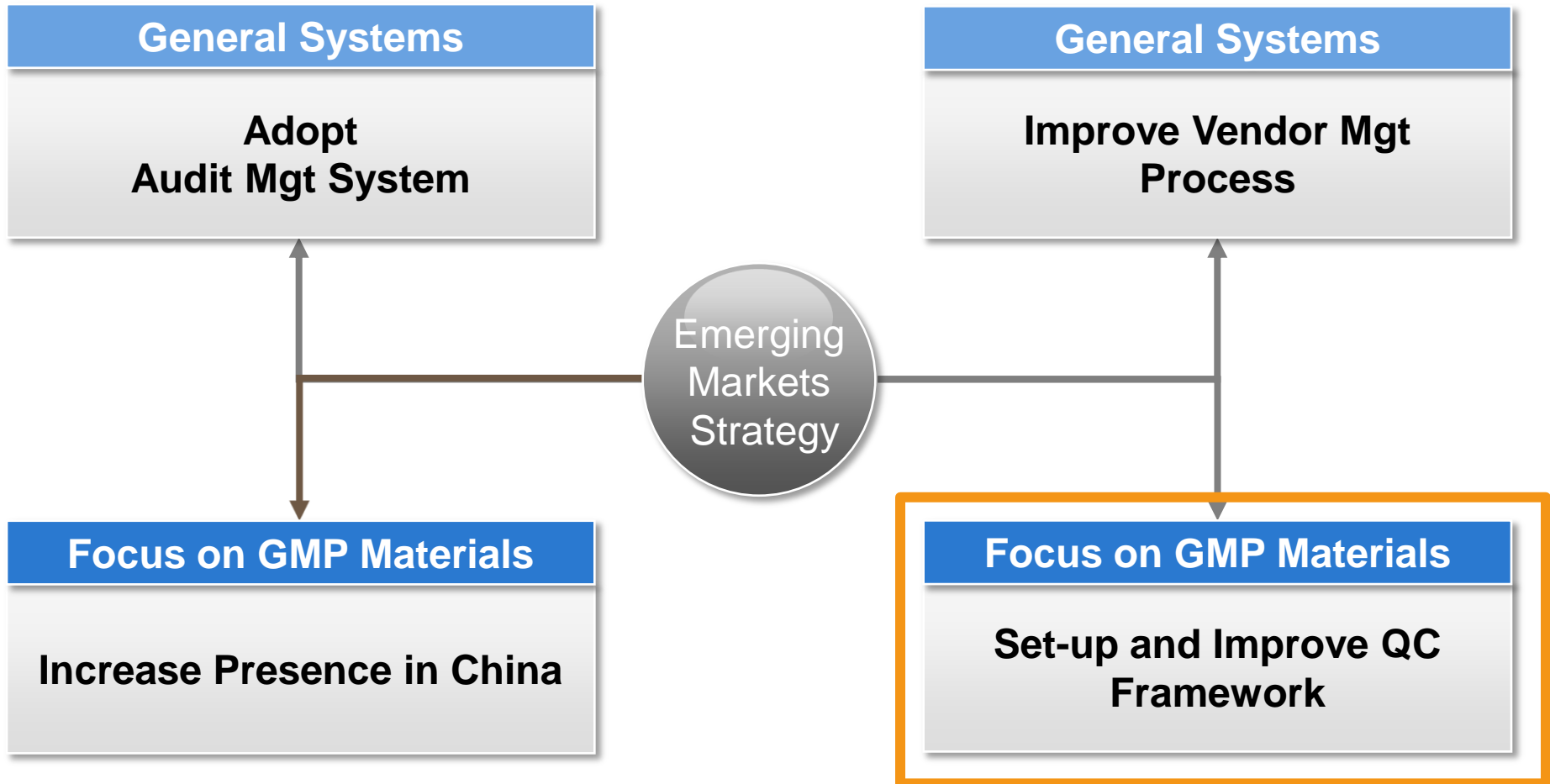# get a insight of your Raw Material

Dr. Jens Schewitz

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Risk mitigation a consequence of experience

The Network on Risk Mitigation: it's more than talking about impurities

General Systems
Adopt Audit Mgt System

General Systems
Improve Vendor Mgt Process

Emerging Markets Strategy

Focus on GMP Materials
Increase Presence in China

Focus on GMP Materials
Set-up and Improve QC Framework

Facing current situation for raw material supply

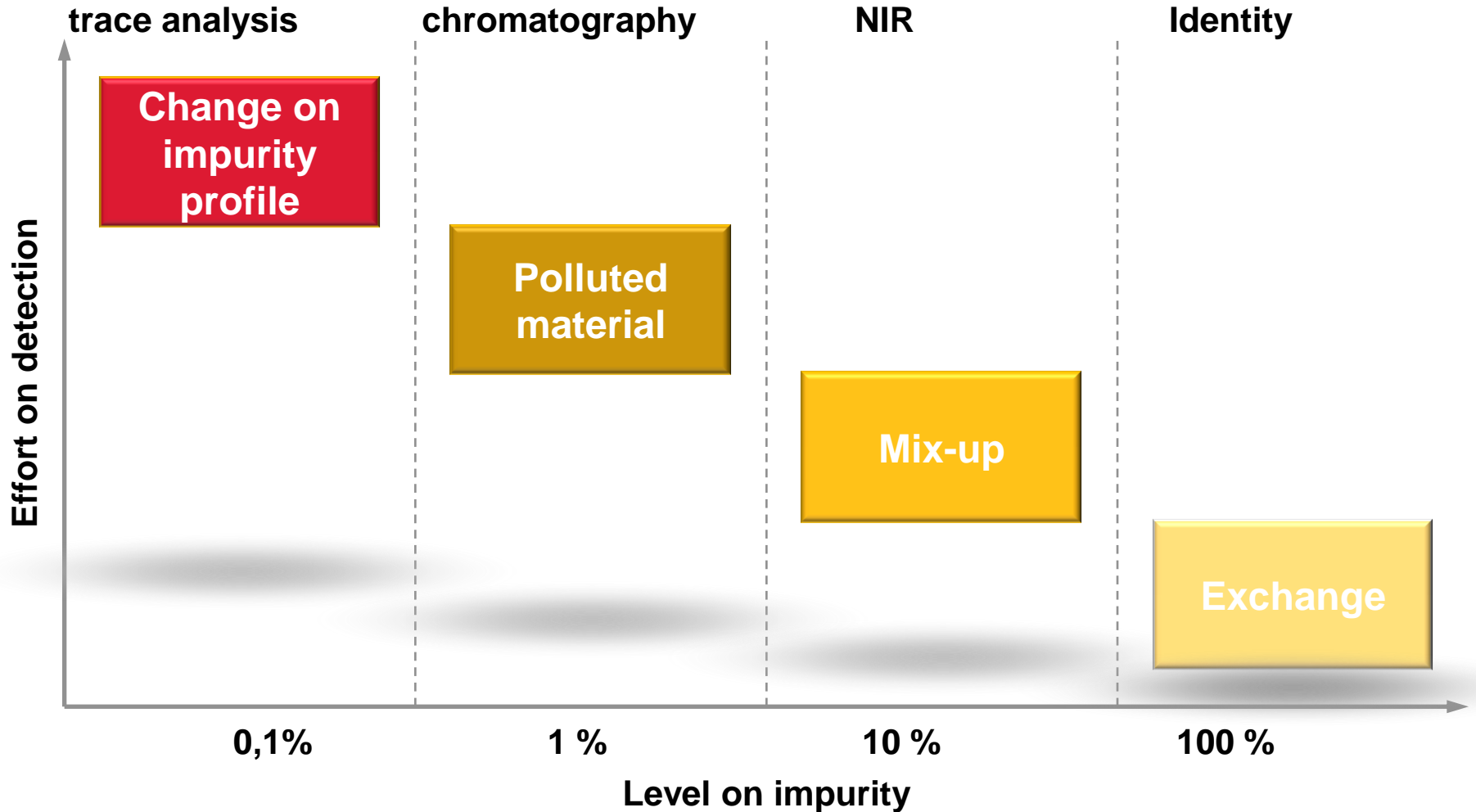Increasing numbers of disqualification and revoke of CEP

Challenges on CAPA due to geographic distance

Different awareness and knowledge of Quality

Vendor Qualification in place, QC protocols based on pharmacopoeia mainly

An increasing number of raw materials purchased in emerging markets

The risk of raw material supply

trace analysis **chromatography** **NIR** **Identity**

Effort on detection

Change on impurity profile

Polluted material

Mix-up

Exchange

0,1%   **1 %**   **10 %**   **100 %**

Level on impurity

All methods have strength and weaknesses

method	physical attributes	chemical structure	impurity profile	needs & targets
NIRS	+++	+++	0	identity, process capability
RAMAN	++	+++	+	identity, process capability
LC-UV	0	+	+	organic impurities
LC-MS/MS	0	+++	+++	organic impurities
GC-MS	0	0	+++	residual solvents
ICP-MS	0	0	+++	catalysts
RFA	0	0	+	Semi quantitative screening of cat.

Using data of routine test and combine them
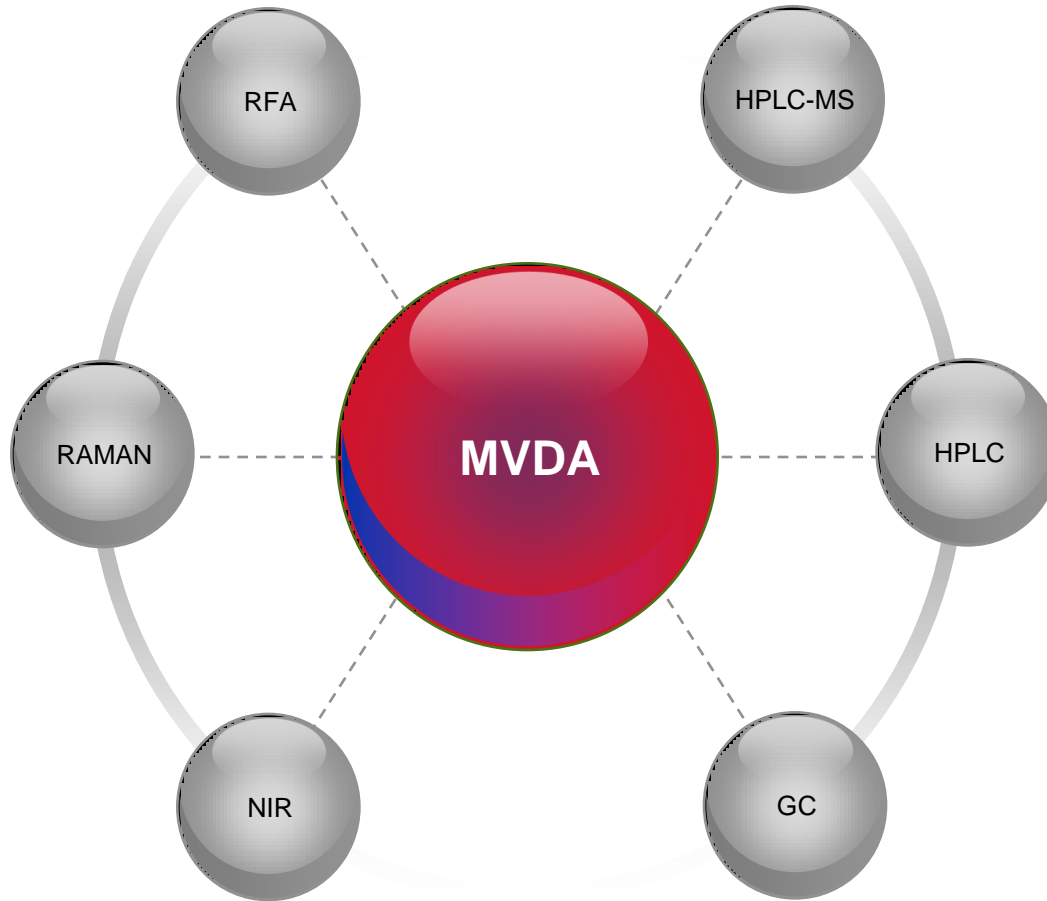
Strategy Emerging Markets: our concept to integrate the approach in QC

Risk evaluation

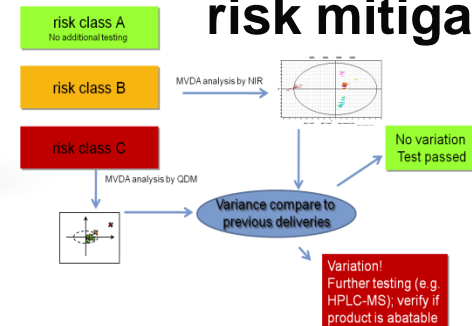| Evaluation Criteria	1	2	3	4	5
Supply history	👍				👎
Use of raw material	👍				👎
Production process of raw material	👍				👎
Quality situation and nature of synthesis	👍				👎
Status of Supplier Qualification and transport situation	👍				👎

Classification of material

Score:

risk class C — Additional MVDA analysis by QDM — one in 4/5

risk class B — Additional MVDA analysis by NIR — two in 3

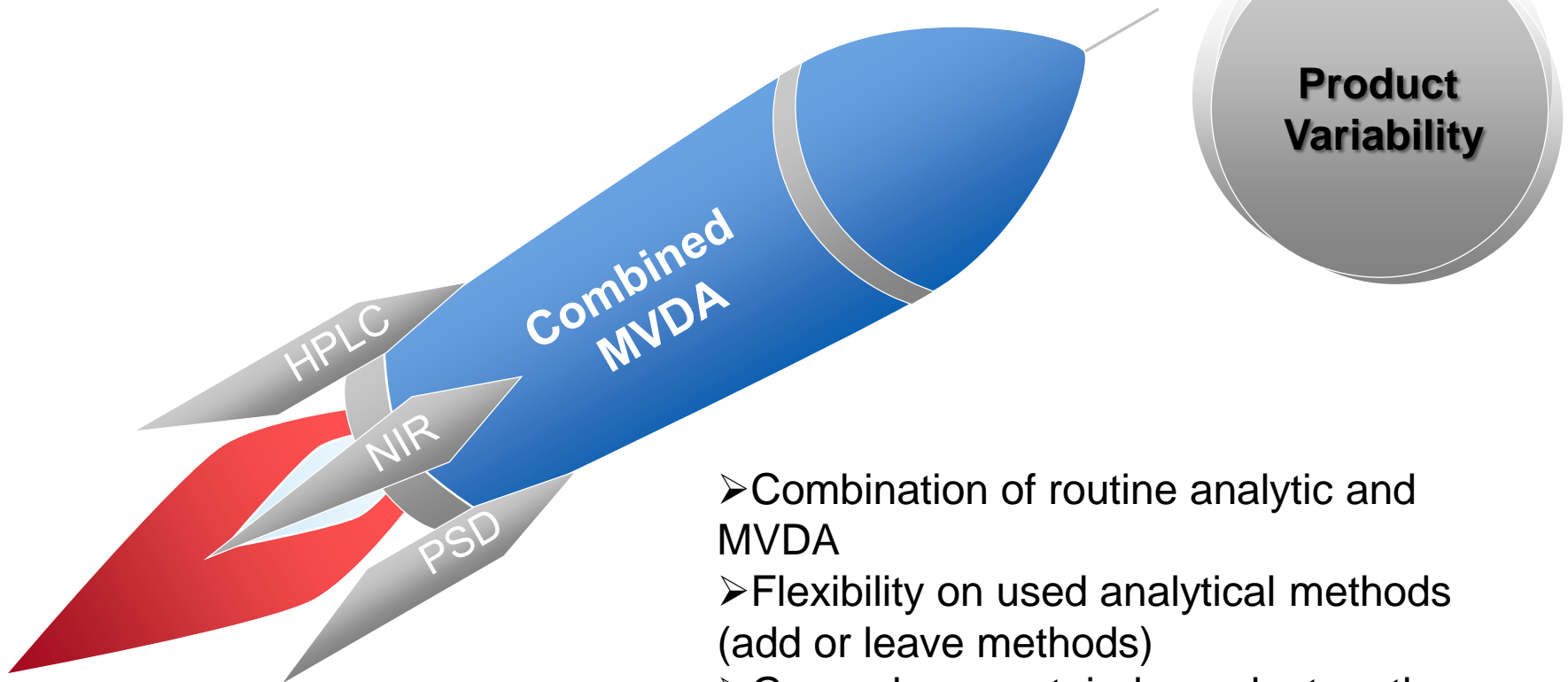risk class A — No additional testing — all in 1-2
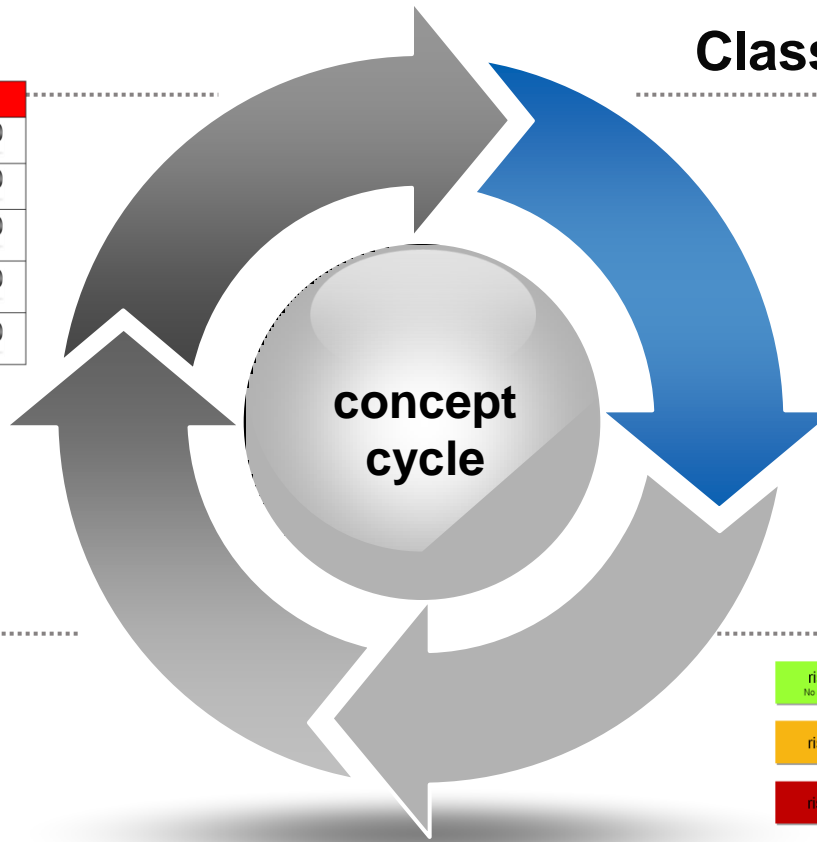
Follow up reduce the risk class

concept cycle

Individual analytical risk mitigation

risk class A — No additional testing

risk class B — MVDA analysis by NIR

risk class C — MVDA analysis by QDM

Variance compare to previous deliveries

No variation Test passed

Variation! Further testing (e.g. HPLC-MS); verify if product is abatable

No Rocket Science: us routine methods and get an insight of the process

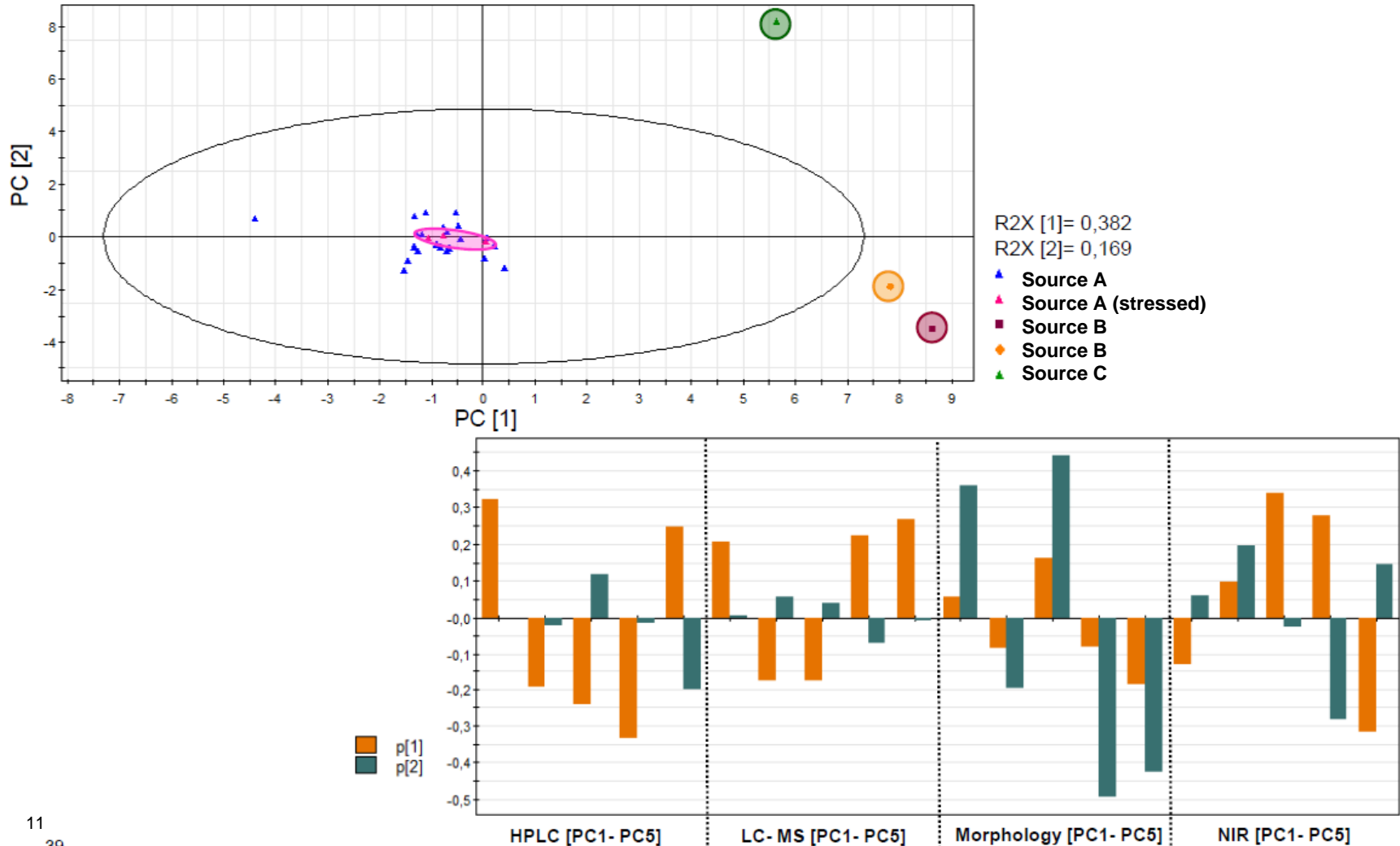**Product Variability**

Combined MVDA

HPLC

NIR

PSD

➤Combination of routine analytic and MVDA

➤Flexibility on used analytical methods (add or leave methods)

➤General concept: independent on the raw material, supplier

Transforming the idea into a routine workflow

Proof of concept	Analytical methods applicable	Combination of MVDA possible
Routine	Most of the methods are part of routine QC	Use of Historical Data possible
Databases	data interfaces	HPLC database, NIR-database, LIMS …
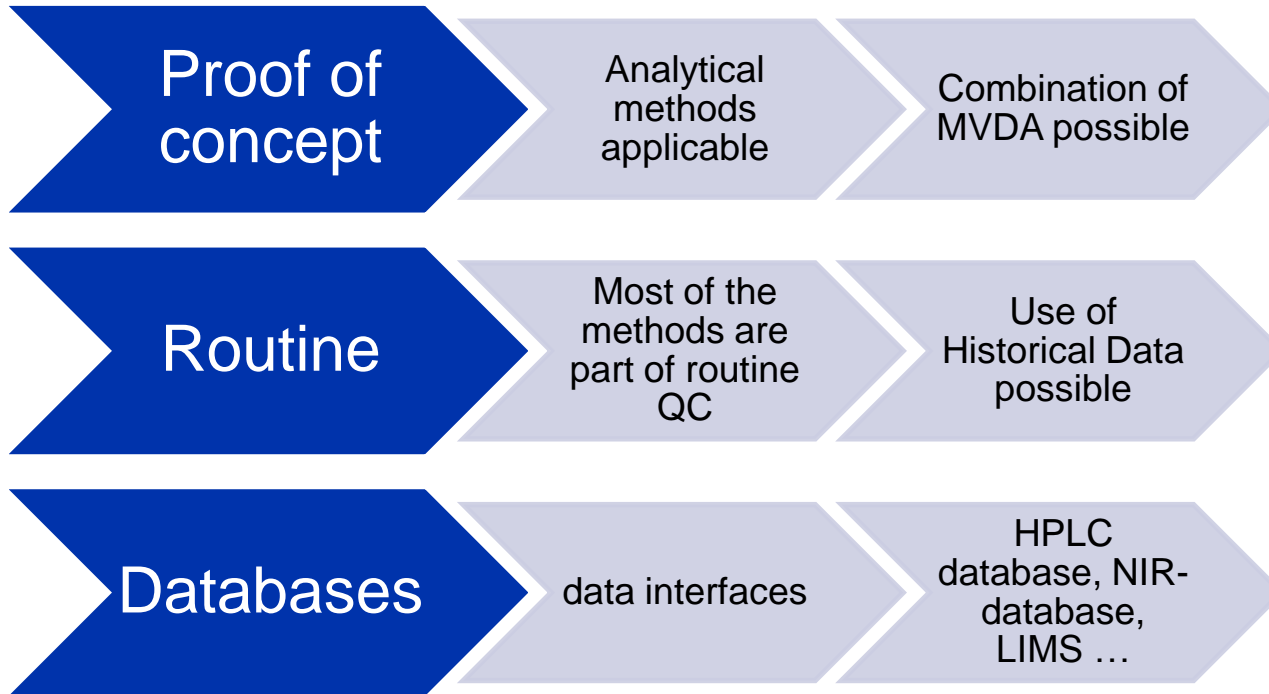
More than analytical data it's a insight view on the raw material and production process

R2X [1]= 0,382
R2X [2]= 0,169

- ▲ Source A
- ▲ Source A (stressed)
- ■ Source B
- ♦ Source B
- ▲ Source C

p[1]
p[2]

HPLC [PC1- PC5]   LC- MS [PC1- PC5]   Morphology [PC1- PC5]   NIR [PC1- PC5]

It's not good and bad

It's changes, differences
→**Variability**
→**fundament for QbD**

Stepping back and have closer look to single methods

- defines the particle size and shape
    - CE-diameter
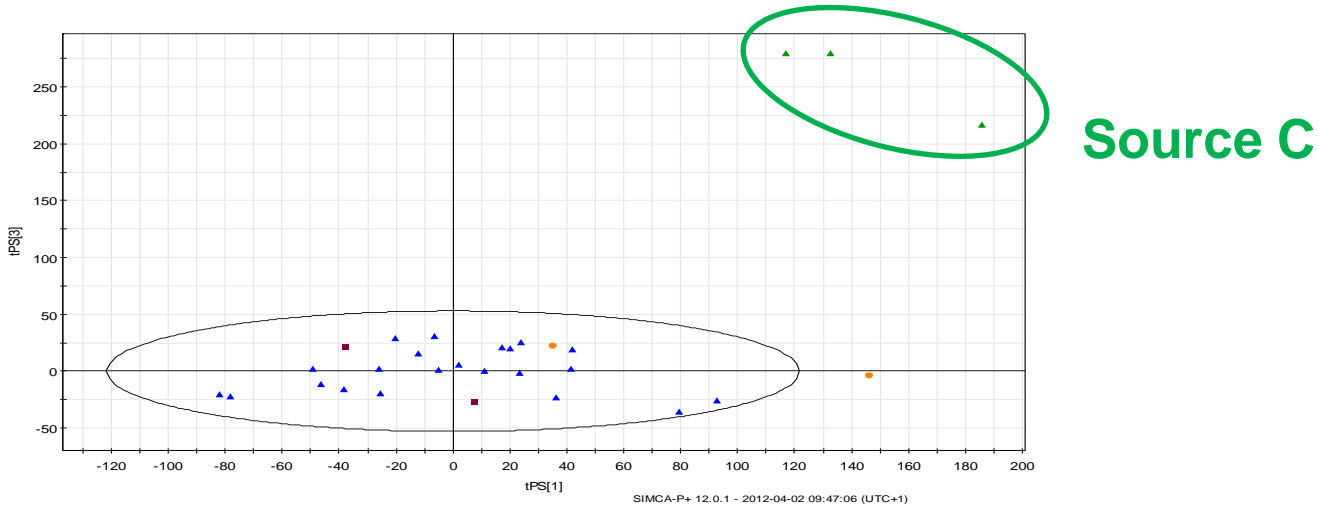   - mean intensity

Circle equivalent (CE)- diameter *

3D particle	Captured as a 2D image	Converted to a circle of same area	Diameter of circle measured

Intensity mean *

Intensity mean = 150   Intensity mean = 95
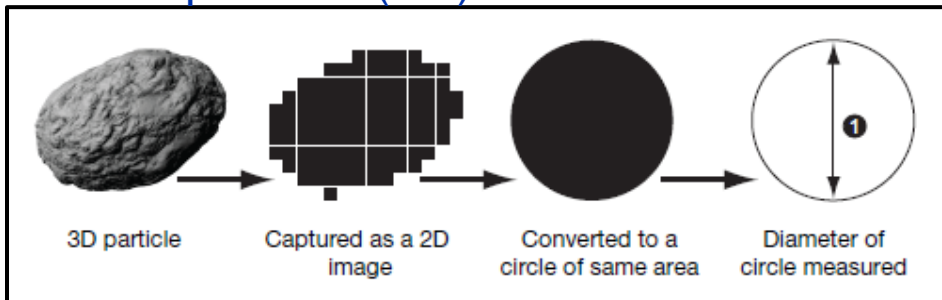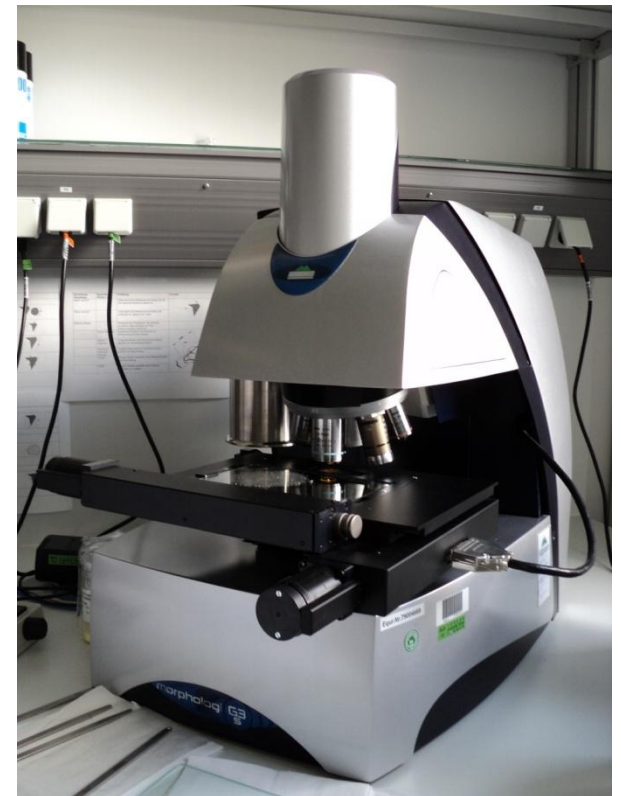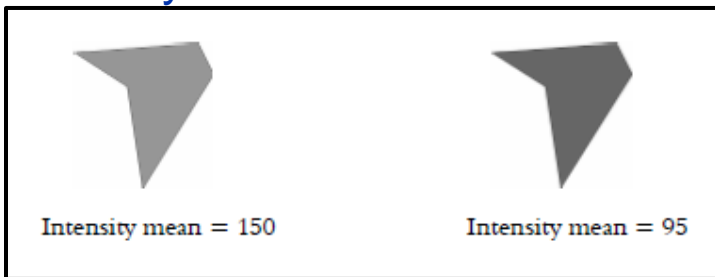
Morphologi G3S

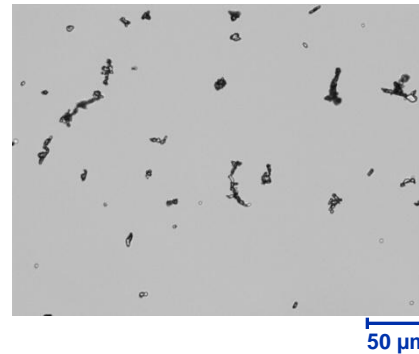* morphologi G3- user manual, Malvern, 2007

Morphology → physical attributes
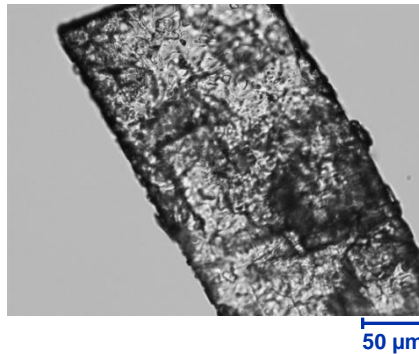

Source C

Source A   **Source C**   Source B   Source B
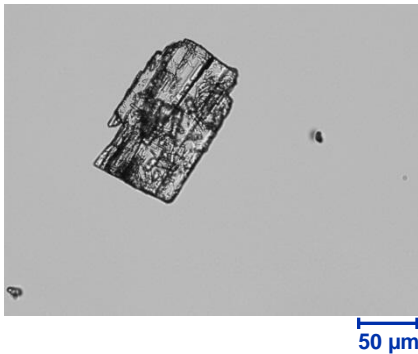
HPLC and LC-MS → impurity are of interest

LC-MS

R2X [3]= 0,116
R2X [5]= 0,038

▲ **Source A**
▲ **Source A (stressed)**
■ **Source B**
◆ **Source B**
▲ **Source C**

HPLC

R2X [4]= 0,066
R2X [5]= 0,036
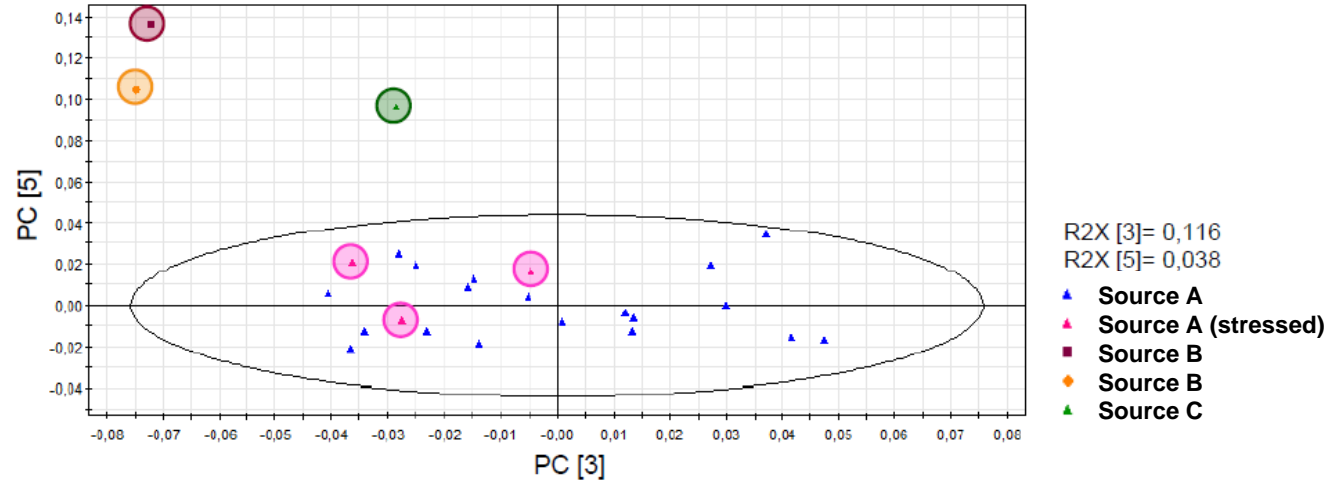
▲ **Source A**
▲ **Source A (stressed)**
■ **Source B**
◆ **Source B**
▲ **Source C**
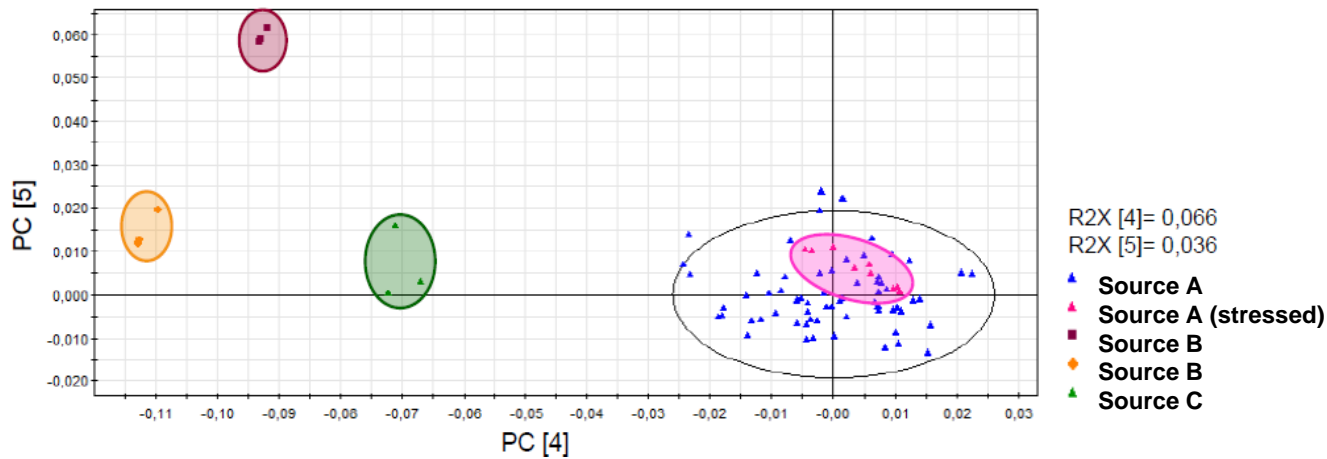
Keep an eye on your raw materials

➢Increasing the knowledge space of raw material

➢Material variability becomes increasingly important for the desired quality in a QbD environment
- Even slight modification can have a tremendous effect on the desired quality
- Fingerprint type information required

➢Insight of the raw materials are access able
- changes in process on physical and chemical aspects

➢Holistic concept
➢Risk based approach
➢ Stronger Supplier Integration in QM process
➢Continues verification of the raw material