Implementation of Empower 3 for CE instrument control, data acquisition and reporting in a global, multi-product QC environment
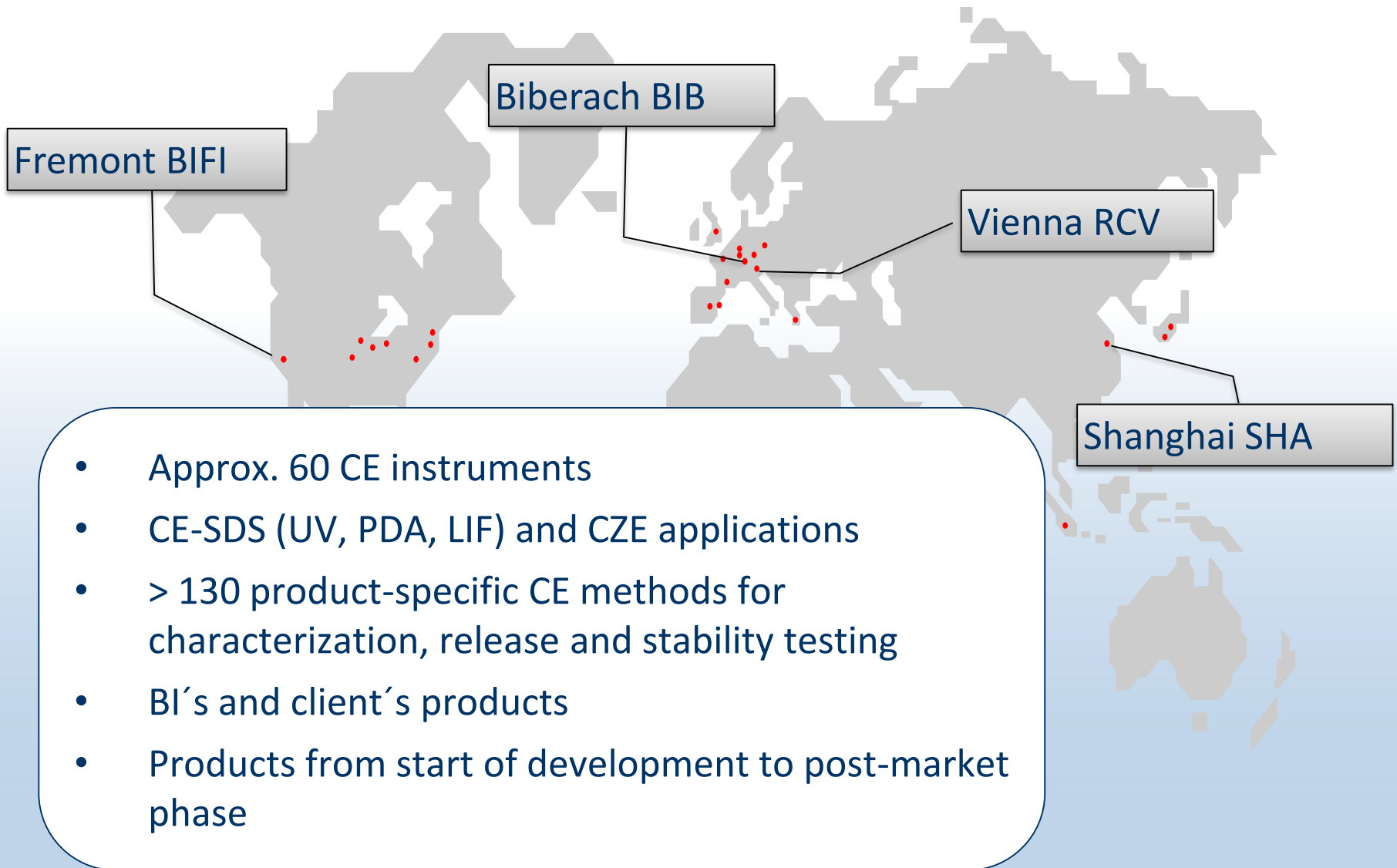
Dr. Edith Binder, Manuel Birke, Anja Brauchle, Marian Gruener, Tina Kohn, Annette Sieron, Johannes Sommer, Kerstin Mueller

Boehringer Ingelheim

Overview

1. Concept and rationale of the software switch

2. Comparability strategy 32 Karat / Empower 3
   - I.   Instrument qualification
   - II. Test case
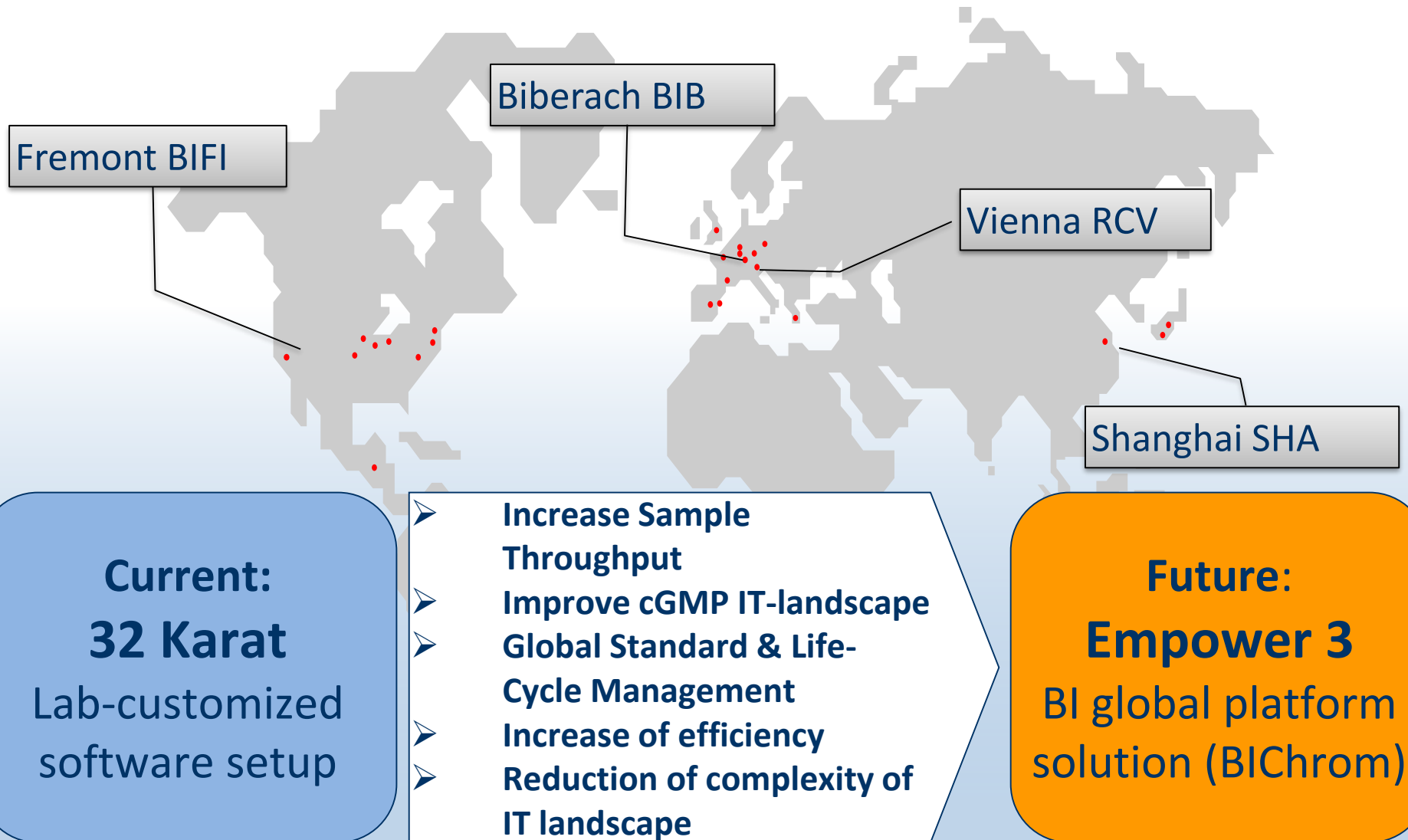   - III. Bridging

3. Product-specific implementation

Boehringer Ingelheim

Concept and rationale
CE applications in a global, multi-product landscape at BI Biopharma

Biberach BIB

Fremont BIFI

Vienna RCV

Shanghai SHA

- Approx. 60 CE instruments

- CE-SDS (UV, PDA, LIF) and CZE applications

- > 130 product-specific CE methods for characterization, release and stability testing

- BI´s and client´s products

- Products from start of development to post-market phase

Boehringer Ingelheim

Concept and rationale
Global implementation of Empower 3 for CE systems

Biberach BIB

Fremont BIFI

Vienna RCV

Shanghai SHA

Current:
32 Karat
Lab-customized software setup

➢ **Increase Sample Throughput**
➢ **Improve cGMP IT-landscape**
➢ **Global Standard & Life-Cycle Management**
➢ **Increase of efficiency**
➢ **Reduction of complexity of IT landscape**

Future:
Empower 3
BI global platform solution (BIChrom)

Concept and rationale
Implementation overview

Client notification

ROLL-OUT:
Global / Local /product specific switch

32 Karat / Empower COMPARABILITY

Preparation of GMP System

Application Test:
Proof of concept

Start of project: **2016** … Start of role-out: **2018** … **ongoing**

Boehringer Ingelheim
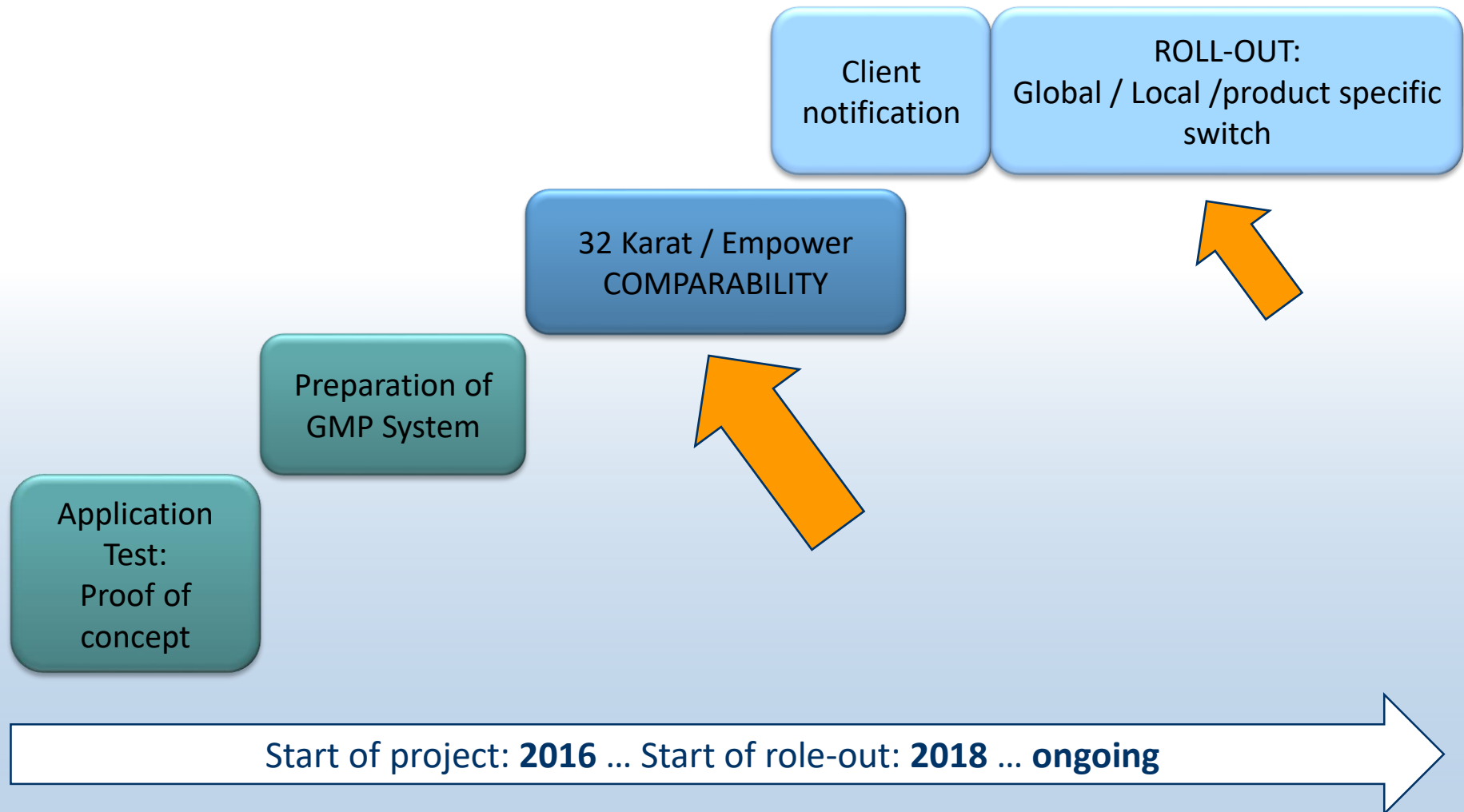
Software switch
Comparability strategy
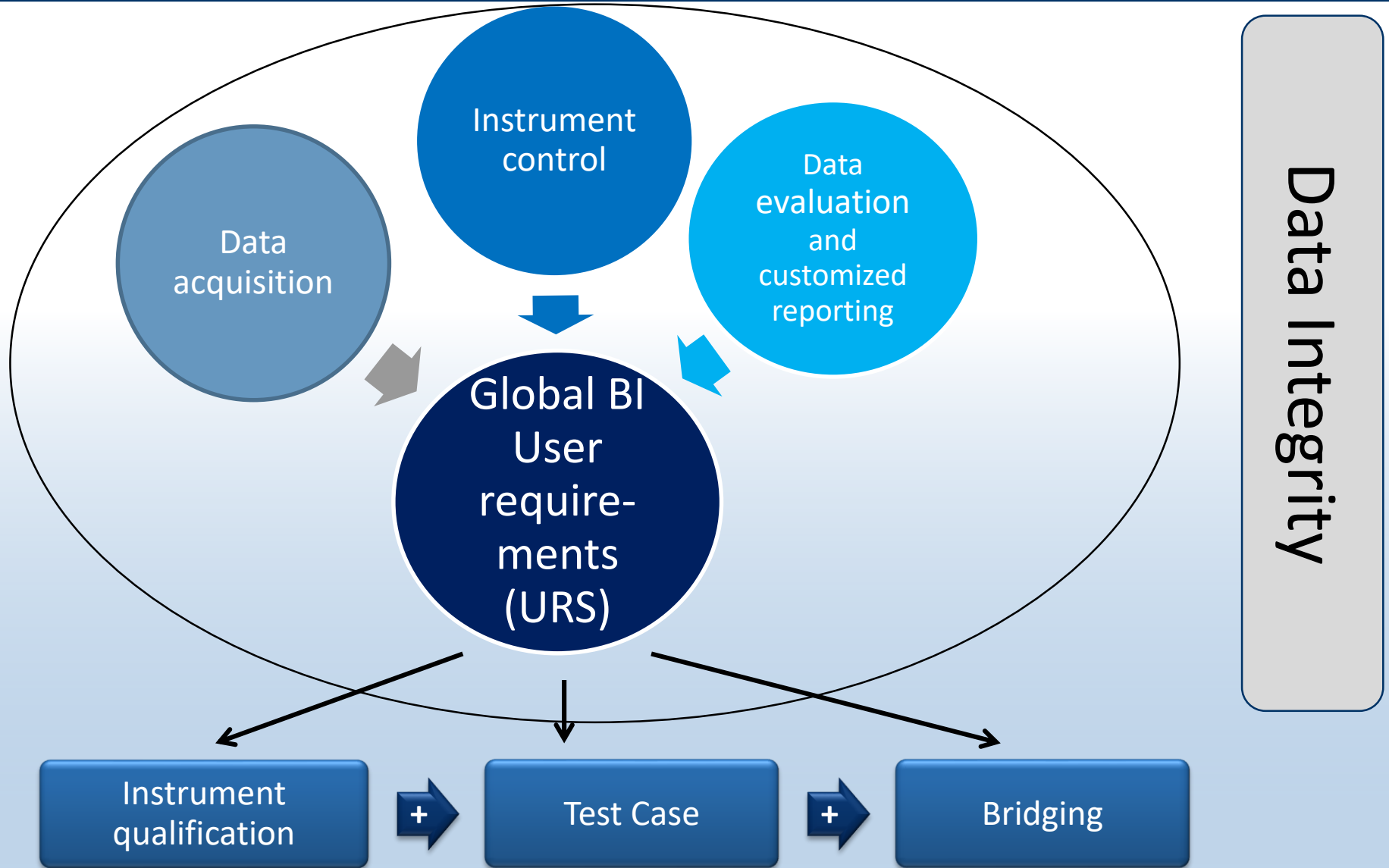
Comparability strategy
Definition of User Requirements (URS)

- Definition of **routine workflow requirements**

- Definition of **4 representative CE method types** from a set of > 130 product-specific test methods

- PDA
- UV
- LIF

- CGE (CE-SDS)
- CZE

Detector type

Method type

Injection mode

Method mode

- Elektrokinetic
- Pressure
- both

- forward
- reverse

Boehringer Ingelheim
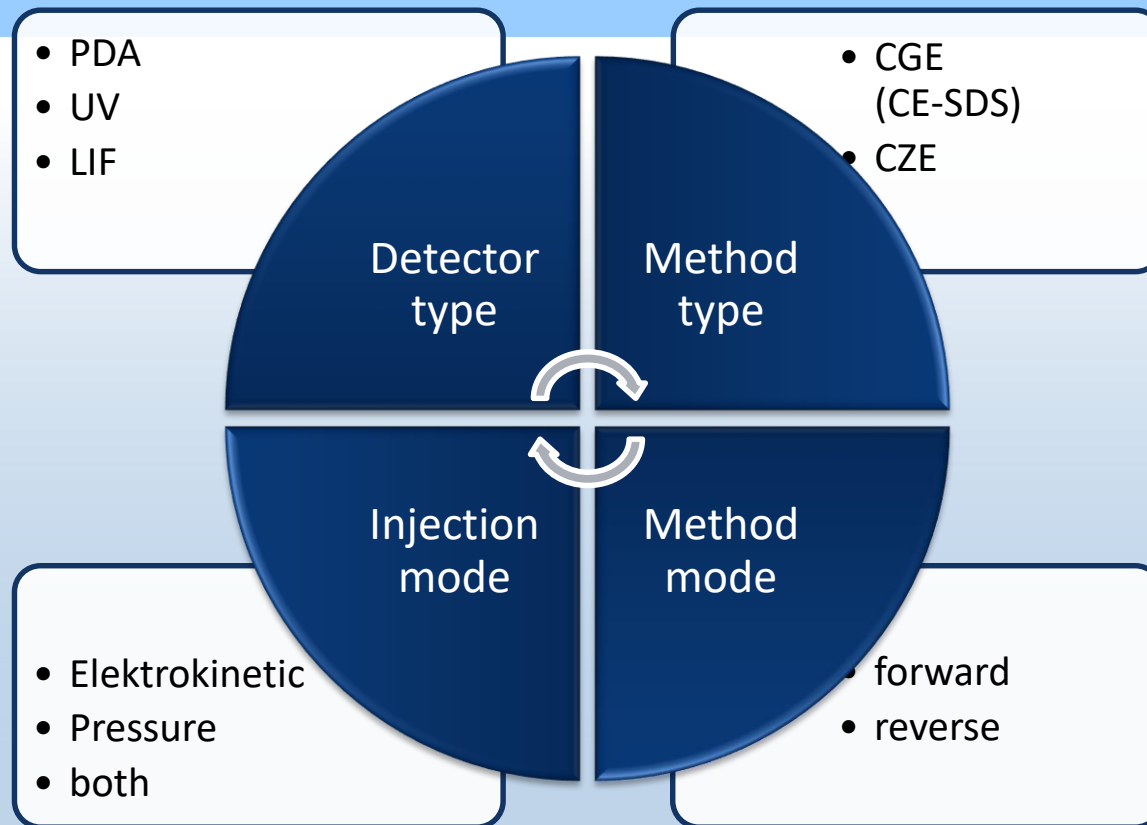
Comparability strategy
Three stages

I. Instrument qualification	+	II. Test Case	+	III. Bridging

"Standard" CE instrument qualification

Qualification of specific functionalities
- Control of specific instrument parameters by Empower
- Switch process 32Karat <-> Empower

Test performance of representative methods

Simulation of complete analysis process and **testing of URS**
Show **driver functionality**

Proof of **comparable method performance**

Evaluation by **Accuracy / precision approach**

COMPARABILITY

Comparability strategy
I. Instrument qualification

Two representative CE instruments

PA800 Plus | PA800 Enhanced | Vendor PC | LAC/E

"Standard" qualification

❖ **Installation qualification (IQ)**
32Karat installation
Empower and LAC/E installation

❖ **Operation qualification (OQ)**
Vendor OQ3 using software Karat32 by service technician

❖ **Performance qualification (PQ)**
PQ for 32Karat using IgG control standard

Qualification of specific processes

❖ **Instrument control by Empower**
Comparability of defined OQ3 parameters using Empower control

❖ **Qualification of software switch between 32 Karat<-> Empower**
In routine for qualification and calibration purposes a software switch is necessary!

Performance of 4 representative test methods

Visually comparable electropherograms of representative reference standard material

Simulation of complete analysis process and testing of URS

- Typical test method
- Typical sample set
- Typical data evaluation

- Buffer incrementation
- Autozero
- Separation
- Shutdown
- Clean & Blow

- Conditioning
- SST
- Interruption
- Insert in running set
- Re-injection

- Data processing
- Reporting
- Audit trails

Comparability strategy
II. Test case – Issues and workarounds

PDA calibration and IQ/OQ by vendor technician only by 32Karat	• Requirement of 32Karat in addition to Empower • Switch in routine operation required	→	Qualification of Software switch procedure
TCA (32Karat) required for all validated test methods	• Implementation of capillary length in Empower • Limited functionality due to need for custom fields for VCA calculation	→	Qualification of new custom fields; adapt routine workflow
Noise calculation (SST criterion)	• Difference in noise calculation between 32Karat and Empower • Replacement of „threshold" by „peak-to peak noise"	→	Re-validation of test methods with „threshold" criterion in SST. S/N criterion for new methods.

Comparability strategy
III. Bridging concept

Performance using 4 representative methods

CGE UV for | CGE PDA rev | CGE LIF for | CZE UV for 8 Hz
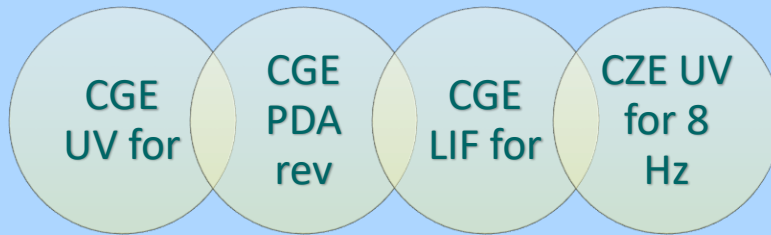
Parameters covered by Bridging
Method Type
Method mode (forward/reverse)
Detector type
Injection type (pressure/elektrokinetic)

➔ Other parameters are not control related

or covered by I. Instrument qualification

or covered by II. Test case

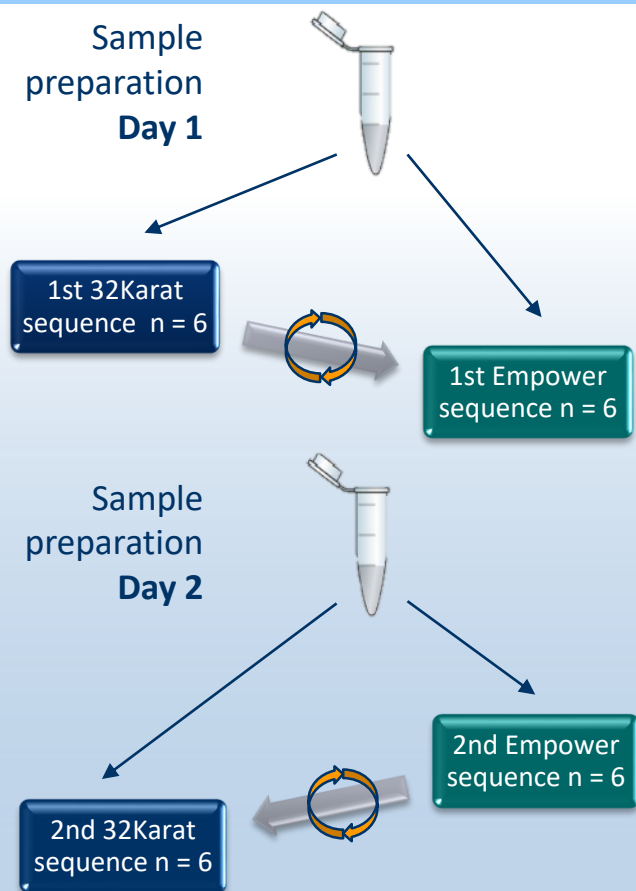| Other parameters |
| --- |
| Aperture |
| Reduced/non-reduced sample preparation |
| Capillary length |
| Wavelength |
| Sample storage temperature |
| Data acquisition |

Comparability strategy
III. Bridging – CGE UV forward method

Experimental setup

One CE instrument - 2 identical sample preparations - 4 identical consecutive sequences

Sample preparation **Day 1**

1st 32Karat sequence n = 6

1st Empower sequence n = 6

Sample preparation **Day 2**

2nd 32Karat sequence n = 6

2nd Empower sequence n = 6

#	Preparation Date	Test Documentation	Sequence Name	Sequence Start Date	Software
1	23.04.18	RL3016/582	CGE-MaK0038	23.04.18	32Karat
2		RL3016/582	180423_RL3016_582		BIChrom
3	24.04.18	RL3016/583	180424_RL3016_583	24.04.18	BIChrom
4		RL3016/583	CGE-MaK0040		32Karat
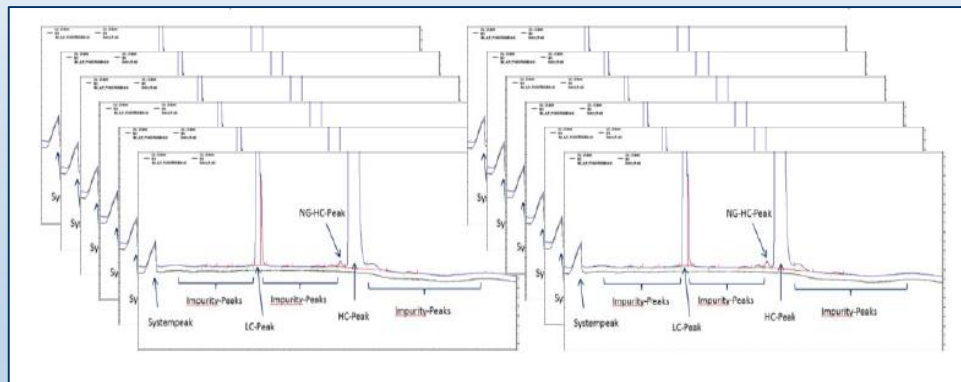
12 test results – 32Karat
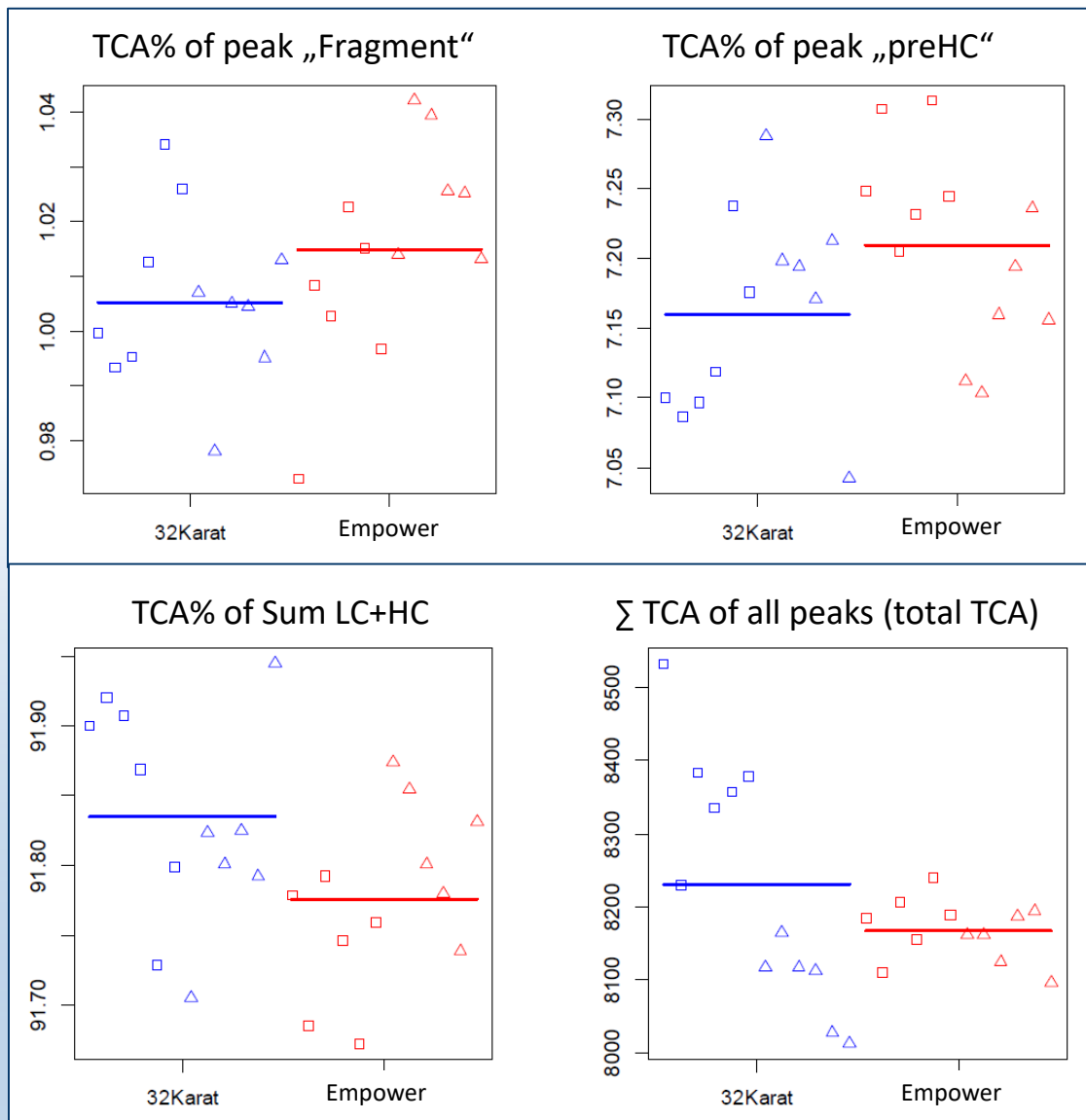12 test results - Empower

Comparability strategy
III. Bridging – CGE UV forward method

Statistical comparison
n = 12 per software

❖ Visualization of data points

❖ Evaluation against acceptance criteria based on historical data

Squares: 1st sequence
Triangles: 2nd sequence

Boehringer
Ingelheim

Comparability strategy
III. Bridging – CGE UV forward method

Data evaluation
SST criteria and parameters relevant for reporting, e.g. %TCA, total TCA, USP resolution, migration time

Method	Parameter	Peak	Mean difference	Criterion $2 \times SD_{hist}$	ACCURACY $\|Mean\ Karat - mean\ BIChrom\| < 2 \times SD_{hist}$	
CGE UV	%TCA	Fragment	0.010	0.073	0.010 < 0.073	pass
		pre-HC	0.049	0.183	0.049 < 0.183	pass
		LC+HC	0.059	0.228	0.059 < 0.228	pass
	Total TCA	All	64	2567	64 < 2567	pass
	USP resolution	Between HC and pre-HC	0.018	0.060	0.018 < 0.060	pass

All criteria passed for all 4 representative methods.

Method	Parameter	Peak	CV 32 Karat [%]	CV BIChrom [%]	$2 \times CV_{hist}$ [%]	Precision $CV\%\ 32 Karat < 2 \cdot CV\%_{Hist}$ (For information only)	Precision $CV\%\ BIChrom < 2 \cdot CV\%_{Hist}$	
CGE UV	%TCA	Fragment	1.502	1.860	7.361	1.502 < 7.361	1.860 < 7.361	pass
		pre-HC	1.003	0.940	2.579	1.003 < 2.579	0.940 < 2.579	
		LC+HC	0.082	0.067	0.249	0.082 < 0.249	0.067 < 0.249	
	Total TCA	All	2	1	29	2 < 29	1 < 29	pass
	USP resolution	Between HC and pre-HC	1.020	0.212	3.957	1.020 < 3.957	0.212 < 3.957	pass

Comparability strategy
Overview

Boehringer
Ingelheim
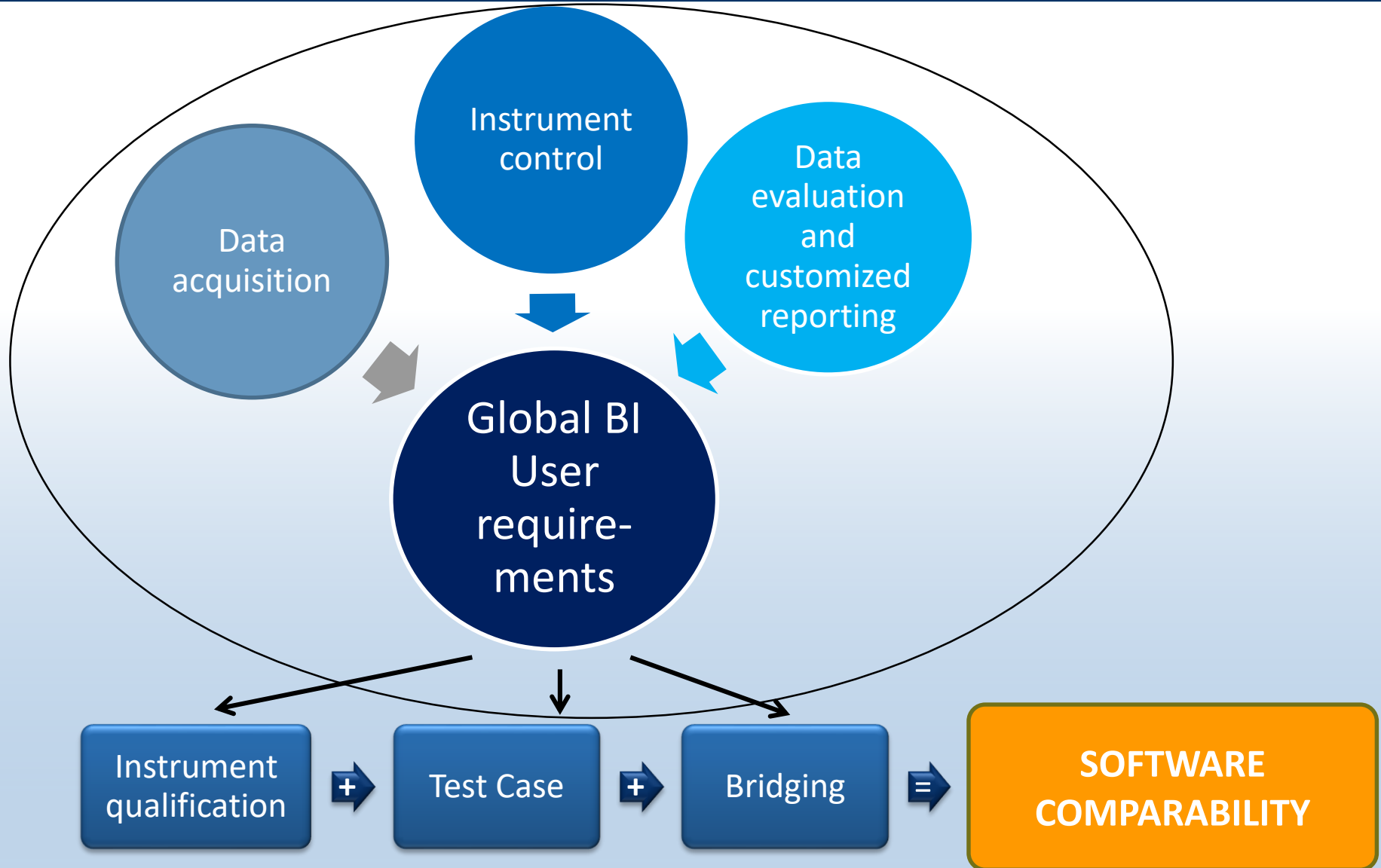
Product-specific role-out for a typical CE-SDS application

Boehringer Ingelheim

Product-specific role-out

General CE documents – Implementation of Empower
- CE Maintenance
- CE PQ document
- CE Handling
- General SST document

Pre-requisites

Step 1 — Method validation

Re-validation of threshold/peak noise, if established as SST criterion

Step 2 — Test method

Setup of method and report in Empower

Revision of SOP to adapt to Empower workflow

Step 3 — Regulatory documents

Mainly marketed drugs

2.1.S.4.2 Analytical Procedures

2.1.4.3 Validation of analytical procedures

Acknowledgement to the CE Empower Team

Manuel Birke	Kerstin Müller
Anja Brauchle	Yao Shu
Marian Gruener	Annette Sieron
Brigitte Gund	Johannes Sommer
Tina Kohn	Patricia Wagner

Thank you for your attention!

Boehringer Ingelheim