The 7 truths of impurities and their reference standards – FDA's and other regulators' viewpoints and further stories (Part 1)

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Webinar Series 2013
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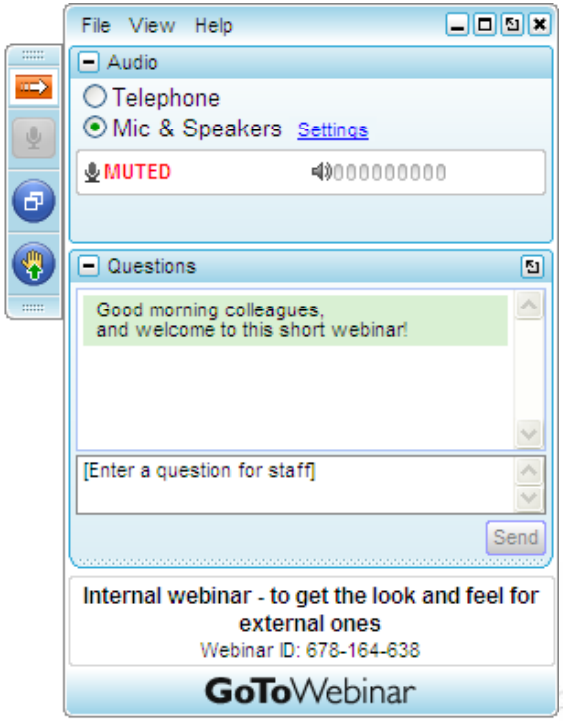
Quick guide to the webinar tools



Content

LGC Standards

Excellence through measurement

- ICH guidelines Q3A and Q3B on impurities are to be applied to generic drugs as well
- An incompletely characterised impurity reference standard might be cheap, but could result in a large amount of hidden costs
- It is not correct to assume an assay of 100% for a USP reference standard when there is no assay information on the label
- Pharmacopoeial monographs might change, and so might the supply of impurity reference standards
- Regulators accept our impurity reference standards
- Impurity descriptions from pharmacopoeias will not necessarily match each other
- Our impurity reference standards can be used universally, and might be less expensive than you think

Our

truths of impurities and their reference standards

Truth #1 – ICH Q3A and Q3B to be applied to generics

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- ICH: International Conference on Harmonisation
  - Members from regulation authorities and industrial pharmaceutical associations
    - From Japan, USA and Europe
- Three ICH Guidelines important (www.ich.org)
  - Q3A(R2): Impurities in new drug substances
  - Q3B(R2): Impurities in new drug products
  - Q3C(R5): Impurities – Guideline for residual solvents
  - A fourth one (Q3D) on heavy metal impurities to come

Truth #1 – ICH Q3A and Q3B to be applied to generics

- Europe
  - European Pharmacopoeia (Ph.Eur.)
    - Two documents of importance:
      General monograph *Substances for pharmaceutical use* (**2034**)
      General chapter *Control of impurities in substances for pharmaceutical use* (**5.10.**)
    - Above documents link applicable
      Ph.Eur. monographs (new monographs) to ICH Q3A and its thresholds

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/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)
> 2g/day	0.03%	0.05%	0.05%

Truth #1 – ICH Q3A and Q3B to be applied to generics

- Europe
  - European Medical Agency (EMA): Guideline on *Control of Impurities in Pharmacopoeial Substances (CPMP/QWP/1529/04)* from 2004
    - Guideline requests that marketing approval for medicinal products should only be granted when referred-to monographs for pharmacopoeial ingredients are compliant with **2034** and **5.10.**
    - Also the guideline requests that EDQM should not grant CEPs (certificates of suitability) based on old monographs not compliant with **2034** and **5.10.**

Truth #1 – ICH Q3A and Q3B to be applied to generics

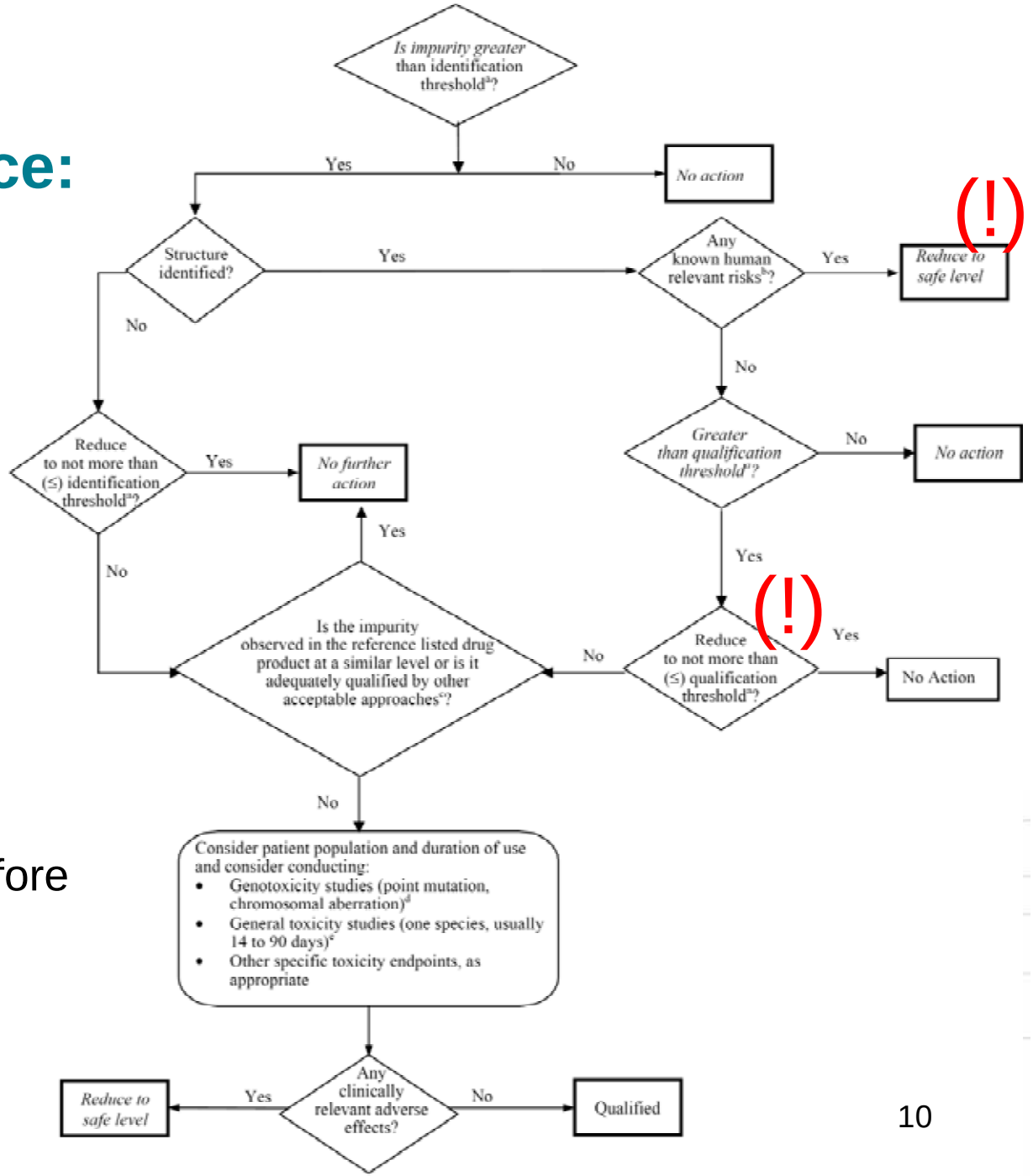
- USA
  - FDA issued two guidances for industry *ANDAs: Impurities in drug substances / products*
    - June 2009 (drug substances), November 2010 (drug products)
  - Statement there
    - ICH Q3A and Q3B were developed for new drug applications (NDAs)
    - However, FDA takes position that ICH principles are applicable to ANDAs (abbreviated NDAs, i.e. generic products) as well:

      "*FDA believes that much of the content of the Q3A(R) guidance applies to ANDAs. See especially sections I through V and the Attachment, Thresholds*."

New FDA impurity guidance: Relevant points

- Setting acceptance criteria
  - First point of reference: Pharmacopoeias (namely USP)
    - If impurity specified in USP, then specification there should be kept
    - Probably other pharmacopoeia specifications would be acknowledged as well
    - If pharmacopoeia specification cannot be kept then impurity enters into qualification process
  - If impurity is not specified in compendia
    - Use decision tree provided (based on ICH design)

New FDA impurity guidance: Decision tree



(!)

Check impurity level with a dedicated reference standards before taking further actions!

Truth #3 – Pharmacopoeial reference standards: Incorrect assumption of assay of 100% when nothing is written on label

Truth #3 – Pharmacopoeial reference standards

- Most common pitfalls
  - Not for universal use, only in combination with the compendial books
    - EP CRS and USP RS only designed for (often) just a single purpose
    - Not suitable necessarily for non-pharmacopoeial purposes
    - User is responsible for off-compendial use

Truth #3 – Pharmacopoeial reference standards

- Most common pitfalls
  - Not for universal use, only in combination with the compendial books
    - **USP General Chapter <11> :** "They *(USP Reference Standards)* are explicitly required in many Pharmacopeial assays and tests and are provided solely for such use. Assessment of the suitability for use in other application(s) rests with the purchaser."
    - **General text 5.12., Ph. Eur.:**
      „EPCRS. A substance *(EP CRS)* ... intended for use as stated in a monograph ... of the Ph. Eur.
      ...
      Reference standards are ... suitable for their intended purpose; they are not necessarily suitable for other purposes. ...
      For any purposes other than that for which it has been established, its suitability ... has to be fully demonstrated."

Truth #3 – Pharmacopoeial reference standards

- Most common pitfalls
  - The “assay rumour”:
    “When there’s nothing written on the label, the assay can be taken as 100%.”
    - Not true, misunderstood USP passage (General Notices 5.80.): "Unless a reference standard label bears a specific potency or content, assume the reference standard is 100.0% pure in the *official* application."
    - 100% pure for official use of identification tests does not mean 100% pure for assay purposes outside pharmacopoeia
    - Ph.Eur. not having such a statement, but similar approach in place for some of their quantitatively used impurity reference standards

Truth #3 – Pharmacopoeial reference standards

- Most common pitfalls as regards impurities
  - Pharmacopoeial impurity standards are often designed only for qualitative use
    - Assay then not known, can be far away from 100%
    - Calculation with 100% for non-pharmacopoeial purposes then can result in serious over-estimation of impurities
    - Causing OOS results, unnecessary qualification studies etc.
  - Better use a dedicated impurity reference standard
    - Apart from pharmacopoeia materials
    - Well characterised, with detailed certificate of analysis
    - We supply approx. 3000 of such impurity reference standards

CofA: Impurity RS

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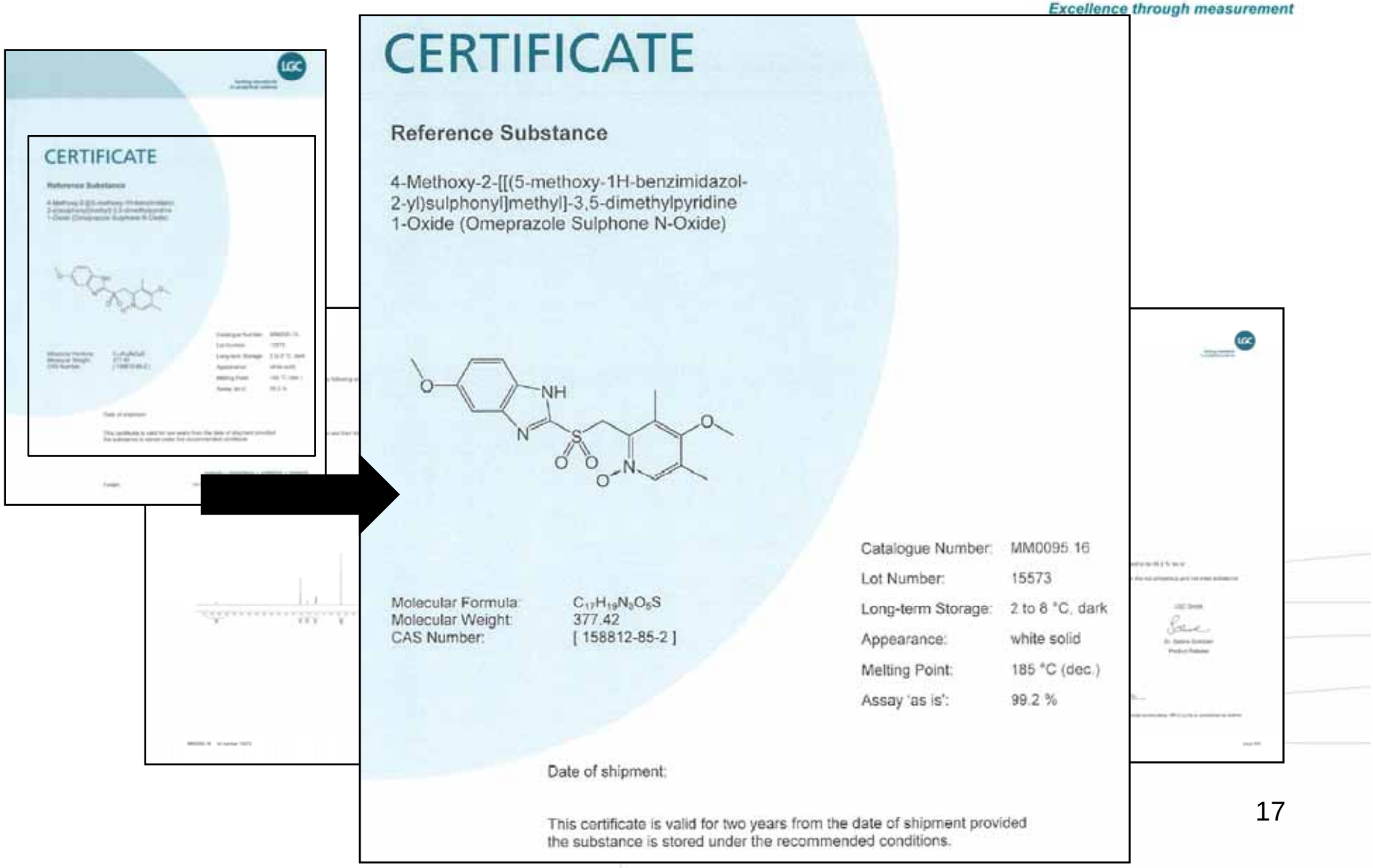
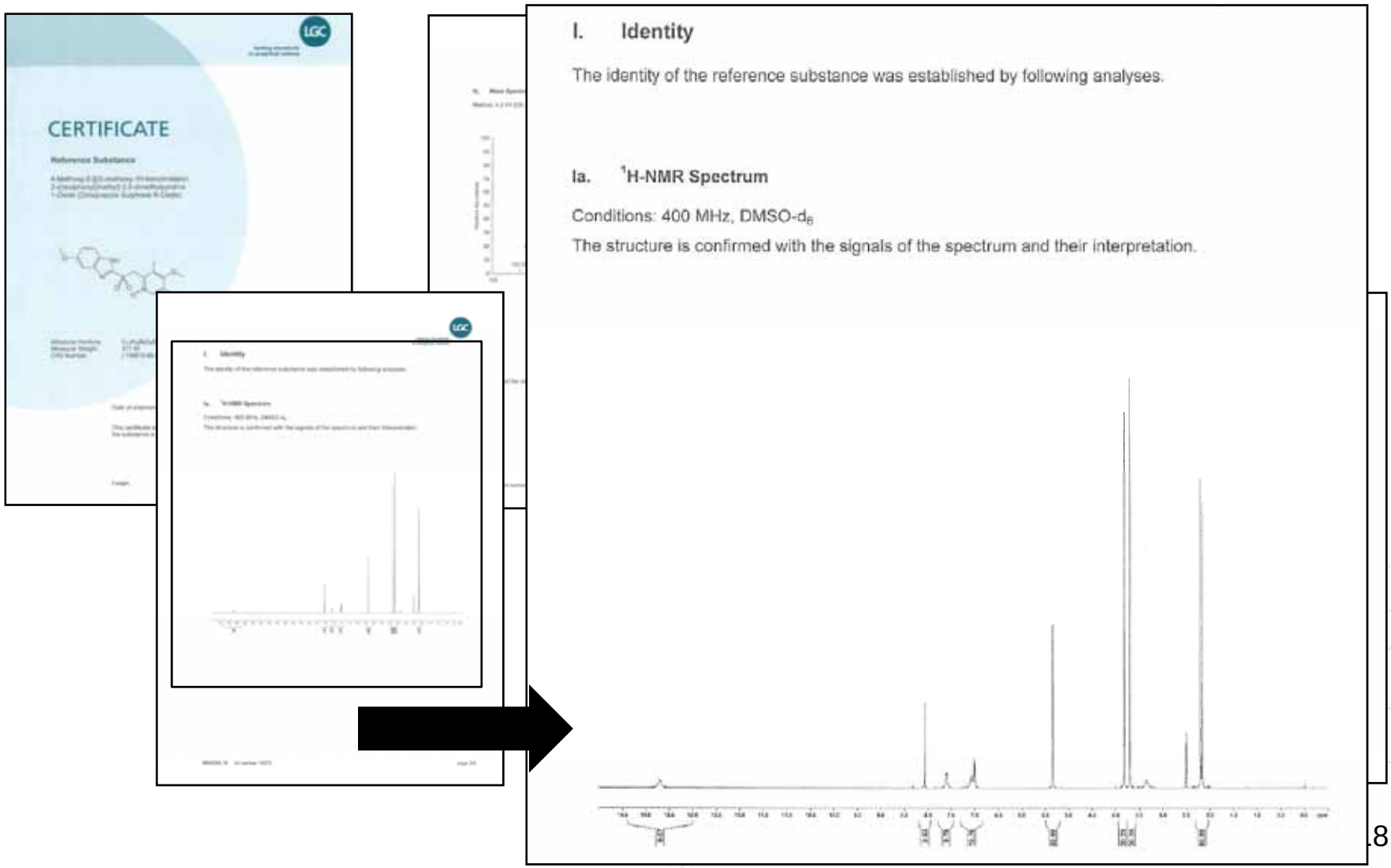
LGC Standards

Excellence through measurement

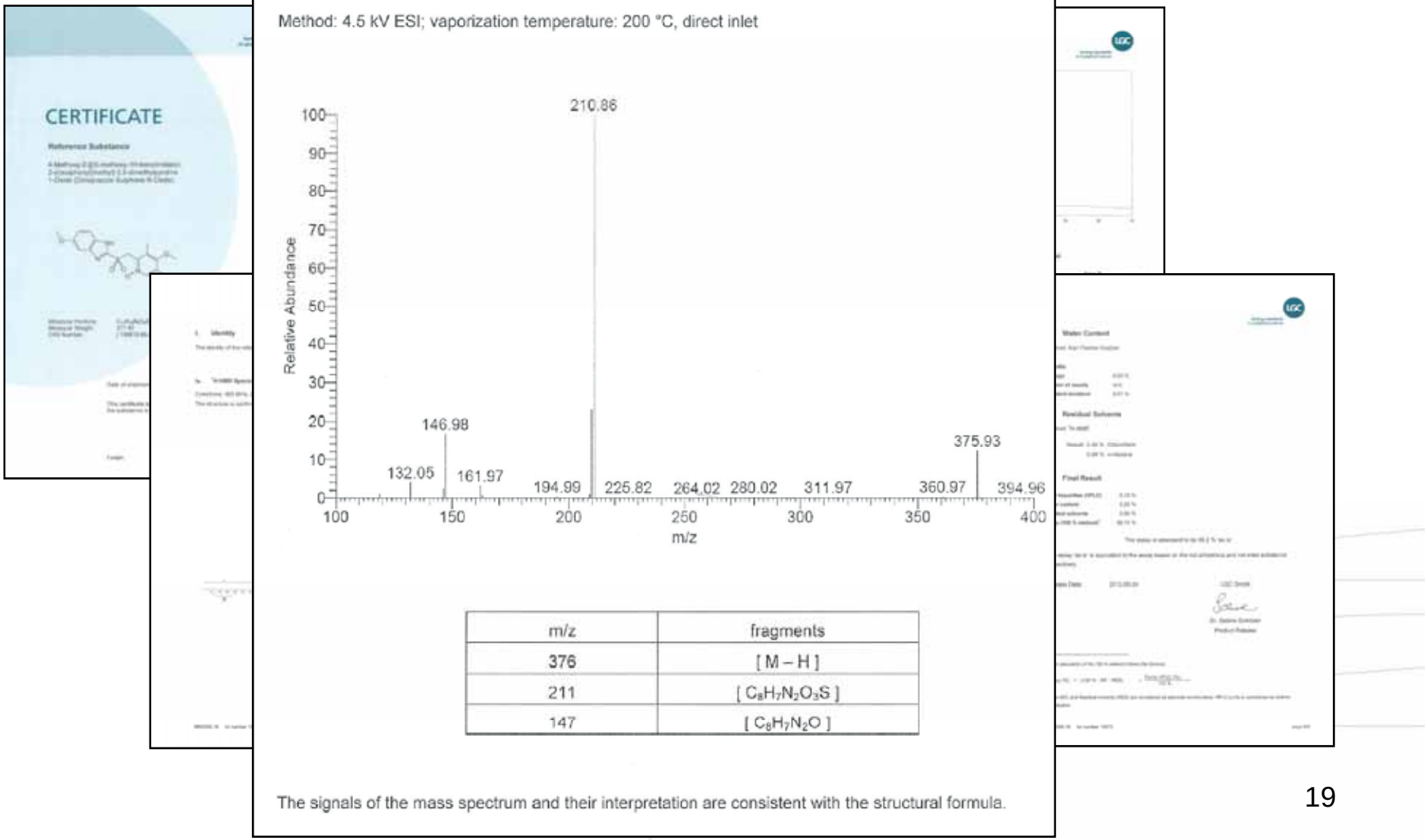


CofA: Impurity RS



CofA: Impurity RS

Excellence through measurement



Ib. Mass Spectrum

Method: 4.5 kV ESI; vaporization temperature: 200 °C, direct inlet

m/z	fragments
376	[M – H]
211	[$C_8H_7N_2O_3S$]
147	[$C_8H_7N_2O$]

The signals of the mass spectrum and their interpretation are consistent with the structural formula.

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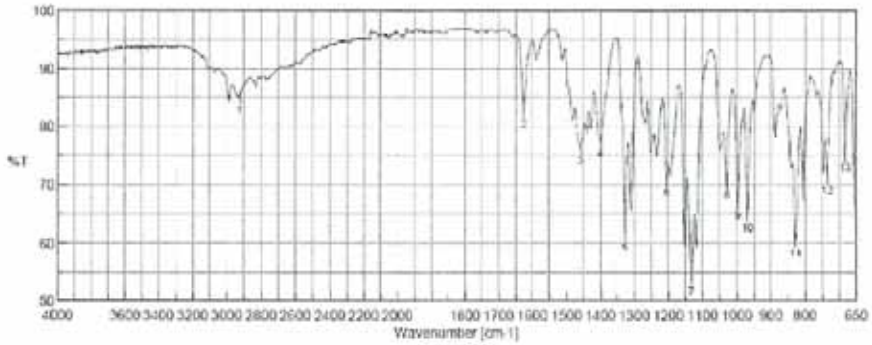
Ic. IR Spectrum

Method: Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) Spectroscopy



Result of Peak Picking

No.	Position	Intensity
1	2925.48	64.8026
2	1824.73	82.8126
3	1458.00	76.1453
4	1400.07	77.3327
5	1326.79	61.9716
6	1204.33	70.5593
7	1132.01	53.7540
8	1028.84	70.1759
9	936.053	66.711
10	869.056	64.5746
11	828.277	60.3426
12	735.71	71.0276
13	682.677	74.981

The signals of the IR spectrum and their interpretation are consistent with the structural formula.

II. Purity

The purity of the reference substance was analysed by high performance liquid chromatography (HPLC).

HPLC Conditions:

Column:	Conditions:	Detector:	Injector:
Hypersil Gold (C18)	1.0 ml/min, 40 °C	DAD	Auto
5 µm, 150 x 4.6 mm	0 – 15 min Water/Acetonitrile 80/20 15 – 20 min Water/Acetonitrile to 60/40 20 – 25 min Water/Acetonitrile 60/40 25 – 30 min Water/Acetonitrile to 80/20 30 – 35 min Water/Acetonitrile 80/20 (v/v); 0.1 % H_3PO_4	220 nm	5 µl; 0.0654 mg/ml in Water/Acetonitrile 50/50 (v/v)

LGC Standards

Excellence through measurement

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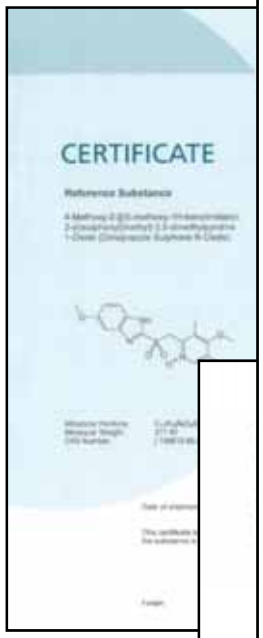
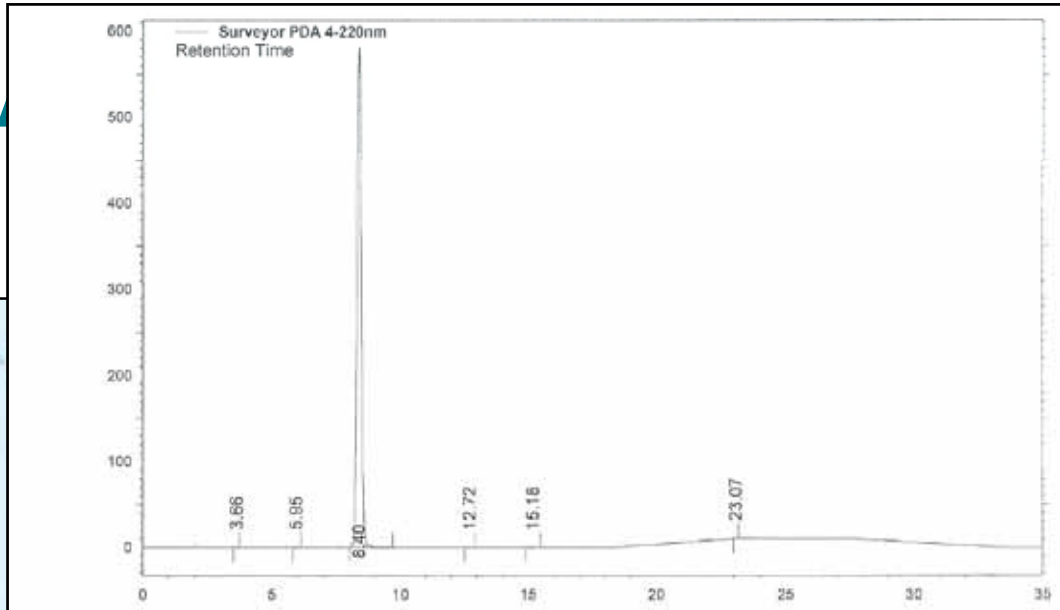




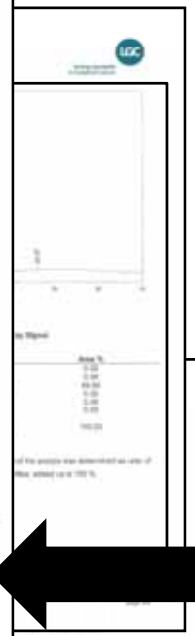
Area Percent Report - Sorted by Signal

Pk #	Retention Time	Area	Area %
1	3.66	1422	0.02
2	5.95	2481	0.04
3	8.40	6745401	99.85
4	12.72	1480	0.02
5	15.18	3383	0.05
6	23.07	1693	0.03
Totals		6755860	100.00

For the calculation the system peaks were ignored. The content of the analyte was determined as ratio of the peak area of the analyte and the cumulative areas of the purities, added up to 100 %.

Results:

Average	99.85 %
Number of results	n=3
Standard deviation	0.01 %



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III. Water Content

Method: Karl Fischer titration

Results:

Average	0.20 %
Number of results	n=3
Standard deviation	0.01 %

IV. Residual Solvents

Method: ^{1}H-NMR

Result: 0.46 % Chloroform
0.04 % *n*-Hexane

V. Final Result

Total impurities (HPLC)	0.15 %
Water content	0.20 %
Residual solvents	0.50 %
Assay (100 % method)[1]	99.15 %

The assay is assessed to be 99.2 % 'as is'

The assay 'as is' is equivalent to the assay based on the not anhydrous and not dried substance respectively.

[1] The calculation of the 100 % method follows the formula:

$$\text{Assay (\%)} = (100\ \% - \text{KF} - \text{RES}) * \frac{\text{Purity HPLC (\%)}}{100\ \%}$$

Water (KF) and Residual solvents (RES) are considered as absolute contributions, HPLC purity is considered as relative contribution.

Truth #5 – Regulators accept our impurity standards

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- For impurity standards, we provide the most detailed certificates available
- Frequently used in dossiers
- Readily accepted by regulatory agencies worldwide
  - FDA in the States
  - EMA in Europe (and national agencies)
  - MHLW in Japan
  - RoW

Truth #7 – Our impurity standards can be used universally, and might be less expensive than you think

Truth #7 – Imps. standards useful universally, less expensive than often thought

- Our impurity reference standards
  - Unit size in most cases 100 mg,
    substances more rare or difficult to synthesise: unit size 50 mg
  - Most customers do not want smaller unit sizes
  - With detailed certificate
    - Identity: NMR (for new batches - since Sept 2011 - also MS and IR data)
    - Organic purity, water, residual solvents
    - Assay calculation
- Can be used in almost any analytical application

Truth #7 – Imps. standards useful universally, less expensive than often thought

- When comparing to other commercial providers
  - On a price per mg basis
    - Other commercial providers often more expensive for their materials, always advisable to check price and documentation beforehand
  - CofA of other providers
    - In most cases deficiencies compared to our CofA
    - No supplier provides more detailed CofA for impurity reference standards

Truth #7 – Imps. standards useful universally, less expensive than often thought

- When comparing to materials from pharmacopoeia commissions
  - Comparison to USP, on a price per mg basis:
    - For most cases, LGC Standards less expensive
    - Furthermore detailed CofA is provided for LGCS impurities
    - USP materials with restricted use
  - Comparison to Ph.Eur, on a price per mg basis:
    - In most cases, Ph.Eur. cheaper
    - But no certificate provided with Ph.Eur. materials
    - Very restricted use for Ph.Eur. materials

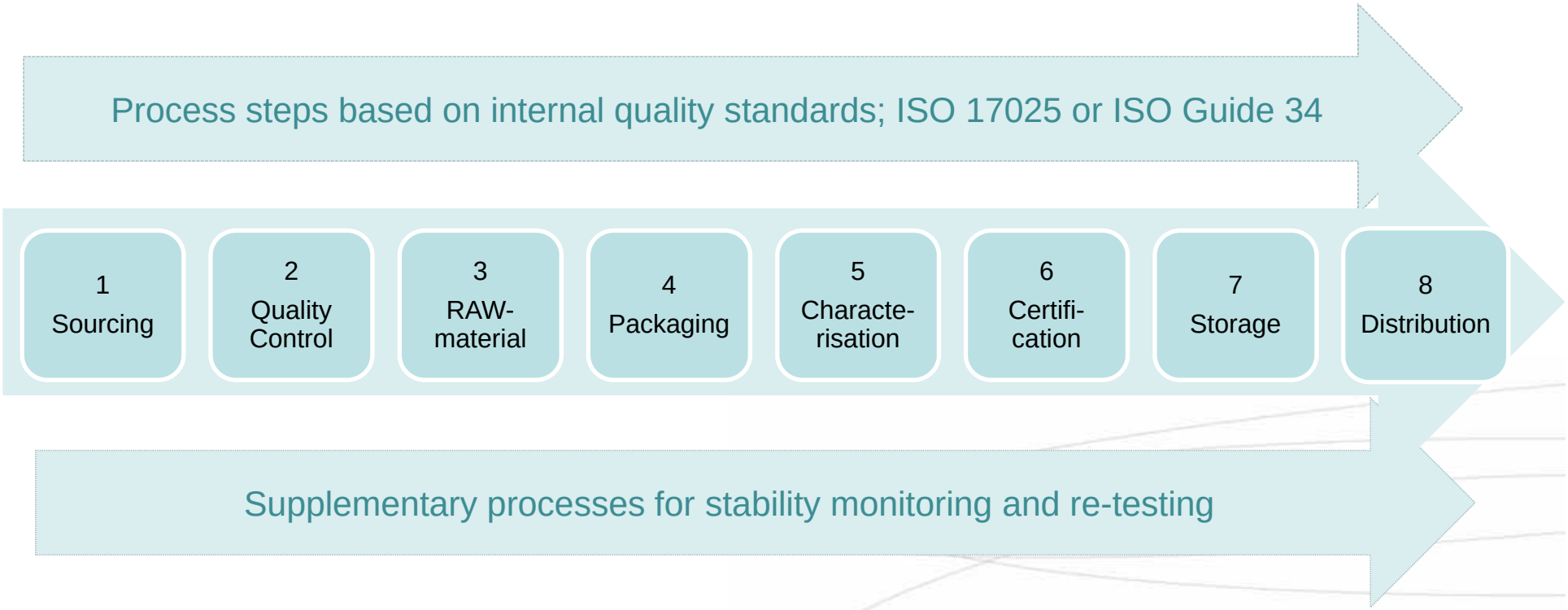
Closing remarks

- LGC Standard is part of LGC group
- S&T section of LGC acts as NMI for chemical and biochemical measurement in the UK (comparable to NIST in the US)

Closing remarks

- Manufacturing of pharmaceutical reference materials
  - For APIs and impurities, over 3,000 standards
  - Metal impurity materials (suitable for ICP-OES and ICP-MS applications)
  - Constantly new developments
    - **Launch of primary standard catalogue products in October 2013!**
  - ISO 34 and ISO 17025 accredited
- Contract services
  - Custom synthesis (for RSs)
  - Custom analysis
  - Characterisation of customer material
  - Customised packaging and storage

Service modules



Closing remarks

- Further webinars in July/August, registration possible under http://pharma.lgcstandards.com/
  - On website, look under ‘Events’
    Always on a Thursday, always 10.30 – 11.15
    - 1st of August 2013:
      Seven truths of impurities and their reference standards, Part 2

QUESTIONS?

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Now, or to christian.zeine@lgcstandards.com