Bioanalysis in China:

working in the intersection of global regulations and OECD-GLP

Philip Timmerman, on behalf of EBF

Outline

1. Overarching principles of working in a regulated environment.
2. Working in a regulated environment applied for bioanalysis
3. China
4. Conclusion

1. Overarching principles of working in a regulated environment

Some questions to ask:

A. Which Guidelines regulate your business?

B. Who regulates you?

- From a ‘Guidance’ perspective.
- From an ‘Accredition’ perspective.
- From an ‘Inspection’ perspective.

C. Who are your business partners?

D. What does succes look like?

A. Which Guidelines regulate your business?

1. Guidelines directly related to your business
   - Specific Guidelines
   - Include general Guidelines related to your industry
2. Guidelines related to your business partners
   - Include Guidelines related to their industry in general
3. Guidelines overarching from your industry
   - Country specific
   - Health and Safety specific
4. Others

B. Who regulates you?

- Health Authorities (HA)
  - Different regions, countries?
- Other Government bodies
- Sometimes Industry itself

Understand difference between:

1. Global guidelines
   - At most, ICH Guidelines; but are they really global?
2. Regional guidelines applicable **when filing** in a region
   - Will/can be inspected @ time of filing in that region
3. Regional guidelines applicable **when operating** in a region
   - Depends on region, never or regularly inspected even without filing
   - May be subject to accreditation

C. Who are your business partners?

- Your colleagues – your stakeholders
  - Discovery, (pre)clinical colleagues
  - Your sponsors
- Peers
  - in your company
  - in industry
- Departments you support
- Departments supporting you
  - don’t forget QA
- HA
- others?

D. What does succes look like?

1. Communicate:
   - Inform your peers and business partners:
     - Provide insight in your technology, including objectives/hurdles
     - Provide insight in the guidelines that regulate your business
   - Get informed
     - Identify regulations pertaining to you
     - Understand objectives/regulations of your business partners
     - … on the when and what way and how of inspections.
2. Interact:
   - With your business partners
   - Create opportunity for interaction with the HA
     - Who regulate in your region
     - Who regulate in the region of your business partners

2. Working in a regulated environment applied for bioanalysis

Most people outside bioanalysis connect regulations for bioanalysis with 2001 FDA BMV Guidance

…but, it is more complex…

Guidelines directly related to Bioanalysis

Some questions to ask

- What regulates you?
- Who regulates you?
  - From a 'Guidance' perspective
  - From an 'Accredition' perspective
  - From an 'Inspection' perspective
- Who are your business partners and apply above questions on that relationship.

- FDA
- EMA
- *MHLW*
- *Anvisa*

Is that all?

- FDA BMV Guidance, 2001
- EMA BMV Guideline, 2011
- *ANVISA BMV Guideline 2012*
- *MHLW 2013 Small*

- Receiving authorities gobally *(can be 'live' (e.g. FDA) or 'remote' (most others)*
- Monitoring authorities cfr. OECD

- For CRO: Pharma customers
- Generally: Discovery teams, (pre)clinical department

Impact of Regulations of your BP on you?

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Is that all?

In addition to primary Guidelines:

- Publications (‘01/’03) authored by industry on LBA - accepted as best practice by FDA
- Publications (‘07/’09), co-authored by FDA/industry, but no ‘Guideline’. Some proposals from these publications are welcomed/accepted, others are challenged by industry.
- ‘Hear-say’ at international bioanalytical conferences (AAPS, APA, LoL, Reid, NBC, EBF, WRIB, JBF,...)
- Observations in Form 483s getting translated in industry

Impact of Regulations of your BP on you?

Precinical development: e.g.

- FDA GLP: 21 cfr 58
- OECD GLP: OECD 1-15
- cFDA GLP
- ICH - S3A:Toxicokinetics:
- ICH - M3 (R2): MIST

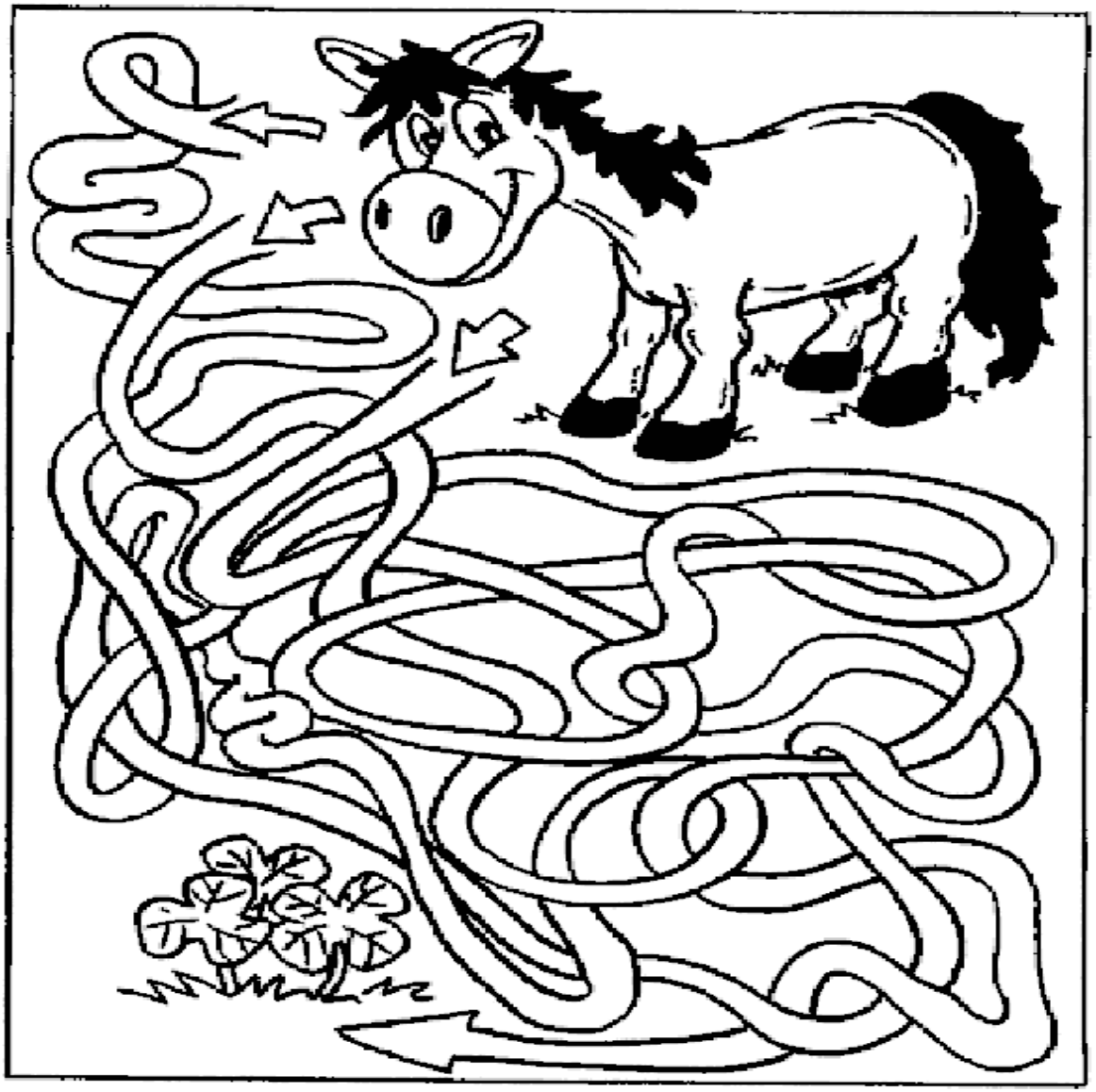
Clinical development: e.g.

- Bioavailability, bioequivalence
  - ✓ FDA: 21 CFR 320.29
  - ✓ EMA: CPMP/EWP/QWP/1401/98
- GCP e.g. ICH - E6:
- MHRA G(C)LP
- EMA GCLP:
  - ✓ EMA/INS/GCP/532137/2010

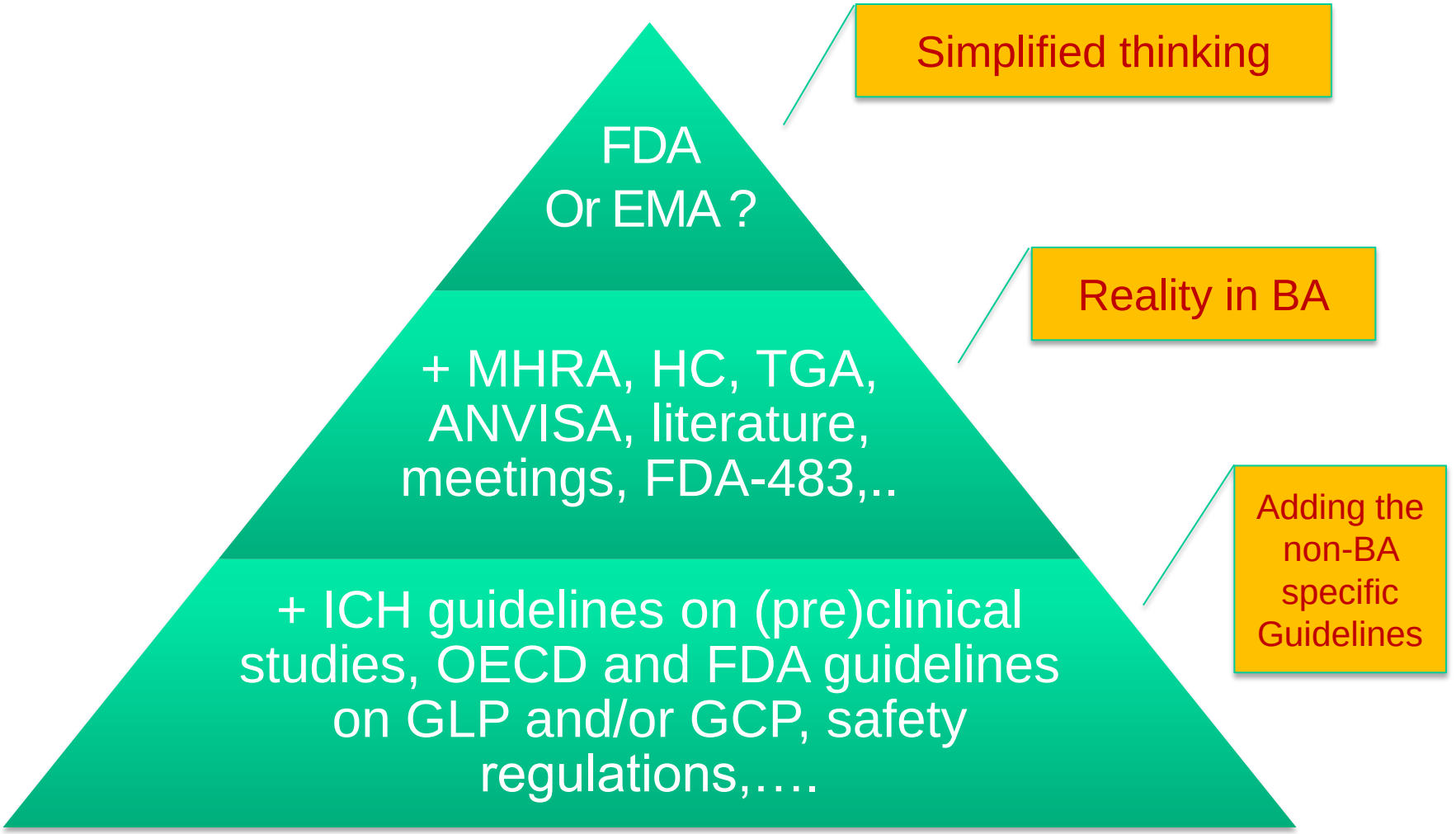
Sub sections or requirements from other HA (Japan, HC, TGA most known to “deviate/add”)

Guidelines overarching your industry

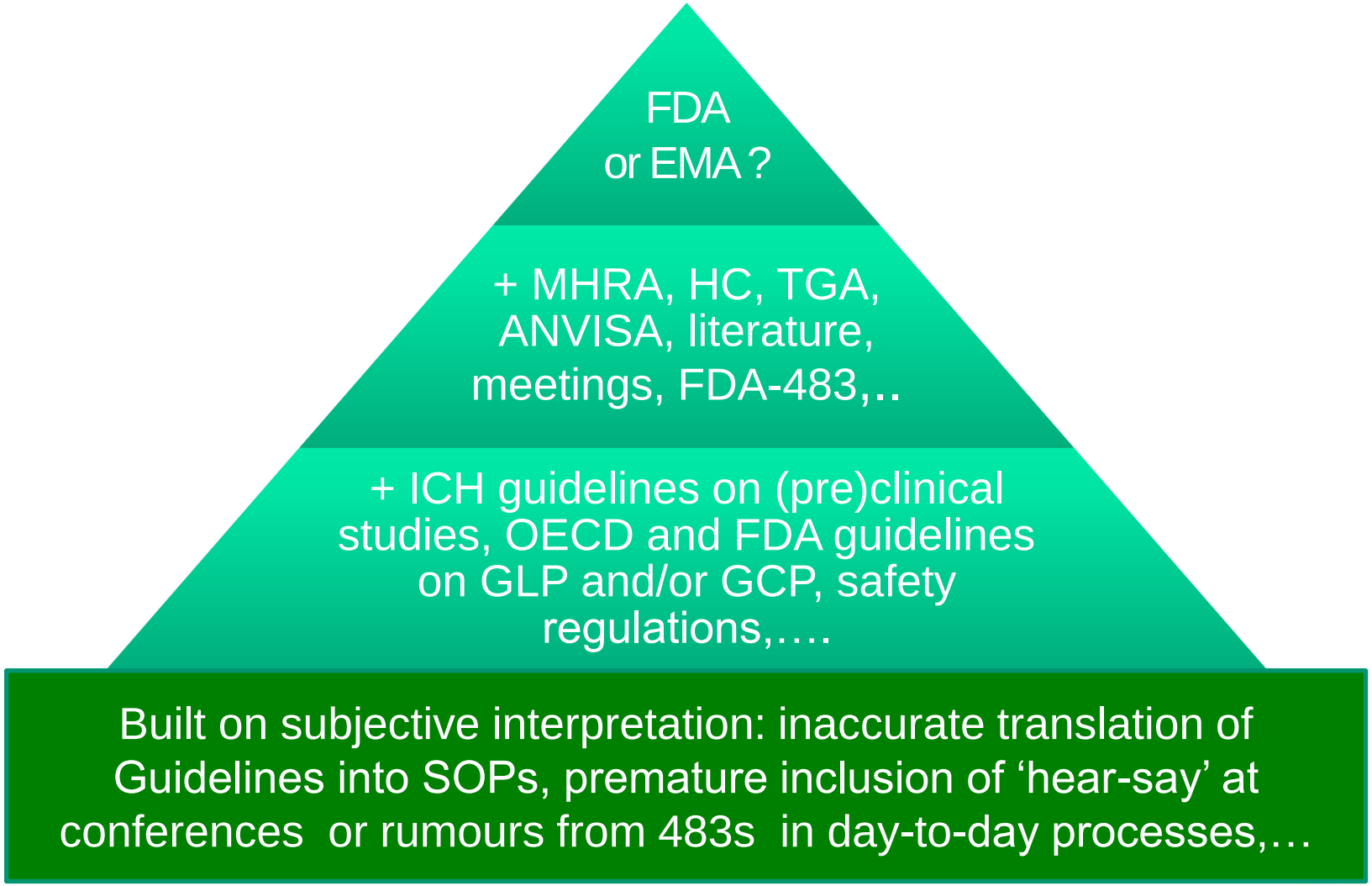
- ISO 9000:2000
- ISO 17025
- FDA guidelines on general principles of process validation
- FDA General Principles of Software Validation; Final Guidance for Industry and FDA Staff
- FDA CFR 21Part 11, Electronic Records; Electronic Signatures — Scope and Application
- Several ICH guidelines related to clinical and preclinical development
- FDA and EMA (draft) guidelines on *in vivo* or *in vitro* testing
- …



From ‘simple’ to ‘reality’



Or surreal


FDA
or EMA ?
+ MHRA, HC, TGA, ANVISA, literature, meetings, FDA-483,..
+ ICH guidelines on (pre)clinical studies, OECD and FDA guidelines on GLP and/or GCP, safety regulations,….
Built on subjective interpretation: inaccurate translation of Guidelines into SOPs, premature inclusion of ‘hear-say’ at conferences or rumours from 483s in day-to-day processes,…

How is this inspected - GLP?

Regular inspections on adherence to Guidelines

- EU: GLP Inspections
  - Based on OECD principles
  - By monitoring authorities per ‘country’
  - 2-3 yearly.

  → Outcome: accreditation to perform GLP studies
- UK: MHRA…adds an additional layer of regional focus
- US: FDA inspections – no accreditation purpose

How is this inspected - Clinical?

Non pivotal studies (early clinical work)

- Part of scientific assessments @ filings, no formal inspection process and no formal push to adhere to regulated standards
- Often industry adheres to regulated standards

Pivotal studies (e.g. BE)

- Part of scientific and regulatory inspections @ filings
  - Can lead to site inspections – e.g. FDA for BE studies
  - Less common for EMA or other inspectorates
- Adherence of industry to EMA and/or FDA regulated standards (EMA, being the most up to date ones = good reference point)

3. How does this relate to China – GLP?

- OECD principles on GLP:
  - Monitoring authorities: Regular inspections by regional inspectorate following OECD principles, for accreditation purposes
  - Receiving authorities: Mutual Acceptance of Data (MAD) of OECD member states in compliance with aforementioned bullet

- China is not an OECD member country:
  - GLP Compliance Monitoring Programmes in China have not been assessed as part of OECD on-site evaluation visit. Consequently, China is not a member of the OECD GLP Working Groups
  - China are not a signatory to the OECD's MAD Agreement and receiving authorities in OECD member states can and sometimes will require inspections on a 'per-filing' basis

→ **Sponsors hesitant to conduct GLP studies in China because of risk of delay in filings (not necessarily risk of quality)**

3. But…Non-OECD Member adherence to MAD

- was agreed in 1997 → as a consequence, full OECD membership is not a requirement for MAD
- separate agreements have been developed to include individual non-OECD member countries to subscribe to OECD GLP principles and join the MAD
  - E.g. South Africa, India – example. see web link http://www.oecd.org/chemicalsafety/testing/mutualacceptanceofdatamad.htm

→ **This may be a valuable evolution for China GLP and preferred above single OECD member countries preforming isolated GLP inspections**

Some recent developments for GLP

CTFG agreed on following with regards to the requirements for pivotal non-clinical studies submitted in CTAs:

- In accordance with EU Directives [1,2,3,4,5], applicants are reminded that all pivotal non-clinical studies (*i.e.* those studies identified in ICH guidelines as needing to be carried out in accordance with the principles of good laboratory practice) conducted to support submissions for Marketing Authorisation Applications (MAA) and Clinical Trial Applications (CTA) must be conducted in, or inspected by, a country that has implemented the OECD Mutual Acceptance of Data (MAD) system.
- Studies conducted at a facility located in a non-MAD adherent country may be accepted if the facility has been subject to a full monitoring inspection conducted in the last three years by a monitoring authority from a country which is a signatory to the MAD agreement. However, if the study is considered to be pivotal to the application, there is a possibility that a study audit will be required by some regulatory receiving authorities at the time of a MAA.
- As applications for CTAs do not include individual study reports, sponsors should include a statement confirming the OECD GLP status, either within the Investigator's Brochure (IB) or within the covering letter.

References

1. EU Directive 2001/83/EC - Community code relating to medicinal products for human use.

2. EU Directive 2004/10/EC - on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (codified version)

3. EU Directive 2004/9/EC - on the inspection and verification of good laboratory practice (codified version).

4. EU Directive 87/18/EEC – on the Harmonisation of Laws, Regulations and Administrative Provisions Relating to the Application of the Principles of Good Laboratory Practice and the Verification of their Applications for Tests on Chemical Substances.

5. EU Directive 88/320/EEC - on the Inspection and verification of Good Laboratory Practice.

Additional challenges of working in a Chinese regulated BA environment, incl. Clinical

Regulations

- Difference in SFDA vs OECD/US GLP
- Absence of Chinese regulations for BA in general
  - For clinical BA, until today only sporadic FB from e.g. EMA and FDA @ filings – mostly positive
  - Open question and unrelated to China: is the BA community (and in extension, the patient) served by another set of guidelines or do we want to stimulate the globe for ICH involvement on BA guidelines
- "China for China" (CfC)
  - Not always preformed in line with global standards.
  - Difficult to control if CfC studies enter global filings via a backdoor and create a risk

Additional challenges of working in a Chinese regulated BA environment

- Communication
  - Time zones difference to EU or US
  - Language - culture
- Logistical - sample
  - Sample import/export process variable and lacks transparency
  - Sample can be held up at customs
  - Some materials take time for purchasing
- Cost – full cost: not necessarily in favor anymore
  - Increasing wages
  - Sample shipping cost with premier courier
  - Some materials expensive
- Security
  - Data privacy
  - Intellectual Property issues?

4. Conclusion

- Regulations are often complex, non-specific to your day-to-day questions and interconnected across disciplines
- Good understanding of interplay between Guidances can separate real vs. assumed regulatory requirements
- Global BA community would welcome emerging Chinese BA regulations to harmonize with global standards.
- Building peer communities can add value to
  - Stay abreast with science, technology and regulations
  - Getting a broader perspective on regulations
  - Fostering a HA – Industry discussion

Acknowledgment

The EBF Community

http://www.europeanbioanalysisforum.eu/