Global Biologics Regulatory Trends

Challenges and Opportunities.....

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VP, Regulatory Policy and International Operations

F.Hoffmann La-Roche, Basel, Switzerland
N-linked Oligosaccharides Analysis by CE

Excess APTS Reagent

IS = internal standard maltoheptaose

CE-SDS / LIF: Silver Staining Sensitivity

Therapeutic rhuMAb

CE conditions:
Fused silica capillary
50 µm x 24 cm;
SDS run buffer (Bio-Rad);
20° C; reversed polarity,
15 kV; Argon-Ion laser,
480 nm excitation / 560 nm emission.

Outline

• Hurdles to Innovation
• Emerging global trends
• Case Study: Life Cycle Management
• Priorities for Biotech
Regulatory environment requires convergence

*Fragmented landscape delays innovation*

- One global submission can lead to **several** separate registration dossiers with different content
- **Complexity for post-approval changes leads to long/unpredictable timelines**

Represents one dossier (for one product)
Approval of a new Biologic through the global systems can take years*

*Gap in years between US approval and most of the world*
Bringing a post–approval change through the global systems can take years*

*example: manufacturing site-transfer for a biologic drug substance
## Development of Modern CE Applications for Biologics

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<tr>
<th>Year</th>
<th>Event</th>
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<tr>
<td>1981-1983</td>
<td>Initial Publication of “Zone Electrophoresis in Open Tubular Glass Capillaries” in Analytical Chemistry (81), followed by a paper in “Science” (83)—both widely credited with the launch of modern CE</td>
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<td>1983-1988</td>
<td>Increased use in academic labs and few characterization or feasibility studies in industry (often in collaboration with academic labs)</td>
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<td>1989</td>
<td>First international symposium HPCE (high performance capillary electrophoresis) held in Boston with the introduction of first commercial CE instruments, indicating growing use within academic centers—First conference was chaired by Prof Barry Karger at Northeastern University</td>
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<td>1997</td>
<td>Submission and approval by the FDA of two CE methods to be used as part of the control system QC release for a MAB—cIEF (identity) and Glycan analysis</td>
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<td>1999</td>
<td>First mention of “CE” in ICH Q6B in appendix 6.1.2 (c)</td>
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<tr>
<td>2001-2005</td>
<td>Advances in instrumentation continued with significant expansion in applications (including CE-MS for Characterization), imaged cIEF and the introduction of platform methods</td>
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<td>2006-2010</td>
<td>Method becomes routine, with general chapters being developed in pharmacopeis</td>
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<td>2010-present</td>
<td>ICH Q4B—Global Harmonization of the General Chapter on CE in USP, EP and JP (initial monographs 2006); expansion of routine use; coupling with orthogonal techniques</td>
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</table>
World is Getting Smaller & the Regulatory Environment More Complicated . . .

From Roger Nosal, Pfizer
The Blue Sky Vision on Technical Requirements
Biotech Industry supports efforts for harmonization at regional and global levels

- Improvements in supply, quality and safety
- Better outcomes for patients
- Global access for innovative pharmaceuticals
Global Regulatory Trends:

Opportunities for accelerated approvals in Emerging Markets

- WHO initiatives on “Good Regulatory Practice” and “Regulatory Systems Strengthening” will facilitate the implementation of approval processes based on “reliance” and “work sharing”

- ICH reform as truly global will accelerate convergence, mostly for Roche key EM’s

- Formation of regional clusters with ambitious plans for work sharing, joint assessment - Establishment of regional guidance based on ICH/WHO

All of the above may shorten global approval timelines and increase predictability
WHO Governing Bodies ...
Global convergence in action.....

- **WCBP, Jan. 2013 DC,**
  (Session: operating globally)

- **CMC forum EU May 2014**

- **CMC forum Japan Dec. 2013**
  (FDA asked for challenges when filing globally)

- **CMC forum Japan Dec. 2012**

- **CMC forum LATAM Aug. 2014**
  (Session: Managing global complexity)

- **CMC forum LATAM Aug. 2014**
  (Challenges of global LCM)

- **Middle East Regulatory Workshop, Nov 2014**

- **Seoul, Sept. 2013**

- **APEC/WHO implementation workshops, Seoul, May 2014 and July 2015**

- **Ottawa, Oct. 2013**

- **WCBP US Jan. 2014**
  (Session: Managing global complexity)
3. Post-approval changes for biotherapeutics - Guidelines under development

- **Updates during life-cycle of products:**
  - Changes after licensure, often improvements, e.g. manufacturing process, state-of-the-art controls
  - Request demonstration of comparability of pre-change and post-change product (comparability exercise)

- **Development of the document has been initiated:**
  - in response to requests from regulators and manufacturers, and in line with WHA 67.21, ICDRA, APEC Harmonization Center initiative
  - 1st round public consultation – planned for Dec 2016 – Jan 2017
  - Consultation with regulators, manufacturers and other experts – April 2017
  - 2nd round of public consultation: July – Sep 2017
  - Submission to the ECBS for review in Oct 2017
Unique Landscape of Asia Pacific with APEC 2020 and ASEAN

21 APEC countries for Convergence: 7 from ASEAN + Taiwan, Korea, China, Japan, Hong Kong, Australia, New Zealand, Papua NG, Peru, Chile, Canada, US, Mexico and Russia
ICDRA* 2016 Key Theme and WHO Initiatives

PATIENTS ARE WAITING: HOW REGULATORS COLLECTIVELY MAKE A DIFFERENCE

STRENGTHENING REGULATORY SYSTEMS THROUGH CONVERGENCE, RELIANCE AND NETWORKS

World Health Organization

ICDRA

17th International Conference of Drug Regulatory Authorities
Cape Town, South Africa: 27 November - 2 December 2016
"Access to quality, safe, and efficacious vaccines, biotherapeutics, and other biologicals is critical. To achieve that, further development of expertise and capacity is a must. Work sharing among regulators and convergence are the way forward."

Dr Ivana Knezevic
Group Lead, Norms and Standards for Biologicals, WHO
WHO Good Regulatory Practices
Focus on international regulatory cooperation

- Agencies have institutional, technical and human resource issues and their capacities and expertise are challenged.

- Recognizes the need for international cooperation, in all its forms.
The way forward for Africa: The African Medicines Agency

2018: AMA Launch
Can Expansion of ICH Guidelines Improve Harmonization/Convergence?

From Roger Nosal, Pfizer
China, is the 2nd Largest Pharma Market With Fundamentals in Place For Future Growth

Growing Pharma Market

<table>
<thead>
<tr>
<th>2015 Top Pharma Markets</th>
<th>'15~'20 CAGR</th>
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<tbody>
<tr>
<td>USA</td>
<td>416</td>
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<tr>
<td>China</td>
<td>108</td>
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<tr>
<td>Japan</td>
<td>78</td>
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<td>Germany</td>
<td>40</td>
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<tr>
<td>France</td>
<td>30</td>
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Increased Healthcare Spend

<table>
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<tr>
<th>Healthcare spend bCHF/ % of GDP</th>
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<tbody>
<tr>
<td>USA</td>
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<tr>
<td>China</td>
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<td>Japan</td>
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<td>Germany</td>
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<td>France</td>
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Huge Unmet Medical Needs

- 25% of the world's cancer patients are from China
- >80% are still treated by chemo therapy only
- Oncology novel therapies are mostly not yet reimbursed

Improved Regulatory Environment

- Availability
  - Accelerated drug review and approval process
- Accessibility
  - Improved medical infrastructure
- Affordability
  - Expanded critical illness coverage and NRDL update

NRDL – National Reimbursement Drug List
Source: National Bureau of Statistics of China, IMS database
China Environmental Changes

CTA Accelerated to 8-14 Months / 60 days...target???

Loosened Case by Case

300

Transparent Predictable

Enabling Global Clinical Development
Approval of a new Biologic through the global systems can take years*

Time (years)

0 1 2 3 4 5 6 7

Core ICH countries
ICH-like countries
CPP countries

US

Core ICH Countries

ICH-like Countries
1-3 years

CPP Countries
2-5 years

China**
1 year

China**
5-7 years
ICH Quality Guidelines: A summary

• Since inception of ICH in 1990:
  • 11 (24) Quality Guidelines developed covering most aspects of CMC development requirements
  • 10 Multidisciplinary guidelines (M-series)
• Most effective mechanism for conversion within ICH regions, but with mixed impact in non-ICH regions
• Guidelines evolved from specific technical requirements (stability, validation, specifications, impurities..) to higher level guidance on overall pharmaceutical development…
• Guidelines cover both small molecule and biologicals
Goals for the New ICH

• Focus global pharmaceutical regulatory harmonization work in one major venue

• Create a venue that allows all key pharmaceutical regulatory authorities and industry stakeholders the opportunity to be more actively involved in pharmaceutical harmonization work

• Maintain efficient and well-managed operations and harmonization work process
ICH New Key Members Since Reform

- **Regulatory Members**: ANVISA, CFDA (China), MFDS (Korea)
- **Regulatory Observers**: India, Cuba, Mexico, South Africa, Singapore, Kazakhstan, Russia, Chinese Taipei, Australia
- **Industry Members**: BIO, IGBA, WSMI
- **International Organizations (Observers)**: USP, EDQM, PIC/S
ICH Quality Guidelines: Key Challenges

• Widely differing stability requirements globally despite ICH and WHO guidelines

• Enforcement of local Pharmacopeia requirements that are often not harmonized leading to significant additional work with NO benefit to patient or product quality

• Stage dependent development approach: ICH Q guidelines are not intended for full implementation in clinical development...

• Life Cycle Management....
The Rationale for ICH Q12

- Implementation of Q8-Q11 provides a science- and risk-based approach to postapproval change management
  - Q8-Q11 focus on product development
- Opportunities for flexibility in post-approval change management have not been fully realized
  - Different requirements around the world are a disincentive to making improvements to increase process robustness
- Lack of alignment exists regarding necessary information and level of detail in the regulatory dossier
  - So-called “regulatory commitments” impact on post-approval change management

From Ashley Boam, FDA
Q12 Scope and Objectives

• **Scope**
  - The proposed guideline will apply to pharmaceutical products, including marketed products, chemical, biotechnological and biological products

• **Objectives include:**
  - Provide a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle
  - Optimization of industry and regulatory resources
  - Support innovation and continual improvement and help to assure drug product supply
ICH Q12 Expert Working Group: The NEW ICH.....
Key Regulatory Enablers

- Risk-based Categorization of Changes (section 2)
- Established Conditions (section 3)
- Post approval Change Management Protocols (section 4)
- Product Specific Lifecycle Management Strategy (section 5)
- Approaches to Streamline Changes to Marketed Products (section 8)

Tell and do
PAS, CBE

Do and tell
AR, PQS only
Established Conditions (EC)

• Established Conditions:
  o Legally binding information defined in MAA
  o Any change to EC: requires a regulatory post-approval interaction
  o Any change to a non-EC: does not require regulatory interaction

• EC’s in submission:
  o Agreement on which sections of CTD contain EC’s
  o EC’s and their classification will depend on the extent to which the firm can apply knowledge from product and process understanding to manage the risks to product quality.
  o Allows for the possibility of EC’s to be outputs based...
<table>
<thead>
<tr>
<th>CTD SECTION</th>
<th>SECTION TITLE</th>
<th>ESTABLISHED CONDITIONS – General List with notes</th>
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<tbody>
<tr>
<td>3.2.S.2.4</td>
<td>Control of critical steps and intermediates</td>
<td>Test and acceptance criteria for critical steps and intermediates</td>
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<tr>
<td>3.2.S.2.5</td>
<td>Process validation and/or evaluation</td>
<td>Supportive information</td>
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<tr>
<td>3.2.S.2.6</td>
<td>Manufacturing process development</td>
<td>Supportive information</td>
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<tr>
<td>3.2.S.3</td>
<td>Characterisation</td>
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<td>3.2.S.3.1</td>
<td>Elucidation of structure and other characteristics Impurities</td>
<td>Supportive information</td>
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<td>3.2.S.4</td>
<td>Control of Drug Substance</td>
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<td>3.2.S.4.1</td>
<td>Specification</td>
<td>Drug Substance Specification</td>
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<td>3.2.S.4.2</td>
<td>Analytical Procedures</td>
<td>Reference is made to Section 3.2.3.3 – Identification of Established Conditions for Analytical Methods</td>
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<tr>
<td>3.2.S.4.3</td>
<td>Validation of analytical procedure</td>
<td>Supportive information</td>
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<td>3.2.S.4.4</td>
<td>Batch analyses</td>
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<td>3.2.S.4.5</td>
<td>Justification of specification</td>
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<td>3.2.5</td>
<td>Reference Material</td>
<td>Reference Material specification</td>
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<td>3.2.S.6</td>
<td>Container Closure</td>
<td>Material of construction and their specification</td>
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<td>3.2.S.7</td>
<td>Stability</td>
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<td>3.2.S.7.1</td>
<td>Stability Summary and Conclusions</td>
<td>Drug Substance Storage Conditions and Shelf-life (or Retest date for chemicals)</td>
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<td>3.2.S.7.2</td>
<td>Post-approval stability protocol and stability commitments</td>
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<td>3.2.S.7.3</td>
<td>Stability data</td>
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<td>3.2.P</td>
<td>DRUG PRODUCT</td>
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<td>3.2.P.1</td>
<td>Description and Composition of Drug Product</td>
<td>Drug product qualitative and quantitative composition</td>
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<td>3.2.P.2</td>
<td>Pharmaceutical development</td>
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<td>3.2.P.2.1</td>
<td>Components of the drug product</td>
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Established Conditions (EC)

Is the process parameter either a CPP or a KPP?

Yes ⟷ It is an EC

Reporting categories for changes to EC

What is the level of potential risk associated with the proposed change, taking into consideration the Control Strategy?

High ⟷ Moderate to low

Prior Approval ⟷ Notification ⟷ Not Reported
The extent of ECs could vary based on the method complexity, development and control approaches....

- Where the relationship between method parameters and method performance has not been fully studied, ECs will incorporate the details of operational parameters including system suitability.

- When there is an increased understanding of the relationship between method parameters and method performance defined by a systematic development approach including robustness studies, ECs are focused on method-specific performance criteria (e.g., specificity, accuracy, precision) rather than a detailed description of the analytical procedure.
# ICH Quality Topics Proposed Timeline

<table>
<thead>
<tr>
<th>Lifecycle Management</th>
<th>API-Starting material</th>
<th>Quality Overall Summary</th>
<th>Enhanced Approached for Analytical procedures</th>
<th>Continuous Manufacturing</th>
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<tr>
<td><strong>ICH Q12</strong></td>
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Our Priorities....

Accelerate approval of new drugs and related changes

Drive regulatory convergence on requirements

Enable Innovative Regulatory Pathways
Thanks to...

ICH Q12 EWG

Sabine Kopp (WHO)

Ashley Boam (FDA)

Roger Nosal (Pfizer)

Thomas Schreitmueller, Kowid Ho, Susanne Ausborn, Melly Lin and Markus Goese, Roche
Doing now what patients need next
Global initiatives driving regulatory convergence

Strategic direction

ICMRA
International Coalition of Medicines Regulatory Authorities

Technical Operation

ICH
International Cooperation on Harmonization

IPRF
International Pharmaceuticals Regulators Forum

APEC/ASEAN/PAHO

WHO
Enhanced Approaches for Development and Utilization of Analytical Procedures

• Potential Elements:
  – Analytical method development & validation, including:
    • Analytical Target Profile (fit for purpose), Risk Assessment, DoE, etc.
    • Link to control strategy
    • Contemporary and innovative methods and equipment i.e., NIR, XRPD, NMR, etc.
  – Analytical method lifecycle
    • Based on enhanced approaches to analytical development and validation
    • Aligned with proposed ICH Lifecycle Framework