VII SYMPOSIUM

SINDUSFARMA - IPS/FIP - ANVISA

Novas fronteiras farmacêuticas nas ciências, tecnologia, regulamentação e sistema da qualidade

New frontiers in manufacturing technology, regulatory sciences and pharmaceutical quality system
Regulations for Post Approval Changes of Biotherapeutics – Needs and Opportunities

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F. Hoffmann – La Roche Ltd, Basel, Switzerland
Innovative Clinical Trial Designs will change the way we develop drugs

Expedited regulatory approval pathways and CMC considerations

WHO’s PAC guideline for biotherapeutics – The solution for driving efficiency

Key features of the WHO PAC guideline

Considerations/Examples for implementation

Conclusions
Helping T-cells to invade the immune dessert

- T cell engagement independent of specificity, activation and differentiation status
- Mode of action may overcome most escape mechanisms that cancer cells employ to evade T cell recognition

**Intravital two-photon imaging of anti-tumor activity**

Significantly higher number of T-cells and high apoptotic tumor fraction 24 h after TCB therapy

*LS174T-RFP (red)/hPBMCs co-grafting (5:1) for 4 days; T cells labeled with CFSE (green); imaging 1 day after therapy.*

Bacac M et al., Clin Cancer Res 2016
Background – Traditional Clinical Study Design

• Historically, phase I conducted with mixture of solid tumors, then phase II and III oncology trials were histopathologic focused (e.g. lung cancer study, breast cancer study, etc.)

• Phase II/III studies ask the question: Does the treatment, with the selected dose and within the context (histology) improve the clinical outcome
Problems with Current Trial Design

- Classical phase I, II, and III models require significant resources
- **Time** to bring a new oncology drug to market 8-12 years
- **Cost** to bring a new drug to market exceeds $1 billion
- 70%/59% of oncology drugs **fail** in phase II/III studies
- Traditional models not designed to address “niche” agents with very small populations expected to benefit
The Promise of Precision Medicine

- Tumor traditionally classified by histology, tissue site
- Extract tumor biopsy
- Extract DNA from tumor to profile for somatic alterations
- Define “actionable” mutation profile of tumor
- Use genetic alteration profile to choose individualized targeted therapeutic
New Trial Designs

**Methodologies**

- Biomarker-guided design
  - Basket trials
  - Umbrella trials
- Adaptive Design

**Major Goals**

- Increase R&D efficiency
- Increase the number of trial participants getting the best treatment
Basket Trial - Definition

Single treatment and single biomarker, different histologies placed in baskets

- Patients with cancers of different histologies enrolled in the clinical trial based on presence of a specific molecular aberration
Typical design of a basket trial

**Objective**: Explore the effect of a specific treatment within a biomarker positive subgroup (in different histologies)
Example of basket trial: BRAF V600 Vemurafenib

Umbrella Trials - Definition

Single histology, multiple biomarkers each matched to treatments

- Different targeted agents investigated in the same tumor type and within independent cohorts of patients defined by specific molecular aberrations that
Typical design of an umbrella trial

Objective: Explore the effect of different treatments in single histology

Note:
- A multiplex assay is used for treatment arm eligibility.
- Each arm is a biomarker enrichment design
Consequences

• **Smaller** Patient Numbers
• **Faster** Development Timelines
• **Tighter** (more specific) Clinical Experience

• Shift of some traditional pre-approval development activities into the post-approval space

Great Opportunities for Patients in Need!!
Regulatory Systems Enabler for Innovative Development Approaches and Accelerated Access

- **Accelerated Approval Pathways**
  - Rolling Submissions
  - Post-approval commitments
  - Reliance
  - CMC-Flexibility

- Robust Pharmacovigilance

- Efficient Life-Cycle Management
### Accelerated Regulatory Pathways: Developed in US, EU and Japan...

<table>
<thead>
<tr>
<th>Designation</th>
<th>Key Elements</th>
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<tr>
<td>Breakthrough Therapy</td>
<td>Sr Mgmt support</td>
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<td>Fast Track</td>
<td>Frequent FDA meetings</td>
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<td>Accelerated Approval</td>
<td>Approval based on surrogate endpoint; confirmation needed</td>
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<td>Priority Review</td>
<td>Shorter review time</td>
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**USA**

**EU**

**Sakigake**

- Principles broadly similar to US FDA Breakthrough Therapy Program
- Priority review: 6 months versus standard 12 months
- Rolling submissions
- Pre-CTA consultation waiting time: 1 month versus 2 months
- Dedicated concierge
...getting traction globally

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<th>Country</th>
<th>Expedited Review</th>
<th>Expedited Development</th>
<th>Reliance Pathway</th>
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Source: EFPIA White paper on reliance and expedited registration pathways in emerging markets, 2017
Accelerated Clinical Programs Compress CMC Development

**TRADITIONAL CMC**
- ~8 YRS

**ACCELERATED CMC**
- 3-5 YRS

**PHASE I/II**

**PIVOTAL Trial**

**ACCELERATED BLA**

**BLA**
Opportunities to Accelerate Development of Medicines

• Drug Substance/Drug Product
  – Provisional/Platform formulation,
  – DS & DP process with limited optimization (e.g. clinical DS/DP)
  – Launch from «Clinical Facility»
  – Opportunity to Scale Out instead of Scale Up
  – Use of prior knowledge (e.g. stability predictions, viral validation)
  – Presentation (e.g. packaging, device)
Regulatory Systems Enabler for Innovative Development Approaches and Accelerated Access

- Accelerated Approval Pathways
  - Rolling Submissions
  - Post-approval commitments
  - Reliance
  - CMC-Flexibility

- Robust Pharmacovigilance

- Efficient Life-Cycle Management
Key components of an efficient post-approval change management system

1. Risk based classification system
2. Common classification system
3. Clear and transparent timelines
4. Novel regulatory mechanisms and tools
5. Expedited approvals
6. Reliance and mutual recognition

Adapted from IFPMA presentation at DIA Euro 2018
Key components of an efficient post-approval change management system

1. **Risk-based classification system**: regulatory approaches based on assessing the potential impact of a change on product quality, safety and/or efficacy

2. **Common classification system**: global agreement on what is:
   - Major - Moderate categories (approval before implementation)
   - Minor category (notification or no reporting)

3. **Clear and transparent timelines for assessment and change implementation**:
   - 3-6 months for major changes
   - 1-3 months for moderate changes

Adapted from IFPMA presentation at DIA Euro 2018
Key components of an efficient post-approval change management system

4. Novel regulatory mechanisms and tools
   • Use of Change Management Protocols (PACMP), Comparability Protocols (CP)

5. Expedited approval of certain variations that are of significant benefit to patients

6. Harmonization between NRAs leading to reliance and/or recognition
   • Global guidance
   • Would facilitate approval of PACs based on previous expert’s review

Adapted from IFPMA presentation at DIA Euro 2018
ECBS meeting,
17-20 October 2017
A comprehensive regulatory framework for biotherapeutic products (BTPs) from WHO is available

- Guidelines on evaluation of similar biotherapeutic products (SBPs), adopted by WHO Expert Committee on Biological Standardization (ECBS) 2009
  http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf?ua=1

- Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (BTPs), adopted by ECBS 2013
  http://www.who.int/biologicals/biotherapeutics/TRS_987_Annex4.pdf?ua=1

- Regulatory assessment of approved BTPs, adopted by ECBS 2015
  http://www.who.int/biologicals/areas/biological_therapeutics/Annex_3_Regulatory_assessment_of_approved_rDNA-derived_biotherapeutics.pdf?ua=1

- Guidelines on procedures and data requirements for changes to approved biotherapeutic products, adopted by ECBS 2017
  http://www.who.int/biologicals/expert_committee/PAC_highlighted_20_Oct_2017.HK.IK.pdf?ua=1
Key features of WHO’s post-approval change (PAC) guidance for BTPs

- Covers the regulation of PACs to BTPs incl. CMC related changes as well as safety and efficacy changes with impact on clinical use and labelling changes.
- Excluding prophylactic vaccines all biologically active protein products which are used in the treatment of human diseases incl. those intentionally modified by as well as protein products used for in vivo diagnosis are in scope.
Key features of WHO’s post-approval change (PAC) guidance for BTPs

• The risk based categorization of changes, reporting procedures, suggested review timelines and the data requirements to support the proposed changes are provided.

• NRAs are encouraged to apply the concepts of reliance, of work-sharing or to use collaborative approaches when reviewing PACs.

• May be implemented as is and thus has a huge potential driving global regulatory convergence of PAC regulatory requirements for BTPs.
Risk based categorization, procedures and suggested review timelines for CMC related and product labelling changes as outlined in the WHO PAC guidance for biotherapeutic products*

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<tr>
<th>Reporting categories</th>
<th>Procedures</th>
<th>Suggested review timelines</th>
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<tbody>
<tr>
<td>Major quality changes</td>
<td>Prior approval supplement (PAS)</td>
<td>3-6 months</td>
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<tr>
<td>Moderate quality changes</td>
<td>PAS</td>
<td>1-3 months</td>
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<tr>
<td>Minor quality changes</td>
<td>Require notification to the NRA</td>
<td>N/A</td>
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<tr>
<td>Quality changes with no impact</td>
<td>Do not require notification to the NRA</td>
<td>N/A</td>
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<th>Safety, efficacy and product labelling information changes</th>
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<td>Reporting categories</td>
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<tr>
<td>Safety and efficacy changes</td>
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<td>Product labelling information changes</td>
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<td>Urgent product labelling information changes</td>
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<td>Administrative product labelling information changes</td>
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*WHO Guidelines on post approval changes for biotherapeutic products Appendix 1*
If any of the conditions outlined for a given change are **not fulfilled**, the change is automatically considered to be at the **next higher reporting category**. The **supporting data** for a given change, either to be **submitted** to the NRA and/or **maintained** by the MA holder.

The almost 70 examples provided in the guidance on CMC related Drug Substance and –Product changes cover approx. 90% of the changes that are frequently made for BTPS.

*WHO Guidelines on post approval changes for biotherapeutic products Appendices 2 and 3*
Examples from WHO’s PAC guidance for BTPs on expedited review procedures supporting WHO’s regulatory systems strengthening efforts

- The **NRA recognizes the decision of other regulatory authorities** and does not perform a review of supporting data, but is notified of the change. The submission consists of:
  - a **cover letter** from the marketing authorization holder informing the **NRA about the change** and including as an attachment a **copy of the approval letter from the NRA of the licensing country** stating the relevant changes.
Examples from WHO’s PAC guidance for BTPs on expedited review procedures supporting WHO’s regulatory systems strengthening efforts

- The NRA performs an assessment of the decision of the NRA of the licensing country to determine whether reliance of that NRA’s decision is appropriate. The submission consists of:
  - a cover letter from the marketing authorization holder informing the NRA about the change;
  - a copy of the approval letter issued by the NRA of the licensing country;
  - assessment reports and relevant correspondence from the NRA of the licensing country (if made available by the NRA);
  - a detailed description of the change; and
  - supporting data submitted as necessary if assessment reports are not available.
Singapore Health Sciences Authority (HSA): Risk-Based Evaluation Routes for New Drugs

- **Product yet to be approved by any regulatory agency**
  - Full Evaluation: 270 wd
  - Abridged Evaluation: 180 wd
  - Verification: 60 wd

- **Product approved by one drug regulatory agency**
  - Full evaluation and Regulatory Decision

- **Product approved by reference regulatory agencies**
  - Evaluation and Regulatory Decision based on assessment report by benchmark regulatory agency

Timelines applied for BTP PACs e.g. MIV-1

Adapted from John CW Lim’s slides to be presented at the APEC RHSC Meeting on 10 Feb 2018

* Reference regulatory agencies:
  US FDA, Health Canada, UK MHRA, Australian TGA, Europe EMA
After finishing successfully a pilot on applying the verification route for PACs (MIV-1) HSA now officially has implemented this pathway.

- In addition to the approval letter or approved product labels from a HSA reference agency, the documentary requirements specified in Appendix 13 and 14 of the Guidance on Therapeutic Product Registration in Singapore (Nov 2016), remain applicable:
  
  i) PRISM Application Form
  ii) Table of Contents
  iii) Cover Letter
  iv) Checklist for MIV(s) and all required supporting documents stated within.
  v) Table of Summary of Changes
  vi) Current and proposed product labels (annotated and pristine copies), where applicable.

Again HSA is serving as an example on how small to mid-sized agencies may focus, optimize resource allocation without compromising on patient safety by not repeating what others already have been doing.
INTERNATIONAL CONCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

Q12

Draft version

Endorsed on 16 November 2017

Currently under public consultation
A PACMP is a regulatory tool that provides predictability and transparency in terms of the requirements and studies needed to implement a change as the approved protocol provides an agreement between the MAH and the regulatory authority.
Conclusions

- New drug development approaches driving R&D efficiency and accelerating access of patients to innovation will also drive the need for highly efficient post approval regulatory systems.

- The WHO guidance on post-approval changes (PACs) is ensuring quality, safety and efficacy of BTPs during the whole life-cycle based on proper science and risk management principles.
Conclusions

- Providing “checklists”, examples and promoting reliance-based assessments it may significantly contribute to regulatory convergence, regulatory systems strengthening as well as to LCM efficiency globally.

- The WHO PAC guidance for BTPs and ICHQ12 are highly complementary – while ICH with “Established Conditions” will tackling the “what” and will providing the PACMP-concept, WHO is focusing on the “how” – ready to implement.