Representation from 9 global regulatory authorities:

- Japan PMDA
- US FDA
- Finland Fimea
- Malaysia MHM
- Korea MFDS
- Taiwan CDE
- Portugal INFARMED
- Germany BfArM
- Contributing to discussions: Canada HC
PRODUCT CASE STUDIES – See slides and contact speakers for specific tech details

- Accumulated cell therapy (Japan Tissue Engineering Co, Ltd)
- Cell-based product QC (Teijin Pharma Limited)
- Bi-specific IgG (Chugai Pharmaceutical Co, Ltd)
- Glyco-engineering Mab (Roche Diagnostics GmbH)

RESEARCH PERSPECTIVES – See slides and contact speakers for specific tech details

- Cell Therapies (Kinki Univ, Japan)
- Engineered Mabs (Tohoku Univ, Japan)
- Also contributing to panel: NIHS, Japan

INDUSTRY PERSPECTIVES

- Breakthrough products (Genentech, MOTRG)
- Accelerated product analytical risks (AstraZeneca)
- Lifecycle of process validation (Pfizer)
- Also contributing to panel: Daiichi Sankyo, Kyowa Hakko Kirin, F. Hoffman-LaRoche
- BPOQ (BioPhorum Operations Group; biotech industry consortium)
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- **Japan PMDA**
  Significantly increasing staff size; strongly supports QbD (pilot program observer); launching Sakigake “Forerunner package” priority review and Rapid Authorization off-label/unapproved drugs; RegenMed program under revised Pharm Affairs Law (PAL) and Pharm Med Dev Act (PMD Act); update on Science Board considerations; now a member of PIC/S; revised process validation standards to align with ICH and PIC/S and product lifecycle strategies

- **US FDA (CDER OBP)**
  Re-organization of CDER to align research, review and inspection activities as Office of Pharm Quality; not a new approach for biotech/biological products (MAPP); OBP remains intact but will go from 2 to 4 divisions for flexibility; defined sponsor meeting plan for biosimilar programs (Type 1, 2, 3, 4); outlined statistics for analytical similarity; guideline on biosimilar interchangeability due 2015

- **Finland Fimea (EMA/CHMP BWP)**
  New single clinical trial assessment pathway via EMA Portal; 2 part assessment but extremely aggressive calendar timelines (biotech can get 50 day extension); increased public transparency of experts, clin trial and MA decision details; adaptive licensing clinical plans (CMC mostly the same); Fimea: “Valley of Death” novice sponsors, Baby Medicines Welfare Clinic (BMWC)
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- Malaysia Ministry of Health (ASEAN activities)
  CMC review of vaccines, therapeutics and RegenMed products; biosimilar guidance 2008 requires strong CMC package and strong risk management plans with post-market surveillance (no quality shortcuts!); big concern over safety risks of ‘biocopies’; sponsor can choose Ref Prod if it has complete dossier (Q, S, E) with sufficient duration/scope of commercial use; CTP tiered levels for low vs high risk product types; GT products only licensed if approved by USFDA, EMA, HC

- Korea MFDS (APEC Activities; ICMRA, ICH, IPRF, WHO....)
  Regulatory Harmonization Steering Committee (RHSC); 9 Roadmaps for pharma products (excluding vaccines, blood products, CGT – separate group); 4 step implementation process; biotherapeutics global initiative goal to have WHO and ICH guidances to APEC nations by 2020; gap between harmonized/non harmonized countries is wide; no common languages or shared principles yet; 2015 convergence discussions (post-approval changes, immunogenicity assessment for biotherapeutics and biosimilars, acceptance of foreign clinical data); Singapore Center of Excellence pertaining to CMC questions in life cycle management and post approval changes
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- **Taiwan CDE**
  Regulatory framework (TFDA and iMPRO); Good Review Practice (GRP) guide reviews for efficiency, quality/consistency and clarity/transparency; tiered review classifications (abbreviated, priority/accelerated, or regular); adopts best practices from many international organizations (ICH, WHO, US FDA, EU EMA, Japan MHLW/PMDA); guidances on biosimilars, sees “Translational GAP” from basic research to clinical development; biosimilars should use Ref Prod of Taiwan (or justify why not); PIC/S member

- **Portugal INFARMED (EMA Committee for Advanced Therapies, CAT)**
  Centralized Market Authorization of ATMPs elements from EU member states (GMP provisions, RA, post-market surveillance for safety and efficacy); 2014 status report CAT (Harmonized ATMP classes and clarified data in MAA across MS; streamline MAA procedures and link to certification procedures, Incentives for academic/non profits; fees for post market obligations)

- **Germany BfArM (EMA / CHMP BWP)**
  Comparisons among EMA vs FDA vs ICH guidance; differences in dossier elements vs inspection practices; similar for Process Validation and Continuous Process Verification; suggests harmonizing terminology for ‘process verification’ to facilitate acceptability of the PV data package in different regions of the world
REGULATORY UPDATES AND PANEL DISCUSSION

Internal Activities:
Outstanding organizational overviews of the regional health authorities (including planned changes to staff size and project assignments)
Outlined and compared the logistical pathways for biotech/biosimilar/biological products (including efforts to coordinate, integrate and streamline)
Explained the history, current status and expected near future of biotech/biosimilar regional regulations and guidance documents
Provided direct links to their official documents that govern and guide health authority policies and practices for biotechs/biosimlars/biologicals

External Activities:
Many speakers adopted a second “hat” to describe activities with other regional or global organizations in which they and their authorities are participating
Comprehensive view of the working groups that are having major positive impact on our product development and approval strategies
Gave detailed updates on the status of each organization with information on key upcoming activities
HEALTH AUTHORITY INTERNAL ACTIVITIES

All are acutely aware of CMC review/inspection scenario:

- Increased number of biotech/biosimilar/biological product filings and inspections
- Pressure on CMC reviews from compressed clinical times (e.g. breakthroughs, fast track/Sakigake, biosimilars)
- Emerging new product classes require adaptation of WCBP CMC models to balance risks/benefits of patient safety with product availability

Strategies being adopted:

- Staff Expansion; Assignment Flexibility
- Streamlining and Simplifying Processes
- Coordination and Integration of Review/Inspection Activities
HEALTH AUTHORITY EXTERNAL ACTIVITIES

Continue to work with other global health authorities and industry via professional organizations to find ways to:

• Increase communications
• Share regional experiences
• Align general philosophies
• Harmonize global policies
• Converge to core common practices
• Leverage historical information
• Compare risks/benefits to regional patients (unique needs?)
• Minimize data redundancies
• Recognize mutual conclusions

But they each must work within the legal constraints of their individual statutory and regional requirements
What are regulatory frameworks and pathways for the potential accelerated approval of promising new products? What are the advantages /disadvantages of different approaches?

**REGULATORY**

- Each agency has different designations for accelerated approval based on unmet medical needs, orphan drugs, off-label use or drugs in national interest.
- None will compromise quality, safety and efficacy for the sake of expediency; all require a risk assessment/risk mitigation plan (quality parameters should not be on the edge of safety limits).
- Emphasized need to significantly ‘front load’ the CMC studies for process and product characterization to allow detailed evaluation of each dossier sooner than for standard product review.
- Cannot make decisions on assumptions; must have data to support conclusions and to review risk assessments and risk mitigation plans.
- May exercise discretion in some CMC elements within regulatory/compendial requirements and balancing risks/benefits to patients.
- Might place strong emphasis on post approval activities (risk-based decisions on pre vs post approval requirements).
- Quality of the dossier can have a major impact on efficiency of review – if it is poor quality it could trigger more questions from reviewers requiring more data to be submitted which will slow down the review process (and annoy reviewer!)
What are regulatory frameworks and pathways for the potential accelerated approval of promising new products? What are the advantages/disadvantages of different approaches?

**INDUSTRY**

- Clinical timeline is shorter so CMC elements become the critical path for the product dossier; Management must increase CMC resources and data collection early vs past project plans (quadrupled CMC staffing!)
- Establish cross-functional teams to avoid CMC duplications/omissions (esp multi-site teams)
- Front-load analytical data collection (do more testing early to get data to relieve testing later)
- Minimize process/method tech transfers to minimize disconnects and save time
- Prepare for PAI sooner; find and remediate quality system gaps (mfr and test facilities)
- Must plan resources to diligently support all CMC post-approval commitments
- For accelerated products, QbD may be best suited for post approval activities (CMC timelines too constrained in breakthrough/biosimilar products to do extensive QbD before approval)
- Some experienced firms have now successfully used QbD approach for product approval (Roche) by generating de novo process-specific QbD data guided by process platform knowledge
- Platform analytical method development/optimization is ok so long as all necessary applicable information is submitted for review to support each validated method (model proteins for platform data?)
What regulatory frameworks and pathways are available for the potential accelerated approval of promising new products? What are the advantages and disadvantages of different approaches?

**BOTH**

Challenges: Limited batches made (spec ranges vs process consistency?); limited real-time stability (shelf life claim?); PV vs CPV (how much data, when?)

Communicate, communicate, communicate earlier and more frequently to avoid making erroneous CMC assumptions

Don’t want sponsors to do too much OR too little to achieve successful review decisions faster and more efficiently

*Health Authorities cannot compromise product QUALITY, SAFETY OR EFFICACY (quality parameters should not be on the edge of safety limits!)*

*Need adequate CMC information in order to evaluate and minimize risks*

*Regulators are taking the risks for patients – so respect their need for your data!*

*Regulations must support good clinical care with adequate safety and control; it is in everyone’s interest to assure good clinical outcomes*

**MANY QUIET PRODUCT SUCCESSES CAN BE DESTROYED BY ONE LOUD PRODUCT FAILURE**
In some regulatory jurisdictions, evaluations of marketing applications may be streamlined if approvals have been made in certain “benchmark” regulatory agencies. How will “breakthrough”-type approaches and accelerated approval pathways, with their reliance on less well-developed data be accommodated?

- Would be hard to accept benchmark approval if it was highly accelerated with limited CMC data available in the dossier
- Even if CMC module is ok still may have questions on suitability of product in regional population; requires detailed consideration of the clinical experiences vs the benefits to patients
- Might base reviewer expectations on current CMC guidance from the benchmark agency on the type of product
- All Health Agencies indicate the final decisions are case by case for each product, so encourages early communication to outline details of required strategy
What regulatory frameworks and pathways are available for the potential accelerated approval of promising new products? What are the advantages and disadvantages of different approaches?

Can every product be treated like a breakthrough product where the real process/method capabilities are only demonstrated after commercialization?

Regulatory can only work within the framework of current regulations

On the other hand there is nothing stopping industry from planning programs like they will be BT (eg add staff and increase data collection) and deciding to use minimalist strategies (simple formulations, limited shelf life, narrow process design space) but commercial process/product will be constrained to those conditions for which data exist

Catch 22 is to do a lot of CMC work early but then product fails in clinic, so firms should choose candidates based on scientific understanding of the molecule and leverage product engineering/screening strategies based on prior knowledge to get highest chance of success

Then can prioritize candidates for possible BT status
What is the level of current activity and future landscape for biosimilar products?

- Highly diverse policies on use of non-national clinical trial data (statutory and/or population pharmacogenomics); Highly similar policies on Mod 3 CMC requirements
- Analytical comparisons to RD are required but wide differences in which RD(s) are legally allowed to be used; 3-way bridging strategies are possible in some regions (check if analytical H2H, clinical H2H, or both needed)
- Increased learning curve from global biosimilars might feed into generating new and/or updating early guidances

Typical problems that cause non-approval of biosimilars in Malaysia

- Insufficient data on process control and process consistency
- Insufficient characterization of product and impurities
- Unclear or inadequate release/stability specifications
- Deficient QC testing strategy (non-orthogonal testing for critical attributes)
- No justification for choice of Reference Product
- Poorly designed analytical comparison studies for biosimilar vs reference product
- Immunogenicity of biosimilar was not adequately determined
- Deficiencies in prescribing information and product labeling
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What is the state of international regulatory convergence and, in particular, how does the picture for Asia appear different than the global picture?

Regulatory actions may vary across global agencies (esp for CMC of new product classes and post-approval notification procedures for biotechs/biosimilars/biologics) but would be highly beneficial on both sides to find a process within the jurisdictional requirements of each region.

Most Asia authorities are heavily involved with key international harmonization/coordination organizations (APEC, ASEAN, APAC, ICH, etc...)

Uniform guidance on global CMC requirements for accelerated/breakthrough products (ie what is require pre vs post approval) is a big challenge due to regional issues and political structures; eg ASEAN: Any future ‘central approval’ procedure among all member countries would require a Mutual recognition process (like EU) but these countries are not legally linked.

ICHQ12 international product lifecycle guidance (review and inspections); desire is better global harmonization of post approval changes and use of comparability protocols (concept paper out now).

Many health authorities here are now members of PIC/S for globally-coordinated GMP practices and fewer redundant inspections for commercial products.
What strategy can be employed for evaluation and control of cell-based products for regenerative medicine in terms of quality and safety? What is a role of specifications in the overall quality control strategy of a specific product?

- EU system for Reg Med is based on the same principles as biotech therapeutics, which starts with characterization of the product and evolves into defining an control strategy to assure the target product profile is met consistently for each batch of Reg Med product.
- There needs to be sufficient appropriate analytical tools to define the Reg Med product’s profile. From these will select a subset of release and stability tests for QC of the product.
- When making Reg Med product/process changes use the same analytical characterization tools to assess the impact of the changes on product quality and consistency.
- It is ok to have highly heterogeneous cellular materials so long as the degree of heterogeneity is controlled and consistent, and safety is maintained (eg no contaminations).
What type of cell-based products for regenerative medicine would be developed as commercial products?

Highly diverse! Skin, cartilage, allogenic and autologous materials; stem cells

Identification of points to consider for specific type of product, taking into account source of cells, raw materials, cell banking, processing of cells, preparation of the final product, quality attributes, intended clinical use etc.

Risk-based approach to each of these, but the dossier should contain justifications for decisions on each (with supporting data). Part of the overall Risk Mitigation Plan for the product type and intended use (inc traceability of sources, chain of custody and long term follow up of patients)

For Regenerative Medicines, can we overcome different legal environments among different countries and regions in the near future?

• Spirited discussions about this! Substantial differences in CMC for RegMed (case study)
• First do no harm! If cell population has fibroblasts, could generate scar tissue; if covering large wound might be better than nothing, but if repairing a highly flexible element scar tissue might be worse than alternative solutions (eg mechanical)
What are the biological and structural features characteristic to engineered antibodies? Compared to conventional monoclonal antibodies, are there any additional CMC issues to be considered for approval of engineered antibodies?

- Analytical strategies for release and stability of bispecific Abs should follow the same structure/function relationship as with Mabs.
- Traditional Mab structure/function analytics should be applicable with selection of an appropriate set of stability-indicating methods.
- Need to have functional assessment of the two different epitope-binding domains plus any other functional elements related to mechanism(s) of action.
- CQA based on product specific parameters vs legal compendial requirements for general pharmaceutical product characteristics (color, clarity/SVP/VP).
- Appearance is the most prominent product characteristic that is detectable by users (main source of product complaints because it is obvious); if specs indicate it can be red or blue that is fine, but if spec says “colorless” it should be colorless.
- When do you remove testing for a process residual CQA eg HCP or DNA? After process validation and sufficient batch consistency is demonstrated (BPOG CPV: 30 DS batches?). Would reintroduce tests after process changes until again show control.
What are the issues that may cause difficulties with the implementation of the new PV concept for biopharmaceuticals?

Differences in process validation vs process verification (continuous, continued?; validation, evaluation?) terminology can substantially affect each health authority’s expectations. These terms have subtle meanings between agencies and across languages; can yield differences of interpretation that complicate specific data needed for each authority depending their individual expectations (translational language differences are not trivial issues; interesting audience comments that showed the problems!).

Terminology is also not harmonized between process and analytical (method validation is different from method verification).

Terminology also confuses the allowable commercial use of the PPQ vs CPV lots for commercial or not; EU and FDA: depends upon GMP compliance documentation for the batches, and state of specifications eg for process residuals.

Some regulatory agencies still follow conventional biotech strategies for 3-PV batches and full specifications; eg Korea does not yet have process lifecycle strategies; Japan evaluates the components of risk related to nature of these batches and the control strategy to make final determination during review.
PROCESS VALIDATION LIFECYCLE PRESENTATIONS AND PANEL DISCUSSION

How do we present the rationale of PV strategy in dossier to efficiently share the PV strategy with the review?

Table generated by Kowid for where PV/CPV information could go in the ICH CTD sections (proposes process lifecycle plan to go in Mod 3 regional section)

Key question is how much of this information in the dossier would be a legally binding commitment to regulators; conventional interpretation would be “all of it”

Might not want to put CPV protocols in the dossier, at least initially, since it is a data gathering exercise that should be for internal use only; regulators would also need considerable details in protocol against which to review the entire dossier as a complete package

Commercial processes must be maintained in a state of control under full GMP compliance in alignment with the approved method of manufacturing; Changes to the process outside of the approved ranges should be managed according to post-approval change guidance with appropriate regulatory communication

BT products/accelerated product approvals put pressure on conventional strategies for PV, but not really sure it should be different from sound scientific approaches for assuring process control and product consistency (no matter what terminology is used). BOPG case study shows strategic outline on how CPV can be executed (white paper)