Recent Trends in the Regulation of Biopharmaceutical Products

Introductory Comments
Takao Yamori, Pharmaceuticals and Medical Devices Agency (PMDA), Japan
- Monthly regulatory update is now being published on PMDA website in Japanese and English
- Active with APEC, DIA, ICH, PIC/S (member), WHO; launched Asian training center for pharm/med dev RA and training sessions; expanding engagement and outreach to international agencies

PMDA Perspective: Recent Trends in the Regulation of Biopharmaceuticals (https://www.pmda.go.jp)
Kazuhiko Chikazawa, Pharmaceuticals and Medical Devices Agency (PMDA), Japan
- 5 topics continuing from 2015 intl strategic plan: Training, SAKIGAKE, Biosimilars, JP, ICHQ12 EC
- 3 pillars PMDA mission (review, safety, rescue) now include 4th pillar of regulatory harmonization strategy

TRAINING UPDATE: Asian training center (PMDA-ATC) designed to expand regulator training in Japan and in partner countries; gave list of 3 past/3 upcoming training events 2016-17 (see PMDA website for remaining dates)

SAGIGAKE UPDATE (rapid authorizn of new drugs): 1) dire need drugs; 2) dev and NDA in Japan; 3) highly effective preclin/early clin trials; 1st round = 6 biotechs; 5 med devices/tissues; 50 applications pending for 2nd round (current cycle, Oct-Nov 2016); Sagigake is not a permanent system yet, only opened by announcement

BIOSIMILAR UPDATE: A new BS Q&A docs issued Dec 15 2016; 25 consults for BS, 66% Mabs and Fc proteins, rest are hormones, cytokines, enzymes; BS becoming common political and media topic; emerging issue is avail of RLD from innovator (not same situation as for chem generic drugs where supply is open); RLD is not avail to BS producers

JP UPDATE: 130th anniv JP17!; JP English is now free on line (.pdf); GT/CT out of scope; vaccines/blood in scope; biotherapeutics: General rules yes, general methods yes; official monographs continue to be discussed: What is the purpose of monos for biotech product?

ICH12 PAC: Complexity of global PMC is understood; drive to have harmonized EC (Japan Mod 1 approved matters); 70% discrepancy of details in App Form vs in company SOP (mostly minor changes and typos); was a point of discussion later
MFDS is rapidly growing their activities in biopharma both at regional level and internationally for traditional (vaccine/plasma/antitoxin); recombinant and cell culture products; GT/CT; Korea granted first approvals to a stem cell therapy and BS Mab product

Biosimilar legislation: launched 2009; established definitions [RPP (recombinant protein product); SBP (similar biol prod), RBP (ref boil prod)]; 5 BS approved in Korea 2012 – 2016 with specific guides issued for them; currently are 21 BSP candidates in Korea

MFDA issued improved policies for assuring patient safety and relief of injury, plus new info on vaccine AER and lifesaving CT; includes risk management plan for new or advanced drugs; info on price rules for new drugs with insurance coverage; launching 5 yr post approval renewal cycle (2018); BioIT: Overseas regulatory information, biologics approval regulations and guidelines, market information, consulting services (www.bpis.or.kr)

Several new MFDS initiatives to streamline biotech development inc communal mfr facilities and pre-approval inspections; encourages QbD models; implemented national lot release; issued new guides for blood products, orphan drugs, exported products. MFDA is now a PIC/S member and is issuing GMP certifications

APEC RHSC (Regulatory Harmonization Steering Committee): A Four-step plan in place going through 2020 (assess, training, assess train, train to goal). Step 2 in progress now with working group. Center of Excellence (CoE) are designed with experts in small topic-based training sessions. Held 2016 pilot programs at Northeastern Univ (US) and Seoul National Univ (Korea); currently planning 2017 AHC and CoE
The China Regulatory Framework: Recent Trends in the Regulation of Biopharmaceuticals
He Bai, China Food and Drug Administration (CFDA), P.R. China http://eng.sfda.gov.cn

CDE is the review group for drugs; **3 filing packages are assessed**: (1) product development reports, (2) facility inspection outcome and (3) QC test results. **CDE has strong alignment with international guidance for biologics eg WHO, ICH, etc..**; CDE review also consider if drug is approved in other global regions; pharm committee reviews imported and domestic products. China also plans to export approved biotech products of high quality.

Biological products are currently designated as preventive biological products, therapeutic biological products and blood screening in vitro diagnostics. There are **15 registration categories** with crossover of some categories; special consideration of biosimilars and CT products. No categories for drug substances and generics. Appendix on Biological Products and Blood Products in GMPs.

**QMS is a major regulatory focus, aligned with international guidance.** Assesses the ability of continuous production, batch-to-batch consistency, product stability, requirements for changing raw materials and excipients, product transportation, post-marketing surveillance, etc..
Post market changes: process is complicated but uses science-based approach; annual evaluation reports required of each approved product; need complete records of doc control for that year.

Reform and emerging initiatives: **Streamlined efficient review approval process** with unequivocal procedures; acceleration of rare/new and shortage drugs; encourage China domestic clin trials with focus on subject protection and clinical value of drug (can do concurrent clin trials in china and other countries); profess tech review teams with re-review of controversial conclusions to assure fair authoritative results; increase **high transparency**: At time of NDA 3 packages review reports, inspection outcome and QC test reports would be publically presented.
Adaptive pathway pilot update: 18 selected from 62 candidates; 6 progressing now. Rejections were based on too late phase stage; limited learning for pilot (ie no real world data planned), or no unmet medical need. Key learnings: (1) involve pts/medical earlier in the process, (2) CMC could be time limiting factor due to accelerated clin timeline, so might need rolling CMC review with concurrent activities (ie PV); might allow leveraged stability data; spec ranges that might be re-adjusted after approval.

PRIME (priority medicines): Two program entry points: (1) Ph 1 small/med firms and academia via proof of principle; (2) Later Phase, any sponsor with proof of concept. PRIME involves early multidisciplinary scientific and regulatory interactions; gives sponsors guidance on product dev plans and critical CMC data sets. CMC for PRIME: Complete Mod 3 required as for other products; but could use PRIME process to get more detailed and more frequent input from regulators.

Biosimilars (BS): Target is to achieve lower prices, affordable healthcare, increased access to other markets; could give pt more options. BS do put pressure on innovators for continuous improvement of legacy products. There has been a sharp increase in BS in the EU since inception (80% of BS are Mabs). Successful program, but with some criticism for inadequate data-driven scientific advice during product development; need a new tool for more access to quality data to facilitate scientific advice for BS development strategies.

NEW! Open access to clinical reports for new medicines: https://clinicaldata.ema.europa.eu Currently just 2 chem drugs listed; will publish both submitted and withdrawn studies (to learn from what failed)
There is now a great amount of scientific and quality knowledge on Mab products and processes, but FDA is not ready to completely abandon oversight of control strategies; FDA must protect patient expectations for quality pharmaceutical products. FDA encourages new technologies and dialog on new approaches (eg MAM) if the focus is on assuring product quality and consistency. Sponsors must provide sufficient data on proposed strategies; historical data may not be sufficient to encompass all potential future process/product variances (see example below).

Two key questions on novel control strategies: (1) is monitoring done at the appropriate step (ie no further changes possible in next steps)? And (2) does ‘monitoring’ mean pass/fail at that step? Gave 3 examples of requests for reduced QC testing with insufficient justification that product quality and stability would be assured (see slides for detailed information).

ICHQ12: FDA issued draft guidance on EC (2015); for EC, sufficient detail is needed in dossier to assure process performance and quality of the product; gives examples in ICH CTD sections; separates supportive historical data sets needed for review/approval from the commitments for commercial product control. Presented an inspection example (see slides!) of a highly atypical process step that should have triggered internal review including all product parameters that could have been impacted, tried to apply non-relevant hold-point data and used passed DS testing as proof of quality but had removed purity as routine QC test (justified by running process consistently....)

New guidance April 2016 on Comparability and Change Protocols; used regularly and successfully at FDA but common gaps: (1) lack of data for justifying AC, (2) comp AC same as release AC (should usually be tighter); (3) lack of comparative stability data plans; (4) inappropriate downgrading requests (eg site change, or lack of validation plans)

Biosimilars: Extensive CMC data required up front; must characterize the RLD, 4 BS BLAs approved; many more in progress. Breakthroughs: Expedited CMC dev with risk/benefit evaluations; but does NOT change CMC requirements for BLA but they work with sponsors to determine timing of key data sets (ie pre vs post approval); advice to mgmt is to start CMC early to avoid it being lagging item for review (BT clinical activities usually move faster than CMC)
Q: Is there CFDA testing of CTM in China? A: Clinical trial in China is doc review, not doing actual testing of CTM samples; inspection team is available to assess control of CTM production/testing; imported CTM will be tested along with doc review.

Q: Time to get China IND is currently 1 yr; when will shorter time be possible? A: Started last year for biopharma INDs from 6 – 12 mo; striving to be even faster for biopharma (special review team formed for efficiency)

Q: When would PV strategy be provided for BT or adaptive pathway products? A: PDUFA has time limit rules on agreements regarding submission to a BLA; but FDA can always send an info request. PV strategy for this type of product should be discussed in advance of pre-BLA meeting if an atypical strategy is being proposed.

Q: Japan CMC Expectations for Sagigake process? A: No specific impact on CMC expectations, but encourages dialog with PMDA on CMC

Q: Sagigake details on prior-review rolling submission process, ie draft or final CMC content submitted ahead of the clinical data? A: Can seek prior PMDA consultant on draft CMC strategies before final CMC strategy is filed. Rolling submission strategy not harmonized globally; some do some don’t (eg Canada); seems globally that CMC work is the gating item for fast track programs (adaptive, PRIME, Sagigake, BT, etc.)

Q: Is Sagigake appropriate for multiple indications? A: Very challenging if too many indications are rolled into the Sagigake process since goal is the targeted unmet need for high risk patients in Japan before rest of world

Q: Since there was 70% difference between Mod 1 App form details vs what was found in practice, and diffs found were only minor errors or changes, what does this mean for level of detail appropriate for AM/EC? A: Needs to be sorted out how to minimize errors/typos in AF but does not mitigate need for sufficient detail in Approved Matters; value vs constraint of the level of EC detail is still being discussed in ICHQ12.
Panel Discussion – Questions and Answers

Q: What other strategies are being proposed by industry, or are under consideration? A: Pay attention to CMC strategies that are scientifically sound, not short sighted (like pooled clones); recognize what data sets are needed to be approved and plan them from the start; EFPIA white paper on CMC strategies for early development (available soon); other industry white papers (and CMC Forum Papers! www.casss.org)

Q: What does panel think are the hot topics in training to rapidly increase understanding of the approval process and issues, eg how to use scientific advice?

• China feels training must start on review elements to assure high quality reviewers; after that will look to including international guidances into training curricula to broaden understanding of the global reg perspectives and common industry practices.
• Korea has provided WHO GMP training for many years; also training on new product types like cell therapies; promotes global understanding of regulatory issues like ICH, WHO.

Q: Training initiatives – do they incorporate internationally harmonized or converging concepts, and if so, is there any consideration for globally harmonized training programs?

• PMDA – Just starting regional training; maybe in future thorough ICH could generate integrated training programs
• EMA – doing quite a lot of training, some open for global reg agency access (eg recent biosimilar training inc Asian and other countries participating); individual member states also provide and obtain global training; Eu has also established network training center with goal of making national and EMA training webcasts available to all regional authorities; curricula being developed with long term view to opening beyond national authorities
• FDA – Currently FDA training does not include international elements at this time, esp for CMC; would be interesting to allow reviewers to share their thinking on ICH elements used in decision making
To assure safety and efficacy, CTP have the same objective of process consistency and product quality/stability as other biological products; referenced ICH guidelines Q5 series and Q6B for general biotech principles (e.g., controlled heterogeneity) but some of which may be adapted for technical issues unique to cellular products.

Same CMC elements as protein products (source materials, IPC, character, specs) but greater data sets on source materials and characterization, with less emphasis on final product testing.

But CTP may require greater emphasis on total quality control (process, procedures, material, equipment), not just final testing specs (due to technical limitations on end product testing) – justification of the specification involves numerous elements of process and product characterization and control, with supportive historical data.

Potency assay needed will depend on what the CT product does: direct function (attachment), indirect response (triggers release of biomarker), or in vivo modulation (e.g., differentiation after implantation).

Potency assay should support prediction of MoA – method should include relevant measurements of activity and appropriate system suitability to assure reliable results.

Potency methods should be validated per ICHQ2 as applicable to the assay technology, with justified adaptations; often no ref std substance for relative potency calculations.

PMDA feels medical specialists have major role to play in some CT products (e.g., at time of administration) so product specs must include those considerations at the point of use.
Development of Allogeneic Regenerative Medicine, TEMCELL® HS inj: Establish Test Procedure and Acceptance Criteria, Especially Specifications and Potency Assay, Kiwamu Imagawa, JCR Pharmaceuticals Co., Ltd., Japan

Human bone marrow derived human stem cells; 12 yrs from initiation of license to first approval (in Japan); injection suspension stored -130°C for up to 5 yrs. Features: donor derived live cells that are heterogeneous; no ref std possible; MoA not well elucidated (likely multiple MoAs in vivo); means specs are very wide to allow for high variability in product attributes

Release tests are in two stages: donor cell bank (intermediate) and release of product batch (final)

Gave excellent overview of multiple orthogonal analytical tests for quality and potency of the product! Many attributes measured (PBMC, gene activation, receptor expression, cell migration) using a wide array of technologies (FC, ELISA, PCR, fluorescence microscopy)

Potency Considerations for a hUTC-derived Therapy, Carl Burke, Janssen Pharmaceutical R&D LLC, USA

Allogeneic cell therapy; Human umbilical tissue-derived cells (hUTC); delivered directly to the retinal tissue (internal needle from above, or external cannula from below); migrates beyond actual injection site to rest of retina

Single donor cells but are not immortal; can go 70 passages before death. Harvest at 40-50 passages

Potency assays: linked to biological activity/MoA; multiple assays needed due to complex MoA; limited product stability (LN2 storage); must be able to detect inactive or degraded materials; some are highly variable bioassays; potency range set on limited data (too wide not useful, too tight not supported by data); can’t increase n of testing due to limitation on batch sizes

Phase specific approach: (see slide); some advantages and disadvantages of UTC see slide
EU Regulatory Activities and Experience
Ilona Reischl, AGES-Austrian Medicines and Medical Devices Agency, Austria https://www.ages.at/en

Gave list of all current guidances on CT and indicated new draft Guideline for Investigational ATIMPs is in progress; new general chapter in EP 5.2.12. on raw materials of biological origin for CT GT; indicates what is out of scope;
No guideline could ever address all specifications for every type of product, so don’t expect one! Each CT product is evaluated case by case, using basic principles of quality and safety (identity, purity, potency, impurities, microbial, cell viability, cell number; plus – are markers unique to your target cells? What else is in the prep? How long will cells be cultured? Are specs covering all manipulations of the material to point of use?

Prefers the terms exploratory vs pivotal clinical trials; may be more accurate than Ph 1, 2, 3 since Ph 1-2 is meant to be exploratory, Ph 3 mean to be pivotal but seeing sponsors trying to use Ph 1-2 as pivotal data sets.

Specs: Acceptance criteria be quantitative limits, not just FIO – intended to provide sufficient control of the active substance; can test at different points (DS, DP, IPC) if adequately justified; content – dose is critical parameter; what is adequate dose?; purity – microscopic examination may not be able to discriminate diff cell types in prep; impurities inc mixed cells with defined allowable ranges (based on historical consistency data); potency assay needed sooner than later; particularly important to assessing mfr changes; surrogate markers ok if they are related to MoA and clinical effects; sterility and advantageous agents (EU directive 2006/17/ec required; might not be able to do sterility of final product but options to test intermediates, but what are your actions if found non sterile after administration?

Pet Peeves slide on Dendritic Cells! - FIO means you don’t understand the role of specs in product control (do you really expect 0% potent material can be used in clinic?); some attribute can be tracked FIO, but core quality cannot be FIO even in clin materials first in human

DON'T SUBMIT unless product is characterized, putative MoA identified, specs in place related to function, analytical tools suitable, strategy to gather more supportive data during clin trial; clin trial can only generate valid data if product is adequately defined and controlled (don’t jeopardize clinical trials with poor CMC!)
Panel Discussion - Questions and Answers

Q: Cell or cartilage generation hard to measure potency in vitro? A: Would require technical discussions

Q: Could use surrogate biomarker assay A: if there is a justified link to the in vivo MoA

Q: Current approved epidermal tissues for skin, how were specs considered for approval? A: Based on MoA and intended clin effect; quality parameters defined for attributes relevant to it, including how medical practice will use it. HC = MoA determination may not be fully elucidated for all products (ie IFN) but agree some quantitative measure of biological activity that can correlate to function is necessary for assuring product quality/consistency. Full secretome of a CT is not possible to determine in vivo, but agree that sufficient metrics should be used to model numerous characteristics.

Q: Control of starting materials vs final product testing be used as a combination for total control using quantitative metrics at different points of the process – in such case qualitative markers (semi quant) combined with quantitative data (cel viability) could work as suitable control? A: Depends on the specific test points and tests done, but matrix approach of control is probably appropriate. But just because cells are alive is not enough to assure they are the correct cells with the correct attributes to be the intended material. Agree that even homogeneous cell preps can vary from lot to lot in quality and consistency.

Q: How do you do PV for CT? How many lots for verification? A: Differs among regions; Japan expects cumulative CMC data to show process control and product consistency; but total amount of data will depend on risk and medical needs. In EU there is early access and conditional approval (compassionate and named patient use) but giving full commercial approval to product that is not fully in control is not acceptable if it exposes patients to unnecessary safety risks due to inadequate CMC data.
Panel Discussion - Questions and Answers

Protein products have more straightforward quality control testing capabilities but basic principles are the same for proteins as for cell products – consistent products of suitable quality to assure reliable safety and efficacy. Treating CT like a complete black box does not help design controlled manufacturing processes to produce designated products.

Proof of concept should be shown early, even if MoA is not fully known for all parameters, but EU would not accept a submission where MoA will be explored in Ph 3 — should be explored in Ph 1-2. For example — characterize the panel of cytokines affected by the CT, then pick a handful of those as ‘fingerprint’ of activity to monitor clinical trial product consistency.

Q: What are good approaches to provide guidance to new developers of CT products? A: Increasing publication or presentation of case studies; guidances are still emerging for CT (new product class); Eu actively engaged in outreach (workshops, conferences, publications) to bring CT from academic ideas to practical products; sponsors can get scientific advice as early as possible; sometimes they find it is less complicated than anticipated; PMDA also encourages dialog for general strategies for CT development if proof of concept is sufficiently develop to have discussions; focus is on safety of course, but PMDA feels CMC is very important as clinical study starts. EU often sees academic/small firms lacking good scientific and regulatory input (need more than just medical and financial advisors!).

NOTE that the less you can characterize the product, the bigger the pressure will be to generate new clinical data each time there is a change in the process or the product!
ICH Q12 Update: Established Conditions in the Manufacturing Process

Introductory Comments
Wassim Nashabeh indicated 6 members of ICHQ12 committee present in the meeting

Introduction and Update on ICH Q12 Guideline; Frank Montgomery, AstraZeneca, UK
Goal of ICHQ12 is to make post approval changes easier and more efficient globally. FDA (US), EMA (EU), MHLW/PMD (Japan), HC, Swissmedic, ANVISA (Brazil), MFDS Korea; Observers: WHO, TFDA (Chinese Taipei), HSA (Singapore)

Osaka meeting summary:
- Change categories (major/minor) - was big discussion topic. Not all regions have tiers of change notification based on risks of the changes. Tiers considered: Tell and Do (Prior Approval); Do and Tell (Notify), and Do under internal PQS (non reportable, low risk); revised EC chapter would have examples of each..
- CTD section outline of EC (similar to FDA draft guideline) – Supporting information (historical or characterization information) vs EC (forward commitments on process/product)
- PACMP Post Approval Change Management Protocols – some regions use them more than others, even for biotech. Desire is to make them more useful and more used.
- Product Lifecycle Mgmt Strategy was also discussed in Osaka (similar to Japan App Form)
- PQS – Major role in EC since it is internal control system; made edits to it in Osaka; discussed relationship of Assessment and Inspection activities which vary across regions.
- Legacy products – How to enter them into ICHQ12 model; generated draft templates for making changes in methods

Version 7 was finalized in Nov; comments open until April 2017; next F2F meeting in April 2017 expecting a lot of comments!
Yasuhiro Kishioka, PMDA

Provided overview of history of App Form to 2005, which now contains 3 change categories
Goal is to be effective, efficient and flexible while still assuring product quality and consistency

Some challenges remain
- Misuse of the mock as template; should be product specific
- Discrepancies between AF and actual practices (70% from yesterday)
- Some lose sight of purpose of AF; control products only per AF
- No detailed discussion of specification

AF vs Review/Inspection alignment with ICHQ12 elements (good cartoon in slides showing overlap)

Kyoko Sakurai, Pharmaceuticals and Medical Devices Agency (PMDA), Japan

ICHQ8, 9, 10, 11 target CMC development; ICHQ12 address post-approval CMC changes; it uses CTD format to clearly communicate EC vs supportive information

EC = legally binding information required to assure product quality; any changes to EC requires some kind of communication with reg agencies per product agreements

Japan Approved Matters = App Form is contained in Mod 1 with AM; these are extracted from Mod 2 CMC elements, which are derived from Mod 3 (CMC); changes to AM are via PCA (partial change application) or MCN (minor change notification)

Provided detailed example of a manufacturing process EC and levels of reportable changes
Case Studies of Established Conditions in the Manufacturing Process  
Toshiyuki Suzawa, Kyowa Hakko Kirin Co., Ltd., Japan; also JPMA Biopharm Tech Working Committee

Presented AM / EC as interpreted using a “model” biopharmaceutical manufacturing process (CASSS A-Mab QbD Case Study; link [here](#) or at [www.casss.org](#) )

Used a 4-step evaluation approach using scientific and risk-based considerations:

1. Describe assumptions in the model process (“A-Mab”) upstream and downstream operations.

2. Prioritize hypothetical Critical Quality Attributes (CQA) of the “A-Mab” product.

3. Assess and rank risks based on hypothetical Process Characterization (PC) studies and historical manufacturing data.

4. Propose and determine hypothetical ECs and their management level (change classification).

(see slides for detailed elements of each step)

Further discussions are still underway for this case study at JPMA, but it might be leveraged for establishing framework on determination of ECs.
Established Conditions and Enhanced Process Controls
Patrick Swann, Biogen, USA

Further showed how ICHQ12 is designed to build on ICHQ 8, 9, 10 and 11 principles (referenced earlier slides; can get these at www.casss.org)

Real-life based examples are valuable exercises to test the higher level policy strategies considered in WGs.

Showed EC for two scenarios using a model Mab with effector function: (1) Traditional controls for bioreactor, UF/DF, and DS testing *) and (2) Enhanced controls* including a Feed Forward control strategy.
Slide with good table on matrix of business impact vs regulatory affairs impact to prioritize efforts, with ranked examples of EC elements.

Showed how a LCM (Lifecycle Management Plan) can be developed and provide value to a complex bio product (see slides): Provides proof that the Company is operating in a state of control with respect to PQS and Provides transparency for Health Authorities and plan to get agreement on how to report post-approval changes

[*Q – moving DS controls higher in the process (glycosylation, pH, conductivity) still means P/F at those steps*]
Panel Session Discussions

Q: Review and inspection examples in ICHQ12 on how they work together and avoid duplication?
A: Goal is to minimize burden on reviewers/inspectors with increased power of PQS to manage changes; there is an example in ver 7; HA noted that it is critical that assessor/inspectors work together but it is vital that assessors are aware of the PQS and agree that it can serve to manage changes internally.

Q: What do companies have to do internally to facilitate the success of ICHQ12?
A: Fully embrace and implement ICHQ10 PQS! Q10 is a critical baseline that must be in place and function appropriately to be sure it can responsibly manage changes as expected by ICHQ12.

Q: Does ICHQ12 have any plans for metrics to determine if PQS are actually successfully managing changes?
A: Not formally; currently all approved product changes are managed under the PQS, many of which require reg notification; nothing will change about the fundamental role of the PQS, it is just which changes will require which level of notification.

Q: In China, all parameters and tests/specs are included in document for biologics; will CFDA use ICHQ12 to manage post approval changes?
A: Reviewers focus on advancements in technologies for products in China; are currently considering the role of EC in post approval change management policies.

Q: Dr Sakurai (PMDA) slides on two options for VI elements; is there a preference for one or the other?
A: It depends on the data that a company provides to support either one.
Panel Session Discussions

Q: Dr. Suzawa (JPMA) ICHQ12 decision tree with risk ranking or model process, how much variability could be incorporated into the EC?
A: It would be stated in the EC what the ranges could be.

Q: EC details that would be needed would be agreed with each region, but what about harmonization on the level of detail across all regions?
A: Ideal would be to get complete consistency across HA’s but not likely; the table in Ver 7 is an attempt to converge HA thinking on specific principles of EC; hope is future examples could be added that could help discussions. ICHQ12 should provide more clarity across regions, which should facilitate convergent practices among HA.

Q: Currently the inherent/implicit ECs, as well as the level of communication, varies widely across regions; ICHQ12 strives to simplify this system. But what if heterogeneity of changes is more significant on the sponsor side, eg different sponsors choose different change pathways for different products/sites/etc... it will be a substantial challenge on HA reviewers. Thoughts from the panel?
A: Since the level of notification is based on risk approach, there is potential for different risk rankings among sponsors. If sponsors use the EC in the CTD format it would at least allow consistency in the nature of the changes being proposed, but no guarantee that will resolve the challenges.

Q: Are biosimilars and their change management (eg comparability), and the categories of change applied to them, included in the scope of ICHQ12?
A: Yes, BS are covered by ICHQ12 and are treated just like innovator products for comparability and other post market changes, and in terms of the categories of changes they would utilize.
ICH Q12 Update: Established Conditions in the Manufacturing Process

Panel Session Discussions

Q: Transparency and consistency is a key element of fair and balanced regulatory review; does the ICHQ12 decision tree facilitate this concept?
A: There differences in the decision tree examples presented by speakers today, some were before Ver 7 was completed. Further improvements in the decision tree examples would come from discussions with industry and regulators. ICHQ12 outlines principles on how to define CPP with an idea to process outputs. The approach to identification of CPP should be risk-ranked by impact on product quality attributes.

But if EC are mandatory to assure the quality of the product, the question is what must process elements must be controlled to maintain product quality and consistency. Alternative control strategies could be acceptable but then that alternative would become the EC for the process/product.

Q: Is it expected that each change category would be well defined in the approved Lifecycle Management Plan?
A: Yes.
Q: Once the category is captured and approved in the application, how easy (or hard) is to change it?
A: To be determined.

Q: Performance-based evaluation is the only thing which will make ICHQ12 successful. Parameter-based evaluation seems most logical but it is the most complex to implement for EC.
A: It is possible that parameter based may not be perfect, but we have to start somewhere to get these concepts in practice.
Panel Session Discussions

Q: Couldn’t sponsors simply make a commitment on the product CQAs for specifications and leave it at that?
A: In principle it is true that we are interested in the product, but just controlling the final product material is not suitable for biologically derived products where slight changes in process can impact product characteristics that could be undetected by final testing alone (Sarah’s example yesterday!). Easier to do with chemically synthesized drugs.

Q: JPMA and PMDA are each working on ways to adapt the AF to incorporate principles of ICHQ12, what kinds of changes would you envision and when would they be presented?
A: JPMA - we showed some examples but cannot know what is possible yet in terms of ICHQ12; PMDA – there are cases where EC are not solely based on risk assessment strategies, so only using that kind of determination for defining EC may not be acceptable for the AF.

Q: As AM evolve from the current state to the future, what kind of outreach or education is JPMA/PMDA planning to do to move the current mind set into a new direction?
A: JPMA has the Mod 1.2 mock in progress with the PMDA, so if that mock is suitable to use for ICHQ12 model then we would be willing to share with industry to get feedback.

Q: How can CDE continue to consider concepts like ICHQ12, and how could China continue engagement and contributions to the knowledge base?
A: Our knowledge and experience could be combined with further interactions with the ICHQ12 activities; if China industries are interested in having us participate in this, we could do so. Also, we would welcome opportunities to get training on these initiatives and emerging concepts; our goal is always product safety, so efforts that allow us to best serve that goal are welcome.
Established Conditions for the Specification and Analytical Procedure – PMDA Perspective
Rie Fujita, Pharmaceuticals and Medical Devices Agency (PMDA), Japan

• Specs and analytical procedures are in AF as AM; any change requires notification via PCA

• If product has compendial procedure in JP, that method must be used for specification testing

• Compendial methods contain very detailed instructions to reliably conduct the test procedure

• AF may refer to the JP methods for details given there; if not using a JP method, must include all method details in the AF sections.

• Goal for level of method detail in JP and AF is that another lab tech can easily perform the method as written and achieve successful data

• PMDA can see the issues of PCA for simple method changes, but is mindful of the need to assure the quality of the product by understanding in detail how it is analyzed for release and stability

• PMDA did not rule out ICHQ12 approach for EC of methods, but much more discussion is needed before decisions can be made about it.
ICH Q12 Update: Established Conditions for Specifications: Relationship with Analytical QbD

An Industry Perspective on Established Conditions in the Analytical Control System
Christof Finkler, F. Hoffmann-La Roche Ltd., Switzerland

Overview of concepts of QbD for analytical methods.

Case study: Control of Mab fragments three scenarios (1) any technology, (2) same technology, different platform, (3) current approach (most changes require notification). Great examples but slides will not be available.

Scenario 2 is given in ver 7 of ICHQ12

Case Studies of Established Conditions in Analytical Procedures
Akira Nonoyama, Santen Pharmaceutical Co., Ltd., Japan (representing JPMA)

JPMA working committee has been discussing analytical QbD for a while

Provided model potency assay for G-CSF from JP/EP/USP monograph

3 options: (1) current Mod 1.2 AM, (2) optimized description (3) performance based description (excellent, detailed examples; see slides!)
ICH Q12 Update: Established Conditions for Specifications: Relationship with Analytical QbD

Panel discussion

Q: How can you avoid conflict of the approved specification with the written compendial methods? A: Do not include too much detail in the method submitted for approval (intended to be a humorous response)

Q: How does the goal of analytical QbD in ICHQ12 to allow greater flexibility in making post approval improvements in methods line up with the legal requirements from compendial methods that are mandatory in most regions? A: Most pharmacopeias have understanding of equivalency of methods; HC and PMDA confirmed that alternative methods are allowed with supporting data and suitable validation of alternative methods. But if you state that following the compendial method exactly as written, but then have to follow the method as written.

Q: Would ICHQ12 approach be suitable for compendial test methods (like the G-CSF example) to change from approved written procedural details? A: it is allowed to make changes in compendial methods after approval with suitable validation and supporting data if the method principle remains in alignment with JP method, but change would require PCA to the product AF.

Q: Would analytical QbD principles allow compendial method modifications to be done by OMCLs who test the product for regional release without notification to sponsors making those products? A: OMCLs use monographs for other purposes than product control/quality, so they should follow the compendial procedures as written. Changes should be managed by the pharmacopeias.

Q: Replacing legacy technologies with new technologies: two cautions – (1) vendor reagents are not always robust/reproducible, and (b) vendor software is not often validated for GMP. How would this ne addressed? A: Would not introduce a new technology directly into GMP lab.
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Q: Performance based EC for methods?  A: The principle of the method is currently considered an EC in the ICHQ12 group, not just the ATP being measured. Changes to the method procedure would be allowed so long at the principle is retained. Changing the principle would trigger a change notification to reg.

Q: Is the description in Mod 3 S.4. sufficient to inform them about how the method is being run?  A: FDA – not usually; most of the time there is not enough information on the method to assess the method validation or even understand the complete method (eg sys suit, or how results are calculated). Reviewers (inspectors) have to see the complete assay procedure in order to make a determination on the acceptability of the method validation package. To avoid delays in review times, FDA often just asks for the method SOP. New FDA method validation guidance (2015) gives very clear info on how much detail is needed in the dossier Mod 3 on method procedures. ICHQ12 approach envisions providing the key elements of the method in the EC for commitment, and would then provide the complete SOP and method validation package as supportive information for each method.

Q: Where would the EC information on the methods be placed in the CTD?  A: ICHQ12 group agreement is that EC would be given in a separate section as extracted from other supportive sections; different agencies have different opinions right now, but where is less important than what information would be included. Current FDA guidance doc on EC defines sections of Mod 3 as established or supportive, but might not classify the entirety of that section as binding. The other side: is everything in Mod 3 non-binding if you have the EC in another section?  No, since EC are derived from Mod 3 details. Observation: Japan system already does this with Mod 3 to Mod 2 to Mod 1.2. (PMDA approach)

Q: How does using just ATP as the EC assure the control of the product specification?  A: The ATP is based on a collection of data that supports the specification; it is the culmination of several layers of CQAs and controls.

Q: How do you handle reference product specifications and methods are specified; would ICHQ12 allow changes in ref std?  A: No, Ref Std is a regulatory commitment as an EC, so cannot make changes in Ref Std without regulatory agency notification and approval.