Table 13: ICH Q12 Regulatory Tools and Enablers: Lessons Learned

Facilitators –

Shirley Chan, *Genentech, a Member of the Roche Group*

Deep Shah, *Omeros Corporation*

Scope:

ICH Q12 provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner across the product lifecycle. The use of harmonized regulatory tools and enablers with associated guiding principles will enhance the management and implementation of post-approval CMC changes, and will encourage transparency between industry and regulatory authorities, supporting innovation and continual improvement. It will allow regulators and industry to better understand and align on post-approval CMC changes. This forum will discuss the case studies and lessons learned from industry examples in implementing regulatory tools defined under Q12.

Questions for Discussion:

1. Has anyone had experience successfully submitting Q12 to the FDA in original application or supplement? Have you seen any benefits from a regulatory perspective for post-approval changes? Any challenges?
2. Has anyone had experience with submitting to HAs around the globe? Challenges? How have you managed the global aspect of Q12?
3. Will the use of the Q12 tools be sub-optimal if only a few countries/regions have implemented Q12?
4. As the industry focuses more on accelerated development i.e., products with breakthrough and RMAT designations, which means less time on process development/experience, how can the industry approach Q12? Are there any elements of Q12 that can help? Challenges?

Discussion Notes:

January 25 –

1. Has anyone had experience successfully submitting Q12 to the FDA in original application or supplement? Have you seen any benefits from a regulatory perspective for post-approval changes? Any challenges?

No one in the roundtable had experience submitting Q12 to the FDA in original or supplement. One company's pilot program was accepted but submissions outside the pilot received Q&A request in writing from the FDA about "pausing" the review. The group speculated if the delay was due to pandemic priorities. The company does not have an understanding of what content is missing or if any regulations were broken. The filing updated established and non-established conditions, listed commitments, and comparability protocols. CMC changes were out of scope.

The group answered questions 2 and 3 together:

2. Has anyone had experience with submitting to HAs around the globe? Challenges? How have you managed the global aspect of Q12?

3. Will the use of the Q12 tools be sub-optimal if only a few countries/regions have implemented Q12?

The group understands that there is support for Q12 in US, EU, Canada, and Japan. The guidelines are useful if implemented only outside of these countries to ensure continuity. EU faces challenges due to existing laws and legal modifications are necessary if Q12 is to be followed. ICH will play a pivotal role in encouraging countries to adhere to Q12, a roadblock is foreseen if US and EU does not take a lead. There are definite benefits to Q12 which enables better protocols in planning and submissions.

4. As the industry focuses more on accelerated development i.e., products with breakthrough and RMAT designations, which means less time on process development/experience, how can the industry approach Q12? Are there any elements of Q12 that can help? Challenges?

January 27 –

FDA has advised not to include Q12 for products designated for breakthrough/accelerated review, perhaps due to constraints in FDA review timelines during pandemic. Accelerated filings may have limited process, manufacturing and comparability information. The group does not have experience with Q12 on accelerated product filing.

Q1: All of the attendees are just starting or in the progress of figuring out how to implement ICH Q12 within their companies and deciding on the scope of implementing Q12. None had experience submitting a Q12 submission in the original application or supplement. It was shared that FDA has been disappointed in the quality of the Q12 packages and what has been submitted has been insufficient, so some are putting together packages to take to FDA for discussion. Many are taking staged approaches and there is discussion on the value of implementing first for legacy products with lots of manufacturing experience instead of new products.

Similar to QbD, attendees are not clear on how to implement Q12 and how consistent regulators will be in evaluating the submissions. Also similar to the Amab case study, the 2020 CASSS sponsored CMC Strategy Forum of ICH Q12 Case studies and various publications have been very helpful materials and further mock case studies would be very helpful for both industry and regulators. Making these mock case studies and outputs to available for companies to use internally is highly desirable to help foster understanding on how to implement Q12. The hesitancy to seek guidance from regulators was also noted to be a barrier, but all agreed that while the pandemic consumes regulatory resources and novel products are pushed to the back burner, topics like Q12 are lower on the priority list.

One of the key challenges is how much of the Quality Management System is expected to be shared and there is a lot of disagreement with everyone having different ideas. The level of information is at too high a level and "trust us" is not sufficiently supportive. Most acknowledged that the Product Quality System piece of Q12 is not as developed. It was noted that Small Molecules is ahead of Biologics and would be a helpful source of information.

Regarding regulatory relief following Q12, there was no direct experience from the attendees for biologics. It was generally agreed that the perception from reports following adoption in small molecules has not yielded regulatory relief, so there is skepticism as to whether Q12 will be worth the investment of resources. Also similar to QbD, it is expected that Q12 will become expected going forward even if regulatory relief does not occur near-term.

Q2/Q3/Q4: None of the attendees had experience with ex-U.S. Q12 submissions or have had experience with consulting with any other Health Authorities ex-U.S. ANVISA has been very open to Q12 and may be one of the first early adopters. There was interest in

the status of adoption by Japan, and reference was made to the latest CASSS Japan CMC Strategy Forum. It was speculated that Japan may lag in adoption of Q12 based on experience with other ICH harmonization measures. It was noted that the 2020 WCBP Plenary session on Q12 that Health Canada laid out specific hurdles to Q12 adoption, and that HC has made significant progress in removing these barriers. Overall, it was generally recognized that the purpose of Q12 would not be realized unless there is global adoption by Health Authorities.

Thoughts shared on how global adoption could be moved forward, besides what has been discussed above, is that the International Pharmaceutical Regulators Programme (http://www.iprp.global/home) could be a forum for global regulators to discuss Q12 case studies. It was noted that Health Authorities, such as FDA, are legally prevented from sharing dossier information. However shared review programs could allow for some consensus building [e.g. Australia-Canada-Singapore-Switzerland (ACSS) Consortium], as could programs like Project Orbis, in which the Sponsor provides full transparency to all documentation to each participating Health Authorities. In these different review paradigms, the cross-Agency discussion could be taken advantage of to build a consensus approach. The use of an independent consortium where information could be anonymously shared was also proposed as a way to move quickly move forward guidance on Q12, which everyone acknowledged as needing hands-on experience.

Unfortunately, inclusion of items that would slow down reviews for accelerated programs is discouraged, both by the Sponsor and the Regulators, since the goal is rapid access of drug to the patient and not lifecycle management. It was noted that the QMS content for each country is also a challenge for the reasons stated above.

February 2 –

1. Has anyone had experience successfully submitting Q12 to the FDA in original application or supplement? Have you seen any benefits from a regulatory perspective for post-approval changes? Any challenges?

No experiences so far.

Genentech has been part of the pilot program. Some of the challenges in taking a marketed product before and determining where could establish an EC and determining if the change would be a PAS or and AR. After going through pilot were able to pick out some parameters that would not be reportable. Have not submitted to other countries yet, still determining feasibility of submitting Q12.

FDA – pilot to take 9 submissions; different molecules and different products; saw a variety of different approaches. Definitions of equipment, kpps, etc. How do we think about products that have a lot of manufacturing experience and how do you translate that into the Q12? Risks to making manufacturing changes to legacy products.

Any impact due to Covid? Publishing of the FDA guidance is not complete as part 5 of the ICH12. Hard to determine if Covid has had an impact.

Q12 is a tool to harmonize globally for changes.

Health Canada – going with a pilot program in Q3 2021 and update to Post NOC guidance to go along with Q12. HC is looking at how others are approaching and implementing

FDA question for industry – in terms of harmonizing to make changes? Where would there be the most value for manufacturing changes and/or analytical method changes?

Method changes would be an area where we could gain traction. Manufacturing parameters do not change that often, but with CMO changes and tech transfers; container closure changes. Depends on the type of product, maturity of the product. Device changes would benefit.

From a patient perspective it will help them form a compliance perspective and safety .

2. Has anyone had experience with submitting to HAs around the globe? Challenges? How have you managed the global aspect of Q12?

Not yet

3. Will the use of the Q12 tools be sub-optimal if only a few countries/regions have implemented Q12?

Is it worth it to put in all the effort for a Q12 package if it is not going to be accepted by other countries? Many do not accept Post approval protocols.

Where is the value if other countries do not accept Q12?

Since no one has yet utilized Q12 what kind of discussions have people had on how to harmonize.

Discussion regarding ECs and what are not ECs. Streamline internally what comparability protocols will look like for most common changes.

Is EC definition good enough in Q12? It has been debated for 5 years

Is it an easy process to establish ECs? Not easy. How to define each parameter takes a lot of discussion.

How do different Health Authorities interpret ECs.

4. As the industry focuses more on accelerated development i.e., products with breakthrough and RMAT designations, which means less time on process development/experience, how can the industry approach Q12? Are there any elements of Q12 that can help? Challenges?

With so many accelerated programs how do you put together validation criteria for a new product?

Maybe leverage platform knowledge.

Anyone used platform knowledge to accelerate program? Biogen has used elements of it for specification settings. Monoclonal antibodies can build on the platform. Genetech has done this for specs and process parameters.

FDA/HC – are they seeing more of this? HC has seen with monoclonals; mfg process is similar across the board. HC is willing to work with industry as long as the characterization, assays and stability has been performed and are supportive of the process. Does help accelerate review. FDA also has seen this with some products. Specifications and platform knowledge of the manufacturing process development can be leveraged.

FDA - Q12 does not change risk assessment, but allows us to develop reporting strategy using prior knowledge.

FDA asked: Does industry feel Q12 will benefit develop programs?

- Maybe for future changes. what are the major post approval changes and how often? May be too early to know
- Maybe for analytical methods as those are not changed during development
- Constantly learning how to leverage previous knowledge.
- Global expansion to new markets – have to build in the market requirements; ex China.

How would FDA like to see Q12 used?

- Industry tool, but will work with industry and if there are changes that do not need regulatory oversight that is a win for everyone.
- Canada has the Post NOC guidance and will look at incorporating Q12. Still too early for HC.

Anything from Pilot that did not work or insufficient information?

- No negative. Did have success in approving some. Understanding the vocabulary in your manufacturing documents and that it translates to what is in Q12. Be transparent with your approach.

HC Pilot – has HC started putting together communication to the industry. How will this impact CPIDs. – current resources are involved with COVID and not sure when they will communicate to industry. May be end of summer or fall 2021. Post NOC and CPID guidance will be updated.

Pilot program for FDA complete. Is FDA accepting any additional Q12 submissions ? FDA had to drop so did not answer.