Expanded Change Protocols

Benefits, Cost Considerations, and Regulatory Views

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The US FDA Office of Biotechnology Products' quality by design (QbD) pilot program defines an expanded change protocol (eCP) as a particular type of comparability protocol that will "describe the quality by design, risk-based approach linking attributes and processes to product performance safety, and efficacy" (**1**). Sponsors have explored a wide range of potential applications for eCPs (e.g., movement within or beyond an established design space, site transfers, and additional process modifications supported by either a QbD or traditional regulatory submission).

Here we summarize the findings of the California Separation Science Society (CASSS) Chemistry, Manufacturing, and Control (CMC) Strategy Forum titled "Practical Use of Expanded Change Protocols," which was held in Washington, DC, on 28 January 2013. This forum evaluated the 2008 definition of eCPs in light of case studies and examples that — although they represent eCP concepts — may not fully realize the original vision.

The forum explored what the "expanded" descriptor of an "e"CP really means, as well as challenges, opportunities, and pitfalls to eCP strategies. Participants discussed the relevance of eCP submissions to support global changes and briefly compared eCPs to Europe's postapproval change management protocols (PACMP). The forum intended to answer the following broad questions:

Strategy Forum attendees and presenters discuss the benefits and challenges of using expanded change protocols.
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- What is an eCP?
- What type of changes should be considered for eCP?
- What are the challenges and benefits of using eCP regulatory strategies?
- How can we as an industry continue to evolve the eCP concept?

What Is a Change Protocol?

A *change protocol* is a specific type of regulatory submission that is submitted in the United States as a regulatory agreement. CPs are submitted as prior approval supplements (PAS) under 21 CFR 601.12(e). In a traditional comparability protocol, sponsors define a change based on a specific business need. Then they describe predefined acceptance criteria and requirements that must be fulfilled upon implementation of that change. This type of prospective definition of change requirements then allows for a reduction in submission category when the change is implemented.

For example, a site transfer is typically submitted as a PAS following execution of qualification lots and generation of data to support the change. Lots produced as part of this change may not be released to the market until four months after the FDA approves the change. Following FDA approval of a comparability protocol, the change then could be filed as a Changes Being Effected in 30 Days (CBE-30) supplement upon the generation of data meeting defined acceptance criteria. Lots produced would then be restricted from supply to the market for 30 days.

What Is an eCP?

In his forum presentation, Patrick Swann (FDA's Center for Drug Evaluation and Research, CDER) distinguished traditional CPs and eCPs. Traditional CPs typically identify critical quality attributes (CQAs) and define a manufacturing process and control strategy. eCPs use a systematic approach for evaluation and understanding, identify functional relationships that link material attributes and process relationships to CQAs, and use quality risk management (QRM) to establish an appropriate control strategy that can include proposals for design space. CPs are limited in scope and duration.

By contrast, eCPs are meant to be "living" transparent and documented strategic and tactical plans for managing the changes that a company

CMC Forum Series

The CMC Strategy Forum series provides a venue for biotechnology and biological product discussion. These meetings focus on relevant chemistry, manufacturing, and controls (CMC) issues throughout the lifecycle of such products and thereby foster collaborative technical and regulatory interaction. The forum strives to share information with regulatory agencies to assist them in merging good scientific and regulatory practices. Outcomes of the Forum meetings are published in this peer-reviewed journal to help assure that biopharmaceutical products manufactured in a regulated environment will continue to be safe and efficacious. The CMC Strategy Forum is organized by CASSS, an International Separation Science Society (formerly the California Separation Science Society), and is supported by the US Food and Drug Administration (FDA).

can predict it will need to make to continue to manufacture product and maintain supply chains worldwide. However, an eCP cannot be a collection of opportunistic or vague changes. Manufacturers cannot say "trust us, we will fill in the details as we go." That is not the spirit or the letter of what eCPs were meant to be.

The Importance of Scope

In a traditional CP, a clear understanding of scope and what is included within the protocol is important. Because an eCP can cover a much broader range of changes (from implementing a design space to providing for future potential changes in other cases), it must also define limitations. For example, an eCP describing potential transfers to future undefined sites must specify limitations to that change such as "approved product and licensed site."

What Are the Benefits of Using an eCP Strategy?

Given the importance of specifying limitations and the complicating factors of harsh realities that sponsors face in global postapproval change management, discussion of the benefits offered by using eCPs include

- downgraded regulatory reporting category (e.g., PAS to CBE-30)
- business need flexibility (e.g., sponsors produce products from more sources; make continuous improvements in existing processes; increase capacity; and decrease risk to supply chain such as from interruptions). Such benefits are particularly useful given the "faster, cheaper" mandate that managers live with.

Establishing a program of eCPs may also add value for sponsors by

- promoting risk-based decision-making throughout a product's life cycle
- generating enhanced visibility into the decision-making processes in a regulatory submission
- establishing a consistent approach to changes
- encouraging efficient regulatory processes, including fewer regulatory submissions and increased consistency
- cost and time savings
- better assuring of supply to patients and mitigation of risks.

The Regulator's Perspective

Numerous federal statutory requirements (e.g., CFR 314.70) address assessment of changes and a slate of US and international guidance documents that can help us manage them (2–5). The importance of such documents should not be underestimated. When manufacturers put their products into manufacturing requests for the FDA, it is a legal contract, and agency regulators have to be cautious about what they can approve. Regulators have restrictions on what they are allowed to do, and manufacturers must be aware of them.

Manufacturers should attempt to take a regulator's perspective. For example, consider the amount of data that a regulator would require to approve a change for an injectable drug product. It is not a trivial task.

Swann presented a slide that caught everyone's attention: It illustrated the number of CPs submitted between 1995 and 2012 for monoclonal antibody (MAb) procresses. Although the total number of approved products increased each year, the number of

CPs peaked between 2006 and 2010 and then sharply dropped. Swann said the FDA could not assign a cause to this drop, but he speculated that manufacturers may be combining many changes into eCPs rather than submitting traditional CPs. He said it is also possible that changes are being filed through other mechanisms such as supplements.

The FDA found a sharp increase (after 2006) in the number of CPs related to moving from single-product to multiple-product facilities. The agency also found an increase in CPs related to facilities, buildings, and locations but none to changes in manufacturing processes and scale.

The study found no CPs relating to analytical methods before 2006, but afterward the category increased quickly. It is unclear whether this observation is due to the incorporation of analytical method changes into overall processes or to site changes that also incorporate method transfers.

Swann suggested that changes made during product development and following commercialization should form part of a scientific continuum of systematically orchestrated plans. Those plans should link process capability and product quality to the safety and efficacy that was demonstrated in clinical trials.

Not all changes are appropriate for CPs, either traditional or expanded. Some changes have to be judged case by case. In 2008, the FDA initiated an eCP pilot program for biotechnology products designed to "gain more information on and facilitate agency review of quality-by-design risk-based approaches for

manufacturing biotechnology products" (6). The program showed that the proposed scope of a change needs to be matched by process and product knowledge. That knowledge then must be conveyed to the FDA. If a change is over ambitious, then it substantially challenges a company to design a plan that adequately measures and monitors for all possibilities. Alternatively, requested changes cannot be too vague, because it would then be impossible to anticipate what body of data would be required to assess the impacts of specific changes. If requested changes are too ambitious or are not adequately specific, then an FDA reviewer does not have enough confidence that a manufacturer can predict and detect their consequences.

However, manufacturers have successfully used eCPs with defined numbers of changes and defined amounts of data to support them. Swann presented a quote that summarized the importance of such definitions: Responding to an eCP request, the FDA wrote, "While the intent of the eCP is to allow for more expanded changes, your proposal to include undefined and significant process improvement changes is not supported by the product and process knowledge conveyed to the agency."

To initiate an eCP, manufacturers must share a sufficient amount of data with the FDA to gain a regulator's confidence. Sponsors face an "iceberg model," in which they have a large amount of analytical data available about their manufacturing process, but they provide a much smaller amount of that data to the agency. Sponsors may be confident about requested changes because of available in-house data, but they must share that information with the FDA. If such information is not shared, then regulators cannot sign off on requested changes. Determining what information a sponsor will and will not convey to the agency is a critical task. If data are not shared with the agency, then that information might as well not exist.

New Tools

Regulatory agencies are encouraging sponsors to develop new analytical tools. Swann highlighted four characteristics that the FDA would like to see in improved analytics.

The first is **adequate sensitivity to changes** that could occur in a product. Providing an example, Swann described a study that looked at the relative sensitivity and specificity of a set of orthogonal analytical methods. Some of those were classical methods such as potency measurement and size-exclusion chromatography, and others were more enhanced techniques such as methods to assess tertiary structure.

Analytics also can be improved with the **use of fingerprint methods**. Such methods would be specially useful for assessing elements such as posttranslational modifications (e.g., improved glycosylation analysis).

Advanced analytics can be used to assess the **impact of manufacturing equipment on product quality,** such as changes in subvisible particles that result from changes to filling equipment. Other factors include changes to a processes, resins, media, and filters. Such modifications can have substantial impacts, even at a final fill stage.

Finally, **more objective analysis of data** is needed, especially equivalency testing of degradation rates of stability samples. That process could include analysis of degradation curves, as appropriate.

Other Strategies: The FDA supports comprehensive risk ranking of manufacturing parameters. Sponsors should conduct that exercise and communicate their results to regulators. Swann highlighted examples of sponsors that had grouped potential changes together as high, medium, and low risk. Each category had a corresponding regulatory reporting level.

Evaluating the direct link between process characterization/qualification and change protocols is beneficial. Data from characterization and qualification work are critically important elements in assessing the risk of proposed changes, which is why QbD and eCPs correlate well. QbD provides product and process understanding, which could lead to more information useful for establishing an eCP.

Industry Perspective

Stephen Notarnicola (Biogen Idec), Toshi Mori-Bajwa and Duane Bonam (Amgen), Alan Gardner (GlaxoSmithKline), and Julia Edwards (Genentech) also presented at the forum. Their companies have put large cross-functional efforts into developing eCP approaches to solve specific change-management situations and to get a down-regulated reporting category for changes. Doing so doesn't mean absolution, however. Manufacturers still must collect data and show that changes do not affect product quality. Approval of a plan is not approval of the outcome of that plan.

eCPs satisfy clear business needs. More than ever before, manufacturers have to obtain more products from more sources. They make continuous improvements in existing processes and balance network capacity — all while facing pressures to reduce interruptions in their supply chains. Using eCPs can lead to great rewards, but it also requires a great deal of effort and expense. Manufacturers often won't know whether eCPs will be worth the trouble until they go through those efforts. Overall, the company representatives that presented their experiences seemed to feel that eCPs were well worth the work in the long run. Examples include retrofitting an eCP to an approved product (Biogen-Idec); applying an eCP to postapproval changes (Amgen); managing changes throughout a product's life cycle (GlaxoSmithKline); and leveraging an eCP for multiproduct facilities and across multiple sites (Genentech).

Presenters described a considerable convergence in strategies. "Paper" exercises conducted by most manufacturers included

- identifying and justifying critical process parameters (CPPs) and critical quality attributes (CQAs)
- thoroughly assessing risk in accordance with ICH Q9 (7)
- grouping changes into risk categories and designing data packages to fit those categories (the amount of

data in a package must be commensurate with stated risk)

• categorizing changes according to the output of those risk assessments and developing supportive data packages that are commensurate with the stated risk

• leveraging historical experiences and process development data to confirm models from which CPPs and CQAs could be drawn

• ensuring that quality system managment and product quality support systems are in place to support and control confidence in the manufacturing operations.

"Wet chemistry" exercises (conducted by most manufacturers) include confirming key parameters using process models. Industry representatives spoke of risks associated with extrapolating too far across process scales. Wet chemistry exercises could also involve developing data plans that include release and ICH stability testing; characterization and comparability studies using extended analytics; and comparative stability studies under stress conditions, which may be predictive of degradation products seen longer term under preferred storage conditions. Forced degradation (chemical and physical) can compare the analytical patterns obtained from pre- and postchange materials to further assess elements of structural comparabiity .

Industry presenters reported many similarities in feedback from regulators. The FDA requested that manufacturers

• clearly define the scope and limitations of what will be included in an eCP and omit changes that potentially present high risk to product quality

• drill down on acceptance criteria — either because the agency needs preliminary data to assure itself that the plan would be successful or because the agency needs more detailed information about how a company plans to set appropriate acceptance criteria if the actual numerical values are not submitted in an eCP.

The agency also emphasized that sponsors should be sure that they have the most current body of data in hand at the time that a change is made. Manufacturers should continue to collect data during new batches and new stability data information before executing a proposed change.

For the European Union (because there are different jurisdictional requirements for facilities the inspectorates are in charge of), it was indicated that manufacturers would need to have GMP certification of their facility's compliance. This is a potentical benefit for using existing, certified production facilities instead of new sites seeking certification, and adds another factor to eCPs if a company has a new site or a new product for a site that has never been exposed to regulatory scrutiny.

The meeting included discussions of the overall value of eCPs, given the significant time and expense that manufacturers put into them. Presenting manufacturers agreed that eCPs are a source of valuable feedback from regulators, which can be useful for other aspects of product development — even for products that are currently still in development. The exchange of information and technical discussions are themselves quite fruitful for sponsors. Furthermore, once an initial eCP is completed — which can be quite time-consuming — it can serve as a template for future eCP applications (e.g., for products using a similar process platform).

eCPs force a team to go through the process of defining and planning a manufacturing process against a tangible deliverable. Those tasks serve to disperse product expertise that otherwise may be restricted to just a few individuals. If original team members leave an organization, then their expertise goes with them. Putting together an eCP helps sponsors harness such expertise before that happens.

The exercise also can be valuable for deciding which changes can be included as part of an initial biologics license application (BLA). A change protocol approved along with a BLA can accelerate implementation of changes that are anticipated in near-term postcommercial launch.

Overall, eCPs seem ideally suited to platform processes for which large bodies of data are relevant to many products. An example is a MAb platform, which incorporates many similar manufacturing steps and analytics, although each MAb is itself unique.

Barriers to Using eCPs

The final portion of the forum was devoted to a discussion of current barriers that may be preventing more widespread use of eCPs.

The good news is that most barriers to eCPs seem to be procedural rather than scientific. In the past decade, industry and regulators have worked to develop technical approaches that would satisfy the needs of regulators to have information they need and would provide businesses the tools to manage the changes they need. The technical body of information is needed for identifying critical aspects and assessing risks associated with them. Many sponsors have had success with such an approach for clearly defined postappoval changes.

The biggest procedural issues seem to revolve around regional regulatory authorities' allowances of eCPs. Although the benefits of using eCPs can be achieved in the United States, the nature of the global pharmaceutical business is such that sponsors often wait for protracted amounts of time to receive global approval.

During the meeting a number of participants noted that the lead time for getting eCPs reviewed and approved globally is very long and heterogeneous. The eCP pathway is available in the United States, but most sponsors have — or at least aspire to have — global distribution of their products. Japanese regulators do not accept eCPs. European authorities have change management plans (CMPs), but those are not truly expanded from the perspective of multiple product changes. The European Medicines Agency (EMA) also has a type II variations guideline, which is similar to an eCP, but it is not used much.

Disclaimer

The content of this manuscript reflects discussions that occurred during the CMC Strategy Forum. This document does not represent officially sanctioned FDA policy or opinions and should not be used in lieu of published FDA guidance documents, points-to consider documents, or direct discussions with the agency.

Some company representatives at the forum questioned the benefit of using a US-based eCP if they still have to produce appropriate bridging stock in advance of non-US approvals. Such inconsistencies can lead to supply chain fractionation. Postchange material can be supplied in the United States, but elsewhere sponsors would have to continue to use prechange material. During the discussion, participants pointed out that big manufacturers can manage such a dual-supply strategy, but small and even midsized companies lack the necessary infrastructure.

If sponsors are trying to manage their global supply chains and have different versions of a product approved in multiple regions, they might have difficulties managing regulatory compliance in processes such as change control. A logical solution to such issues would be a multinational convergence effort on regional regulatory requirements that could provide guidance on globally acceptable elements of eCPs. For example, such elements could include the nature and extent of data required to support a design space. That effort would have to be driven by industry because regulators have legal constraints on what they can share internationally.

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