Established Conditions and Its Applications

Bhagwant Rege
Division Director
Division of Modified Release Products
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality

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Regulatory Background

- CDER regulations at 21 CFR 314.70 state:
  - "an applicant must notify FDA about each change in **each condition established** in an approved application beyond the variations already provided for in an application" (i.e., an NDA or ANDA)
  - Similar language exists in 21 CFR 601.12 for BLAs
- Historically, confusion about what is "each condition established"
- Part of the motivation for development of ICH Q12 (Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management)

Real World Concerns

- Lack of clarity regarding which elements of the application are a “condition established” leads to:
  - Unreported changes or supplements at the wrong categorization level
  - Confusion over which changes are supplements vs. to be managed under Pharmaceutical Quality System (PQS) only
- Partly driven by a lack of alignment regarding necessary information and level of detail in the application
- Desire between industry and regulator for more post-approval ‘operational flexibility’ regarding change management
- Desire to realize intended benefits that result from Q8, Q9, Q10, Q11 implementation

Post Approval Changes

- Change may not mean that the applicant didn't get it right the first time and something must be fixed or improved
- Changes may indicate continual improvement including implementation of advanced manufacturing and analytical technologies among others
- Change can be a sign of a mature quality system as it gains product and process understanding
- FDA would like to:
  - Encourage behaviors where applicants take more responsibility for product quality
  - Incentivize deeper and holistic implementation of ICH Q8-11 principles
  - Ensure appropriate and well-functioning PQS is in place (ICH Q10)
  - Facilitate the streamlined implementation of changes that improve quality

Why now?

- FDA, global regulators, and industry acknowledge that the post approval change reporting process needs improvement
- Various improvement steps taken, e.g.;
  - FDA: CDER and CBER developed guidance (draft) to explain their thinking about what "each condition established" meant and to support development of ICH Q12
    - Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products (May 2015)
  - PMDA: approved matters
  - Health Canada: CPID
  - ICH: Q12

ICH Q12

- Provides a framework to streamline the management of post-approval CMC changes in a more predictable and efficient manner
- Encourages innovation and continual improvement
- Bring envisioned operational/regulatory flexibility to fruition, e.g., by demonstrating how enhanced product and process knowledge contribute to a reduction in the number of post-approval regulatory submissions
- FDA draft guidance on ICH Q12 published on May 30, 2018, public comment period closed on Dec 15, 2018
- ICH Q12 EWG Interim Meeting in Tokyo (Feb 11-15, 2019)
  - Revision of guideline based on public comments

Established Conditions (ECs)

- ECs are legally binding information [within an application] considered necessary to assure product quality
- As a consequence, any change to ECs necessitates a submission (PAS, CBE, AR) to FDA
- ECs govern the scope of reportable post approval changes
- All changes require management under the pharmaceutical quality system (PQS)

Established Conditions (ECs)

As envisioned in ICH Q12, ECs provide a platform to:

- Reduce submission of unnecessary supplements
  - Effective post approval submission strategies
- Encourage pre-application development work
- Encourage post-application continual process improvements
- Allow FDA to better regulate post-approval changes
  - More flexibility for manufacturer
  - Risk-based principles allow focus on most important changes during assessment and inspection

Established Conditions (ECs)

As envisioned in ICH Q12, ECs are expected to:

– Focus FDA's limited resources on
  - Assessment and inspection efforts on facilities, products, and operations that pose the highest risk to patents, where there is insufficient product / process understanding
  - Verifying appropriate and well-functioning PQS is in place (per ICH Q10)

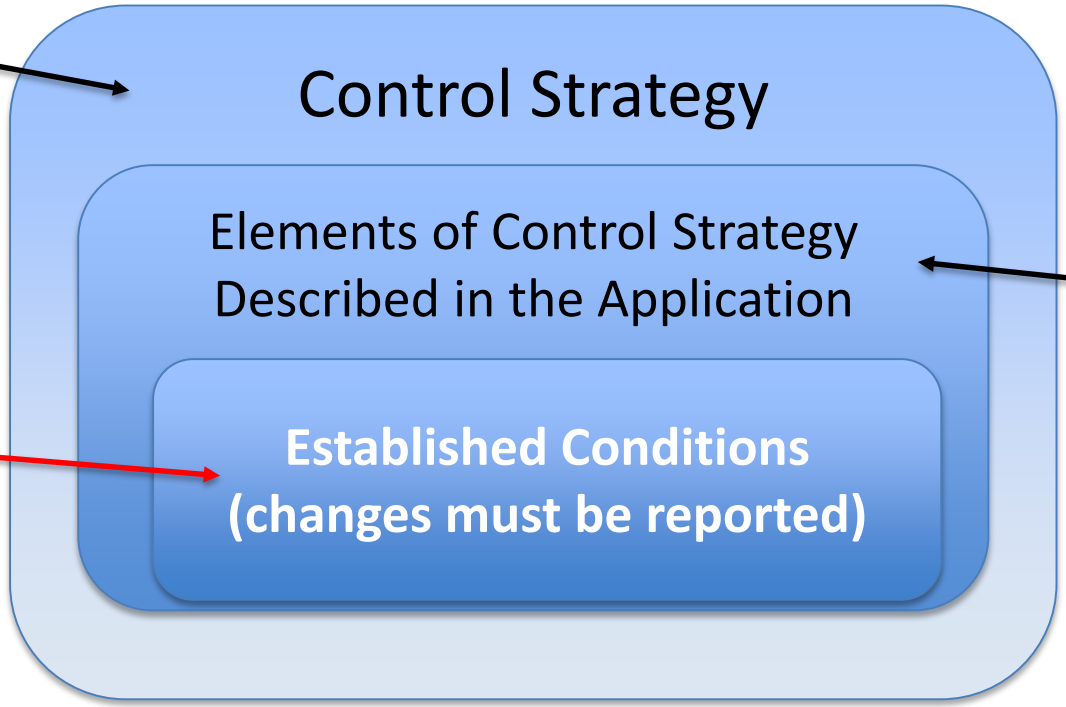
– Encourage monitoring and trending (i.e., continued process verification) to identify opportunities for improvement

Established Conditions (ECs)

- All regulatory submissions contain a combination of ECs and supportive information, i.e., not all information in an application is an EC
  - Supportive information is not considered to be ECs, but is provided to share with FDA the development and manufacturing information at an appropriate level of detail, and to justify the initial selection of ECs and their reporting category

Overall Control Strategy

Entire control strategy including facility, environmental controls, etc.



Described to support product and process

Elements necessary to assure process performance and product quality

Typical ECs

Examples include:

- Drug substance name and structure
- DS and DP manufacturing sites
- DS and DP specification, methods, acceptance criteria
- DS and DP manufacturing – unit operations and sequence; *for inputs/outputs, see slide 19*
- DS and DP container closure material(s) of construction and specification
- DP batch formula
- DP storage conditions and shelf-life

ICH Q12 includes a table listing sections of the eCTD where ECs are generally located

Typical Locations for ECs*

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.S	DRUG SUBSTANCE	
3.2.S.1	General Information	
3.2.S.1.1	Nomenclature	Drug Substance Name, Structure
3.2.S.1.2	Structure	
3.2.S.1.3	General properties	Supportive information
3.2.S.2	Manufacture	
3.2.S.2.1	Manufacturer(s)	Drug Substance Manufacturing Site(s) (including testing)
3.2.S.2.2	Description of manufacturing process and process controls	Individual unit operations and their sequence in the manufacturing process For levels/details of ECs for inputs (process parameters and material attributes) and outputs of individual unit operations, reference is made to Chapter 3.2.3.1 – Identification of ECs for the Manufacturing Processes
3.2.S.2.3	Control of Materials	Starting material specifications (test, elements of analytical procedure and acceptance criteria) Raw material/reagent/solvent critical controls Source of materials (e.g., cell and seed source, raw materials) and control of critical materials of biological origin Generation and control of Master - Working Cell Bank / Master, Working Seed Lot, etc. (B)
3.2.S.2.4	Control of critical steps and intermediates	Specifications (e.g., test, elements of analytical procedure and acceptance criteria) for critical steps and intermediates including storage conditions of critical intermediates
3.2.S.2.5	Process validation and/or evaluation	Supportive information

*From Step 2 ICH Q12 document

What's different?

- Current:
  - Though each application had "conditions established" when approved, specific established conditions for an application are interpreted through regulation and guidance
- Future:
  - Established conditions for each application may be specified and documented when FDA approves and application
  - This brings clarity to those changes that require a submission and those that can be implemented solely by quality system

Defining Established Conditions

- Under the current system, there are established conditions not articulated by FDA or the applicant (e.g., specifications) and the applicant makes changes to them according to 314.70 and existing guidance related to post-approval changes (e.g., SUPAC)
- Under ICH Q12, ECs can be specifically identified and proposed by the applicant together with their proposed reporting category as part of a regulatory submission (original or PAS)
  - Appropriate when either the proposed EC or reporting category is different than regulation or FDA guidance
  - Proposal must be justified by applicant

Example ECs (from ICH Q12)

CTD Section	Section Title	Established Conditions Note that identification and justification of ECs are presented in the relevant section of CTD	Reporting Category when making a change to the Established Condition	PACMP or Post-approval CMC Commitment, if applicable
3.2.P				
3.2.P.3.3	Description of Manufacturing Process and Process Controls - Unit Operations			
	Powder Blending Operation	Input Material - API PSD 5-200um	Notification Moderate	
		Input Material – API Moisture <1.0%	Notification Low	
		Excipients Specification Pharmacopeial	By regional requirement	
		Equipment Type Diffusion blender (V-blender)	Notification Moderate	
		Scale 200kg	Notification Low	PACMP included in the MAA for expanded range for scale to be submitted as a Notification Low
		Blend speed 10-20rpm	Notification Low	
		Blend time 15-25 minutes	Notification Low	CMC commitment to monitor dissolution performance for 10 batches manufactured at upper end of blend time range due to potential over lubrication at the proposed commercial scale
	Roller Compaction Operation	Equipment Type Roller compactor with 10cm rolls	Notification Moderate	
		Roll Gap 2-4mm	Notification Low	
		Roller Compaction Force 5-10kNcm^{-1}	Notification Low	
		Roller Speed 4-10rpm	Notification Low	

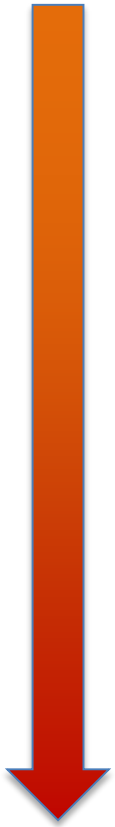
Identifying ECs and the Role of Risk

- The extent (number and how narrowly defined) of ECs will vary based on a number of factors, including:
  - Product and process understanding including an assessment of criticality and risk management approaches
    - CQAs and CPPs
  - Product characterization
  - Product development strategy
  - Control strategy
  - Desired product performance

Identifying ECs for Manufacturing Processes

- Unit operation and the sequence of steps
- Considering the overall control strategy, those **inputs** (e.g., process parameters, material attributes) and **outputs** (may include in-process controls) necessary to assure product quality
  - critical process parameters (CPPs, as defined in ICH Q8(R2))
  - key process parameters (KPPs)
    - parameters of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly controlled to assure process consistency as it relates to product quality.
- Several comments on KPP received in the docket; planned update

Identifying ECs for Manufacturing Processes and the Development Approach



- A **parameter based approach**, in which product development prior to regulatory submission provides a limited understanding of the relationship between inputs and resulting quality attributes, will include a large number of inputs (e.g., process parameters and material attributes) along with outputs (including in-process controls).
- An **enhanced approach** with increased understanding of interaction between inputs and product quality attributes together with a corresponding control strategy can lead to identification of ECs that are focused on the most important input parameters along with outputs, as appropriate.
- In certain cases, applying knowledge from a data-rich environment enables a **performance based approach** in which ECs could be primarily focused on control of unit operation outputs rather than process inputs (e.g., process parameters and material attributes).
- Several comments on development approach received in docket; revision is under discussion in ICH Q12 EWG

In many cases, likely to be a combination of these approaches

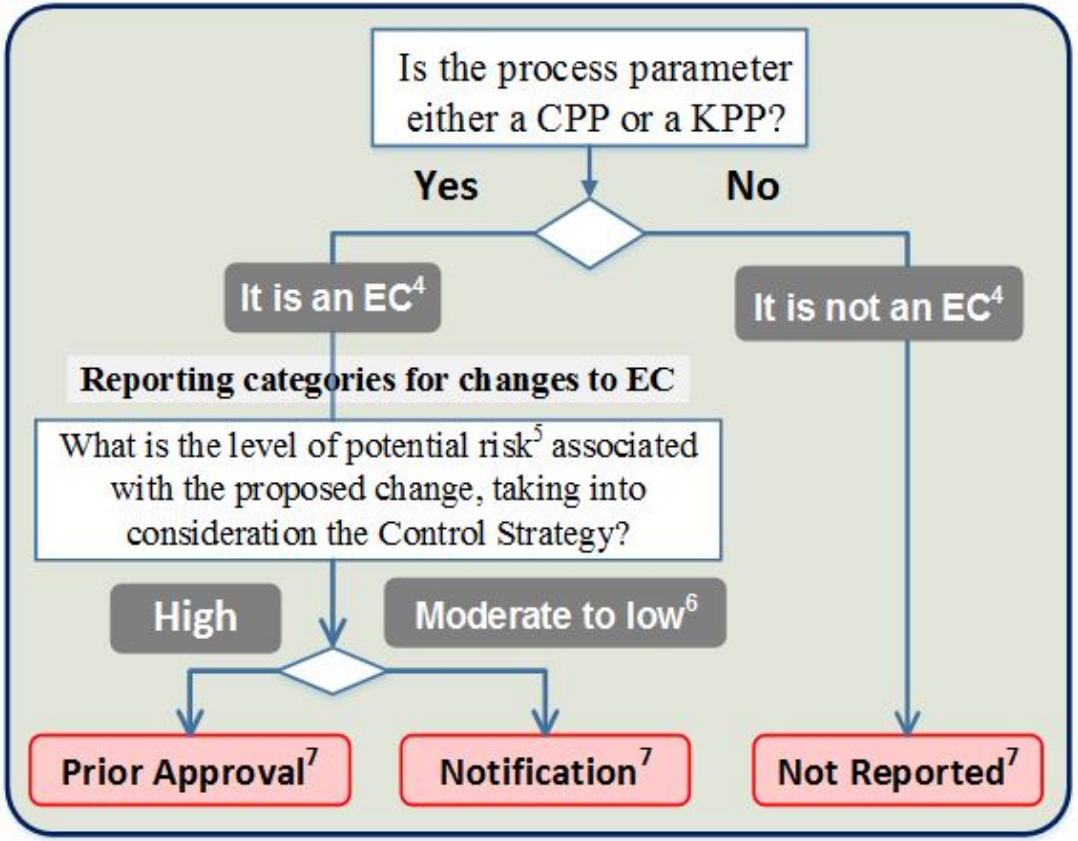
Parameter vs Enhanced vs Performance-Based

	Parameter	Acceptable ranges and reporting categories (White boxes are ECs, and orange ones are not ECs.)			Comments/Justification Refer to section 3.2.P.2. for detailed justification and experimental data
		Parameter Based Approach	Enhanced Approach	Performance Based Approach	
Input Materials	Powder Blend	from blending operation	from blending operation	from blending operation	Enhanced Approach Understanding of the inter-relationship between roll force/gap and roll speed allows for consistent process operation in achieving a target ribbon density. This provides the optimal input for the subsequent milling operation. Following milling, granules with the desired particle size distribution, flow and compressibility characteristics are generated. These quality attributes verified following the milling operation minimise the need for output performance measurements in the roller compaction operation. Expanded knowledge from experimental studies allows definition of operating ranges and lower reporting categories to be proposed. Performance Based Approach Using a performance based approach (online NIR analyser) in the control strategy allows ribbon density to be confirmed in real-time. This allows more flexibility in the type of roller compactor equipment and operating conditions. These output measurements ensure process performance and acceptable ribbon quality attributes. Online measurement of a defined ribbon density with feedback to roller compactor operating parameters reduces variability and ensures lot to lot uniformity of granules for compression. Typical operating conditions are described in Module 3.2 as supportive information and monitored to assure performance.
Equipment and Parameters	Equipment type	Roller compactor with 10cm rolls (PA)	Roller compactor with 10cm rolls (NM)	Roller compactor with 10cm rolls (NL)	
	Roll gap	3mm CPP (NM)	2-4mm KPP (NL)	3 mm (NR)	
	Roller compaction force	8kNcm^{-1} CPP (NM)	5-10kNcm^{-1} KPP (NL)	7.5kNcm^{-1} (NR)	
	Roller Speed	8rpm CPP (NM)	4-10rpm KPP (NL)	7rpm (NR)	
Output performance measure	Ribbon Density Method	Not Tested	Not Tested	NIR online analyser (PA)	
	Ribbon density (solid fraction)	Not Tested	Not Tested	0.7-0.9 gcm^{-3} IPC (PA)	

Proposed Reporting Category

- After identifying ECs, applicant proposes reporting category (PAS, CBE-30, CBE-0, AR) for post-approval changes
- May follow existing regional regulations and guidance or propose alternate reporting category
- Reporting category is dependent on the potential risk to quality
  - Risk assessment activities should follow approaches described in ICH Q9
  - Consider the overall control strategy and any possible concurrent changes

Identifying ECs for Manufacturing Process*



*Does not apply to the performance based approach

Identifying ECs for Analytical Procedures

- ECs for analytical procedures should include elements which assure performance of the procedure
- Where the relationship between method parameters and method performance has not been fully studied at the time of submission, ECs will incorporate the details of operational parameters including system suitability
- When there is an increased understanding of the relationship between method parameters and method performance defined by a systematic development approach including robustness studies, ECs are focused on method specific performance criteria (e.g., specificity, accuracy, precision)rather than a detailed description of the analytical procedure

Where Will ECs Be Submitted?

Q12 proposes a Product Lifecycle Management (PLCM) document

- Serves as a central repository of the ECs, reporting category for making changes to approved ECs, comparability protocols, and post-approval CMC commitments
- Provides a high level summary of product control strategy to clarify and highlight which elements of the control strategy should be considered ECs.
- Facilitates and encourages a more strategic approach to lifecycle management
- Enables transparency and facilitates continuous improvement
- Currently ICH Q12 does not specify a location – Under discussion in ICH Q12 EWG

After Application Approval

- List of ECs needs to be maintained
  - Updated list should be submitted with each supplement or annual report
  - ECs should be updated based on knowledge gained during the lifecycle
- ECs may be reviewed and reconsidered if observations on inspection indicate problems with the quality system that call into question the firm's ability to manage changes

What's Next?

- Established Conditions Pilot Program: FR notice published on 02/15/2018
- The objectives of this pilot program are to gain practical experience in:
  - assessing proposed ECs (i.e., explicit ECs);
  - engaging with applicants during the review cycle to refine proposed ECs;
  - ensuring assessment decisions are made without negatively impacting the ability to meet user fee timeframes; and
  - identifying agreed-upon ECs at the time of approval
- Experience gained from pilot program will help guide the implementation plan

What's Next?

- ICH Q12 EWG currently revising the Step 2 document based on comments received
- Aim to get consensus on core guideline in the next ICH meeting in June 2019
- Implementation period/details to be determined

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Questions?