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AN INDUSTRY PROPOSAL FOR CHANGE NOTIFICATION PRACTICES FOR SINGLE-USE BIOMANUFACTURING SYSTEMS

BPSA℠
Bio-Process Systems Alliance
Advancing Single-Use Worldwide

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TABLE OF CONTENTS

INTRODUCTION

Current practices surrounding change notification in the biopharmaceutical industry are neither efficient nor conducive to accelerating the adoption of single-use systems (1, 2). From a drug manufacturer's perspective, it is common to observe that change-data packages are lacking in technical content or detail and that the time allowed for change implementation is too short. Occasionally, changes are learned of after the fact, possibly even by happenstance. From a supplier's perspective, it is difficult to understand the potential impact of a change on a customer: the regulatory environment is a murky picture, how drug manufacturers use supplier data is likewise opaque and drug manufacturers do not have a uniform set of needs and expectations.

Thematically, these observations may be attributed to industry-wide deficiencies in communication and process standardization. Communication requires that customers explicitly inform suppliers of their regulatory, business, technical drivers/expectations related to change notification and the ways in which the supplier's products are being used. Suppliers likewise are required to communicate changes clearly, promptly and with technical rigor. Aligning all parties to a change notification process, to definitions of terms and to clarified roles and responsibilities would greatly facilitate communication and process standardization across the industry.

The above discussion is more fully illustrated in White and Ott (1). In this article, the authors, writing on behalf of the BioPhorum Operations Group (BPOG) and the Bio-Process Systems Alliance (BPSA), discuss the industry's change notification problem, the impact of ineffective change notification, the collaboration between the two organizations and the key elements of a best practice for single-use systems. Since this publication, the collaboration team, comprising the authors and contributors from 17 drug manufacturers and 12 suppliers, has strived to turn the vision of the first paper into a proposed Practice for the Industry, which is the subject of this paper.

More than simply a prescription for rote change notification practices, this paper strives to provide the requisite background to put the proposed Practice into context, from the perspectives of process, quality and regulatory expectations. Thus, the paper contains sections that describe the team's collaborative process, and general quality and regulatory expectations of drug manufacturers. We then transition to a discussion of change, best practices for content of pre-change notifications and change notifications, a process workflow and a template that is the unifying tool for our proposal.

The team's objective is that this proposal be adopted by the vast majority of customers and suppliers in the single-use supply chain, to the point where parties reflect it in their own quality management practices and in formal business agreements. To this point, the reader should bear in mind that the term 'customer' refers to the party who purchases a product and that it is not synonymous with 'end-user' or 'drug manufacturer'. Thus, many companies can adopt the Practice both as a supplier and as a customer. Finally, the team solicits ongoing feedback to monitor efficacy of the Practice and adjust it accordingly over time.

THE COLLABORATIVE PROCESS

This Practice for Industry has its origins in a stimulus paper with end-user authorship (2). It is the product of a very large, diverse team that came together to solve a problem that we believe detracts from the industry's core mission of bringing lifesaving and life-enhancing drugs to the public. Team diversity was reflected by one's place in the supply chain, spanning from drug manufacturer to plastic resin supplier. Diversity was likewise found in the size of the companies that participated, in the functions of the individuals who collaborated and in the experiences of these individuals. Given this backdrop, it was apparent that compromises would need to be made: few if any on the team were in total agreement with the entire output. This is a natural outcome of such a process.

On the other hand, we believe we have addressed the main elements of an effective practice to a point where implementation will lead to substantial net benefit. Bidirectional communication is stressed. The fundamental need to explain clearly what the change is and is not, and to declare the products affected by the change, is stated clearly. The need for high-quality data is made apparent, as is the need for ample time to implement. A Change Notification Template has been created to facilitate uniform change handling and to constantly remind change originators of the requisite information to support a change. A series of examples is provided to serve as an educational mechanism as one orients to the meanings of the change level in this Practice.

We do not represent that the Practice is a work of perfection; in fact, it was a guiding principle to not strive for perfection. As such, we anticipate that on widespread adoption, certain elements of the Practice will need to be amended. To this point, we seek ongoing feedback and we intend to update the Practice as the need dictates.

The overarching goal of the collaboration is industry-wide adoption of the Practice delineated herein. Companies involved in its creation have witnessed the process, progress, philosophy and decisions that have led to the outcome. Even for these companies, altering the way one manages change will be an effort at internal mobilization; we anticipate adoption to be a protracted effort. For companies not involved, the effort to acclimate to the Practice and natural curiosity about the team's process and philosophy make the adoption curve even steeper. For this reason, the following discussion points related to team dynamics and philosophical approach are presented:

Scope to include only supplier-initiated changes. The team agreed that customer-initiated changes were the exception rather than the rule. Moreover, such changes require detailed bilateral discussions and lead to change that is well understood and managed by the customer. As this was not viewed as a problem, it was kept out of scope.

Use of 80/20. We agreed that our solution will not resolve all change notification issues. Thus, we attempted to adhere to the figurative 80/20 rule and not allow special-case situations to derail the effort. We further agreed that even if certain cases were not covered, the increased quality of communication that the Practice encourages will have a positive impact.

Alignment to existing change notification guidance documentation. It was not the team's intent to create new structure when existing practices appear to be effective. Therefore, the team benchmarked a number of documents and practices from industries with strong change management programs, namely, Excipients, Medical Device and Semiconductor. Where possible, conceptual alignment with these documents was sought. The specific documents evaluated are listed below:

- *The IPEC (International Pharmaceutical Excipients Council) Significant Change Guide for Bulk Pharmaceutical Excipients* (3)
- *USP <1195> Significant change guide for bulk pharmaceutical excipients* (4)
- *FDA Guidance for industry: Deciding when to submit a 510(k) for a change to an existing device* (5)
- *FDA Guidance for industry: Changes to an approved NDA (new drug applications) or ANDA (abbreviated new drug applications)* (6)
- *EMA post-authoriation procedural advice for users of the centralized procedure* (7)
- ASME BPE Standard 2016 (8).

Change levels. Changes may be categorized by using alphanumeric labels (e.g. A, B, C or 1, 2, 3) or by using verbal descriptors (e.g. major, minor, significant). As seen in Table 1, verbal descriptions are used by several industry groups and with divergence of meaning. The team therefore chose an alphanumeric classification scheme to remain unencumbered by perceptions associated with words such as 'major' or 'minor'. The team further chose to use three categories of notifiable change to allow for greater granularity and to prevent a singular response to all changes regardless of their complexity or impact.

Change levels and the concept of 'non-notifiable'. Where is the line that separates notifiable from non-notifiable? This was a protracted discussion. Drug manufacturers were split, with some not wanting the noise and volume of non-impactful changes, and others wanting to 'know everything'. Ultimately, we agreed that non-impactful changes might be non-notifiable

Table 1: *Change categories of several regulatory and industry bodies*

ORGANIZATION	NON-NOTIFIABLE CHANGES	NOTIFIABLE CHANGES		
This Practice	Level 0	Level 1	Level 2	Level 3
FDA (5)	N/A	Minor	Moderate	Major
EMA (7)	N/A	Minor (type IA)	Minor (type IB)	Major (type II)
USP <1195> (4)	Level 1: Minor change	Level 2: Might be significant		Level 3: Always significant
IPEC (3)	Level 1: Non-significant	Level 2: Significant		
ASME-BPE (8)	Minor	Significant		
FDA 510(k) Guidance (5)	Not significant or major	Significant or major		

provided that the supplier still manages the changes with rigor, allows for them to be tracked and operates under a quality management system that will ensure such rigor. As non-notifiable change qualification data is likely to be used by customers both infrequently and primarily retrospectively in root-cause analyses, the important point is that the data is generated and maintained, and not that the data is routinely transferred.

Scope – single use only or inclusion of raw materials. The scope of the effort began with single use only. However, because the principles and the tools can be more broadly applied, the team contemplated the inclusion of raw materials changes (e.g. cell culture media and chromatography resins). Because its constitution was largely of single-use components and systems providers and users, the team decided to focus solely on single use. Future effort will be needed to derive specific change-level definitions and case studies to other product categories.

Decision tree. Initially, it was agreed that a decision-tree approach to change categorization would be effective because it could contemplate several change attributes and impacts, and guide the supplier to assign a given change level. Thus, multiple parties evaluating a given change would be likely to derive the same level for that change. Such a strategy has been adopted by IPEC and by the US FDA for medical device change guidance (3, 5). After extensive discussion and multiple-draft decision trees, the team concluded that the number of single-use articles, including finished assemblies, components and raw materials thereof (e.g. resins and additives), combined with the large variety of product usage (which leads to variable impact from user to user) rendered a decision tree ineffective. The team was unable to design a tool that would sufficiently constrain the categorization outcome. Ultimately, the decision-tree concept was abandoned in favor of a less-prescriptive approach.

CUSTOMER EXPECTATIONS

The change notification procedure described herein presumes a high level of stringency in change management and, more generally, in the holistic practice of quality (e.g. as per ref. 10). Without such rigor, there can be little confidence that the content of change notifications is grounded in solid process and is traceable and defensible. Expectations that customers should have of suppliers who adopt this practice include:

Quality:

1. supplier has a robust and actively managed quality management system
2. supplier practices quality risk management
3. supplier follows Good Documentation Practices (GDP) to document the handling of the change from beginning to end
4. supplier has a robust supplier quality management program within supply chain, including:
    - quality agreements
    - audit program
    - change notification agreements
    - traceability of the change through the supply chain
    - sub-supplier qualification
5. supplier has a documented change notification process, including:
    - a statement of commitment to effective communication of changes
    - documentation to accompany a pre-change notification
    - documentation to accompany a change notification
    - description of notifiable changes
    - responsibilities related to change management, highlighting, for example, the role of the single point of contact (SPOC) and the subject matter expert (SME).

Supply chain:

1. control over product
2. traceability to manage pre- and post-change product
3. change management
4. control over variability (specifications, certifications, understanding and monitoring of process parameters)
5. lot release, including understanding of non-conformances and corrective and preventive action (CAPA) implementation
6. timing of the switch from pre- to post-change product
7. quality controls
8. control/monitoring/tracking of materials
9. traceability
10. audits
11. incoming material (tests, certificates, variability)
12. change management
13. lot acceptance (timing, last and first lot post-implementation of the change)
14. good documentation practices.

Manufacturing practices:

1. implement environmental control and understand environmental impact on process and product
2. maintain effective cleanroom etiquette and gowning practices
3. implement 'real time' in process monitoring and controls to signal impending issues related to key process parameters.

Technical:

1. use of subject matter experts to ensure scientific understanding of process and materials and whether equivalence can be established
2. understanding of capabilities/design space
3. test performance post-change and compare to pre-change performance to assess impact or confirm equivalence over full shelf life of the product
4. understanding of process variability
5. characterization/qualification testing
6. qualification/validation plan
7. understanding of the biopharma market/product application/end-user process
8. technical collaboration and communication with sub-supplier
9. impact of external processing on supplier's product (i.e. sterilization and its impact)
10. shipping validation (e.g. following ref 10).

THE REGULATORY CONTEXT OF CHANGE MANAGEMENT

In keeping with the team's belief that education is a key aspect of effective change management, the following discussion serves to highlight the regulatory environment in which drug manufacturers operate. The team brings this perspective to the reader to promote dialogue among members of the supply chain and to foster collaboration in the management of uncertainty and risk by drug manufacturers and health authorities (HAs) worldwide.

Drug manufacturers file applications for marketing authorization to the HA of each country or region in which the manufacturer intends to market a drug. They are then responsible for manufacturing and controlling the drug in accordance with the specific content of the regulatory filing and with Current Good Manufacturing Practices (cGMP). With respect to manufacturing equipment, including single-use equipment, cGMP dictate that drug manufacturers are obligated to specify and maintain equipment in a state where they "shall not be reactive, additive or absorptive, so as to alter the safety, identity, strength, quality or purity of the drug product" (12). Equipment changes are allowed, but they must be managed rigorously to ensure ongoing product safety, efficacy and supply. This holds true for supplier-initiated changes as well as changes initiated by the drug manufacturer. Management of supplier-initiated changes has intrinsic difficulties, including reliance on a third- party for notification and for all the requisite information to allow drug product safety and efficacy impact assessment.

Change management often requires that one must either inform the HAs before a change is implemented or receive regulatory approval before a change may be implemented. Thus, a single change may lead a drug manufacturer to amend filings with a great number of HAs. The specific conditions that govern the HA notification requirements are rooted in both the country- or region-specific regulations or regulatory guidance, and the company-specific language of a given regulatory filing. Suppliers must be aware that, depending on the number of HAs involved and the complexity and potential patient impact of a change, regulatory approval could require from one to five years.

Conceptually, attributes of high-impact changes include, but are not limited to, the following:

1. the change affects an item used in a drug manufacturing step close to the end of the manufacturing process
2. the change involves transitioning to use of an animal-derived component
3. the change leads to a new extractables and leachables profile
4. the change leads to the need for real-time drug stability studies.

Among the steps a supplier may take to support these high-impact changes are:

1. continue to learn the regulatory landscape
2. ensure a robust dialog with customers
3. issue a pre-change notification as early as possible
4. plan on long lead times for implementation
5. plan on the need to stock pre-change materials
6. allow for purchase of pre-change material prior to change implementation
7. plan on the need to provide samples for evaluation
8. provide a thorough change qualification data package that can pre-empt end-user questions and concerns, thereby facilitating their qualification of the change.

It is impossible for suppliers to accurately and routinely predict the impact of a change on a given customer or on a population of customers. Nevertheless, drug manufacturers rely on suppliers to accommodate their regulatory needs as they work toward implementation. It is therefore essential that suppliers understand the fundamental regulatory structure associated with change management, which must

be practiced by drug manufacturers. That of the US FDA provides an apt example:
As stated in the *Guidance for Industry – Changes to an Approved NDA (New Drug Applications) or ANDA (Abbreviated New Drug Application)* (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm077097.pdf), changes related to: (1) components and composition, (2) manufacturing sites, (3) manufacturing process, (4) specifications, (5) container closure system, and (6) labeling, as well as (7) miscellaneous changes and (8) multiple related changes might require post-approval in accordance with section 506A of the US Federal Food, Drug, and Cosmetic Act (the Act) and s.314.70 (21 CFR 314.70).

Based on the type of change, the reporting categories are described as follows:

A **minor change** has "minimal potential to have an adverse effect on the identity, strength, quality, purity or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product." The applicant must describe minor changes in its next annual report.

A **moderate change** has "a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product." Commonly, these changes require that the drug manufacturer submit a supplement called 'Changes Being Effected in 30 Days' or a 'CBE-30'. This supplement will include information describing the effects of the change. The drug manufacturer must wait 30 days after submission of the CBE-30 before implementing the change and must not implement the change if the FDA responds with a request for more information to support the change.

A **major change** has "a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product." These changes require that the drug manufacturer submit a supplement called a 'Prior Approval Supplement' or a 'PAS'. The drug manufacturer must wait for FDA approval of the PAS before implementing the change.

Notably, although many HAs employ a generally similar structure, specific requirements vary worldwide. This lack of harmonization requires that more resources and time be applied to regulatory approval, a dynamic of which suppliers should be aware, especially for high-impact changes. Moreover, even within a given HA, expectations are not entirely uniform as to the categorization of a change. Thus, whereas some HA representatives may agree with the drug manufacturer on the categorization of a change, others may not.

ATTRIBUTES OF AN EFFECTIVE CHANGE NOTIFICATION PRACTICE

The process of change notification begins well before customers are notified of a change. Changes may be initiated either by an N-level supplier or by an N-X level supplier[1]. Thus, by analogy to reference 9, changes should be traceable through the supply chain. As described above, regardless of who initiates the change, the change must be managed to the expectations of drug manufacturers, who are required by law to ensure effective change management through their supply chain. A principle underlying concept is that any material that contacts a regulated product or process, directly or indirectly, must be sufficiently qualified to preclude substances from being transferred to the product in quantities large enough to endanger human health, to bring about an unacceptable change to the composition of the product or to affect the process.

Attributes of effective change notification, which are the foundation of our proposal, are listed below:

1. well-defined terms
2. defined lead times and timing for change milestones and deliverables
3. a well-understood workflow
4. clear and aligned expectations
5. high-quality data packages
6. content that anticipates customer needs
7. standardized report template
8. educated suppliers who continue to learn customers' ways of working
9. common understanding of roles and responsibilities of suppliers and customers
10. single point of contact to facilitate and manage formal communication
11. ample opportunity and expectation for bidirectional feedback, as relates to individual changes and to overall process effectiveness.

[1] N-level supplier is a supplier who sells directly to a customer. The N-X designation describes supplies who are 'X' levels removed from a customer. By way of example, an N-1 supplier will sell to an N-level supplier, who will then sell to the final customer.

CATEGORIES OF CHANGE

In the Practice, there are 5 levels of change: Emergency, 0, 1, 2 and 3. 'Emergency' is included to recognize that there will be instances in which a change must be managed in an accelerated manner. *Force majeure* events are a common example. Level 0 describes non-notifiable changes. They are included in the structure to acknowledge that they are still expected to undergo a formal and documented change process that includes assessment of complexity and customer impact. Levels 1, 2 and 3 align with other organizations (e.g. FDA, EMA) that have adopted a three-level, notifiable-change structure.

The impact on bioprocessing, the complexity of the change, and the magnitude of qualification and implementation efforts associated with a change will drive its categorization. This may be derived by using risk assessment techniques and will generally be guided by a supplier's statement of intended use and customers' typical use of the affected products. The following should be considered:

1. impact on form, fit or function
2. size of study required to qualify the change
3. size of study required to demonstrate equivalence to the pre-change state
4. potential patient effect.

Because higher impact, more complex changes require a longer time to qualify and implement (Fig. 1), the team has defined the three notifiable-change levels by periods of time required for most customers to process the change (Table 2). Appendix 1 provides an illustration of changes that have been summarized and categorized by level. These change examples are intended to aid in orienting the user of this Practice to the kinds of change that may typically be allocated to a particular level.

The following points illustrate ramifications of relying on time, as the surrogate for change complexity, as the defining characteristic of the change levels:

- in effect, suppliers are using their understanding of customer regulatory constraints and applications, as well as technical, business and supply chain practices, to convert an anticipated magnitude of impact into a time frame for qualification and implementation. This requires that suppliers understand customers very well, and it accentuates the need for robust, bidirectional and timely communication
- the level of change is independent of the nature (e.g. technical, supply chain, regulatory or business systems) of the change. All of these could have high impact or be complex to qualify or to process, and therefore all could be categorized as Level 1, 2 or 3
- the term 'minimum' in Table 2 must be highlighted. Thus, a 12-month time frame for customer qualification and implementation of a Level 3 change is the shortest time frame to be provided by a supplier. It is possible for a change to require multiple years for full implementation, especially in cases that have multi-region regulatory impact.

Figure 1: *Time frames associated with implementation of changes of varying complexity*

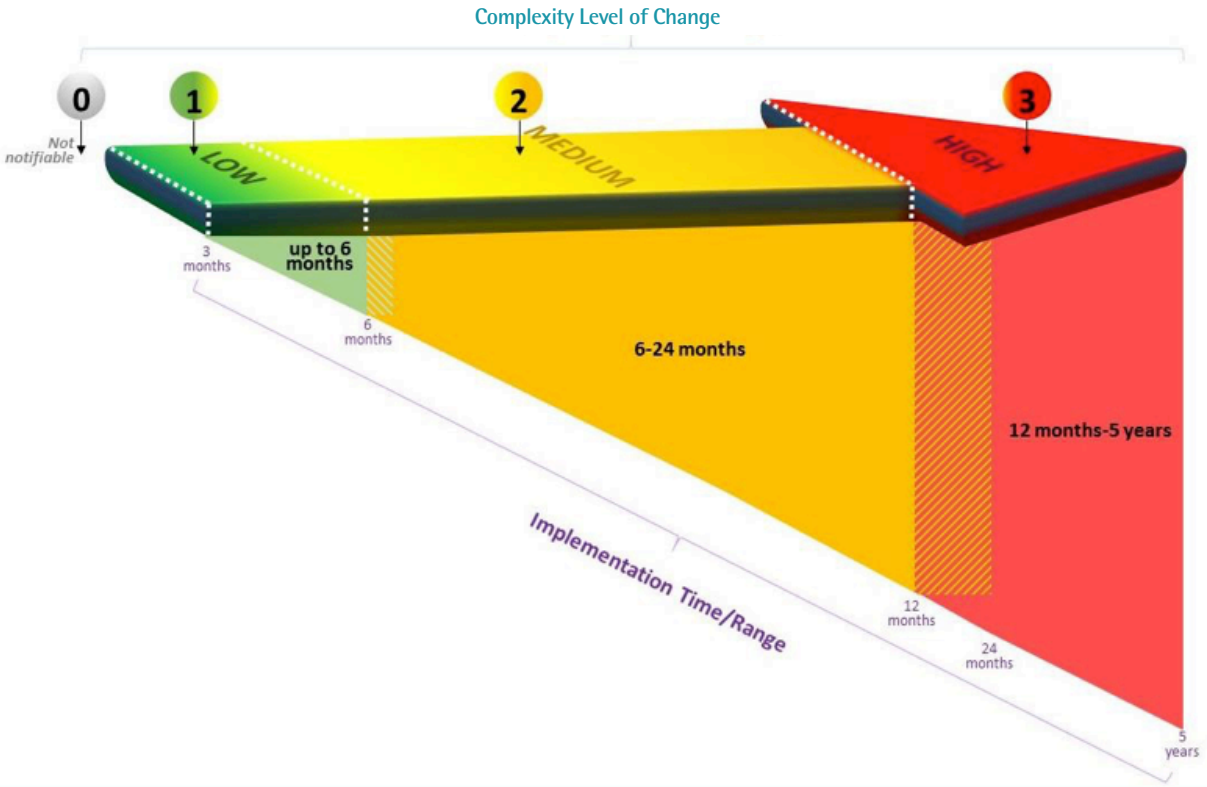


Table 2: *Change levels of this practice*

CHANGE LEVEL	PRE-CHANGE NOTIFICATION MINIMUM TIME (T0[1] – T1[2])	CHANGE NOTIFICATION MINIMUM TIME (T1 – T2[3])	PRE-CHANGE NOTIFICATION REQUIRED?
3	6 months	12 months	Yes
2	3 months	6 months	Preferred best practice
1	N/A	3 months	No
0	N/A	N/A	N/A
Emergency	N/A	Expedited per business needs	No

Notes:
1. T0 is the date on which a pre-change notification is issued.
2. T1 is the date on which a change notification is issued.
3. T2 is the date on which the supplier implements the change.

CONTENT OF A PRE-CHANGE NOTIFICATION

The purpose of a pre-change notification is to inform customers of the intent to initiate a relatively complex change, the implementation of which is predicted to take substantial time or resources. Typically, these will be categorized as Level 2 or Level 3. A pre-change notification may help the customer to gather resources and begin planning for qualification and implementation well before the actual change. Additionally, pre-change notification provides an opportunity for customers to ask for clarification or to request that certain information be part of the eventual notification package.

The pre-change notification should indicate:

1. the reason for the change
2. affected products
3. the anticipated date of the notification
4. the initial proposed qualification plan for the change, including timeline expectations and an outline of the anticipated qualification plan and report content
5. recommendations for stock inventory
6. anticipated sample availability for end-user/customer evaluation

Not all changes will require a pre-notification (see Table 2). For those that do, items 1-3 should always be included. Item 4 is mostly related to changes of form, fit or function. Items 5 and 6 will be most relevant for more impactful changes that are anticipated to require laboratory work (stability, process performance or leachable studies) and extended timelines to achieve customer qualification.

CONTENT OF A CHANGE NOTIFICATION

The purpose of a change notification is to provide the customer with the requisite information to understand the nature of the change, assess impact (or determine equivalence if applicable) and manage the impact to maintain drug supply to patients. The quality of the content of a change notification is critical.

The following points should be addressed when developing a change notification:

Recipient. This will of course be the customer. The customer is commonly defined by a supplier as the party who has purchased a product within a given period, which is commonly two or three years. Parties requiring a longer time frame should consider specific contractual agreements.

Thorough description of the change.

- Detailed descriptions are requisite to allow a customer to fully understand the change and be able to react to it internally. Included in this should be a description of what is not affected by the change. Such a listing will prevent customers from asking several questions to confirm that the change is, in fact, limited to the description provided. This will favor a smoother implementation by the customer
- As appropriate, one is encouraged to provide photographs, drawings, or renderings of articles that represent the pre- and post-change states, and, in general, to describe fully the current and future state.

Rationale. It is helpful to the customer to know why a supplier is making a change. This understanding puts the change-qualification package into context and allows for a more effective impact assessment.

Affected products. Current practice when managing off-the-shelf products is for a supplier to issue a generic list of all affected parts to any customer who has purchased one or more of these parts in a given time frame. Best practice will be to issue customer-specific notifications.

Change level. The change level provides an initial understanding as to the relative impact of the change, as judged by the originator. This should be achieved by applying systematic risk-assessment techniques, assessing the extent of the change and the required effort to assess equivalence. The following should be considered:

1. impact on form, fit or function of the changed part
2. impact on part chemistry or materials of construction
3. product or process contact potential
4. complexity of the implementation
5. qualification/equivalence
6. potential for patient impact.

Timeliness. The customer must have time to react to the change notification:

- drug manufacturers may need to engage in laboratory work to qualify the change, to supplement regulatory submissions worldwide or to update/modify internal documentation in response to a change
- suppliers may need to perform testing on their assemblies to qualify the change and implement manufacturing or design changes to ensure qualification.

Timing communication.

- estimated internal qualification completion date
- estimated date on which a summary report will be available
- estimated date of implementation.

Identifiers. Change notifications must be traceable. Changes that originate from further back in the supply chain, i.e. not the customer's immediate supplier, should maintain the alphanumeric identifier of the originator of the change. This allows the customer to recognize if multiple suppliers are implementing the same change from the same sub-supplier and to apply resources more efficiently.

Impact assessment. The change originator should include a statement of likely impact of the change on their customers, not only from a form/fit/function perspective, but also from the perspective of supply chain, inventory management or any other potential aspects that could impact the customer or supply continuity. Although it is not possible for suppliers to be fully accurate, the impact assessment has value as

an orthogonal means of describing the change and it may reveal an aspect of the change that might otherwise not be apparent to the customer. A preliminary impact assessment may be provided in a pre-change notification. For changes originating further back in the supply chain, it may be appropriate to provide assessment of the change on the immediate customer and on downstream customers.

Qualification package. The originator should provide information on how to request a qualification package. For notifiable technical changes (e.g. related to material, process, release or facility), the thoroughness of the data package should be commensurate with the magnitude or likely impact of the change. As such, the qualification package may include the following:

1. product risk-assessment summary, including impact on manufacturing process and on quality attributes of the changed part
2. generic assessment of customer impact (e.g. business, technical or regulatory). Inputs may be supplier's stated product intended use and supplier's general understanding of customers' regulatory and quality constraints. The assessment must not take the place of a customer's evaluation of their own risk, but rather may serve as input into the customer's risk assessment
3. qualification plan
4. qualification report (including data summary and conclusions)
5. technical equivalency/comparability discussion, as applicable
6. conclusions related to the qualification and the possible customer impact
7. any other aspects identified as part of the bidirectional discussion within the supply chain.

Sampling. Include information on how the customer may receive samples of materials that represent the changed state, as applicable.

Supply chain considerations. The originator should inform the customer of how to know when they receive product that has incorporated the change. This is usually related to a date, such as the date past which the change will be incorporated; or to a lot number, such as the last lot number to incorporate pre-change parts.

Last time buy options and quantity restrictions. Note that in certain cases, risk may be mitigated by execution of a supply agreement to allow the customer to secure a required amount of the pre-change product.

THE CHANGE NOTIFICATION REPORTING TEMPLATE

The team developed a Change Notification Reporting Template (Appendix 2) and an accompanying procedure, both of which will be available on the BPSA (bpsalliance.org) and BPOG (biophorum.com) websites.

Companies are encouraged to adopt both documents. The template may be adopted as is, or may be adopted by assuring that company practices require communication of the information called for in the template. In either case, adoption should be through a formal means of amending current practices in accord with Good Documentation Practices (GDP), structured document control and appropriate training.

The team would like to highlight the following key points:

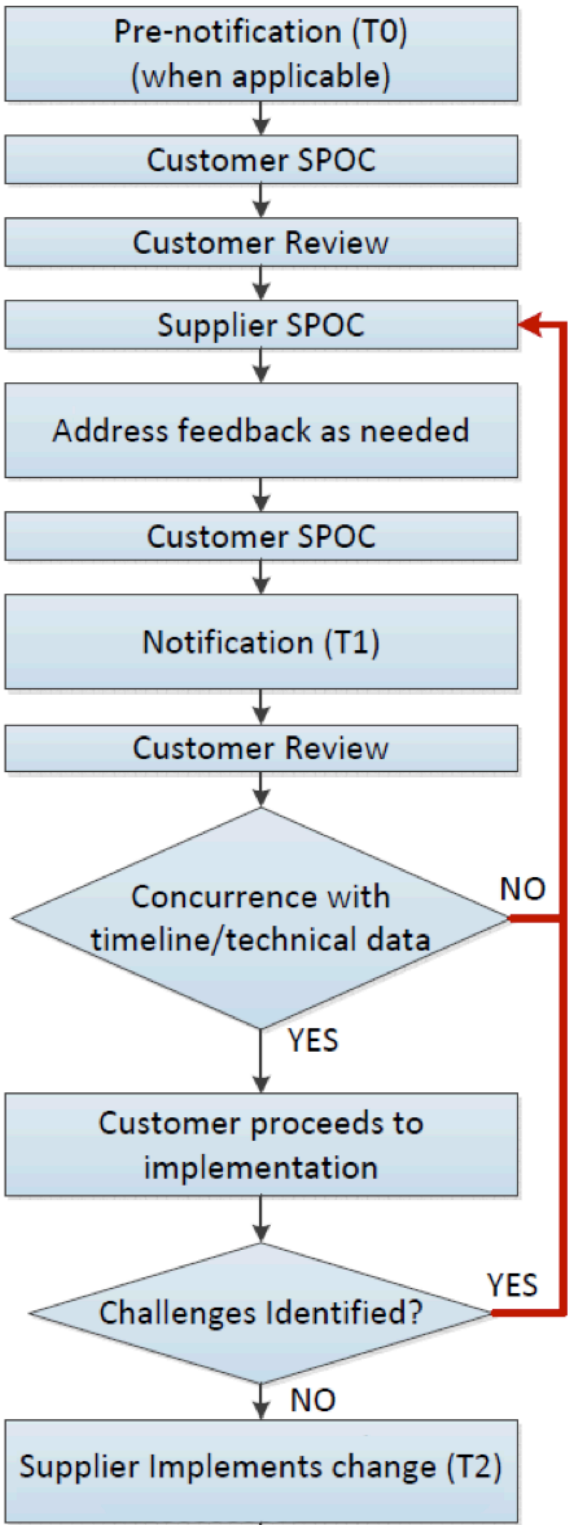
1. the template may be used at all levels of the supply chain. At the N-X level, a change notified to the N-level supplier may or may not be propagated to the drug manufacturer. For those that are, one should note the likely impact on change implementation timing: both the N-level supplier and drug manufacturer will need time to implement and these time frames may not overlap
2. the template is meant to be used in the context of a healthy communication flow between change originator and customers, especially in cases of more impactful changes
3. the template may be issued multiple times. For example, it may be used first as a pre-notification of a change, then as an initial formal notification and finally as a means of updating on the progress of change qualification
4. customers of the change notification are encouraged to acknowledge receipt
5. The template may be used for all changes, not just notifiable changes. Level 0 changes, although not notifiable, are still to be managed, tracked and documented – functions for which this form may serve.

THE CHANGE NOTIFICATION WORKFLOW

Perhaps the single most impactful aspect to the Practice is the increased level of high-quality communication, which includes elements of timeliness, interactions between and among the correct individuals and a right-first-time objective for communication content. Central to this aim is the role of the single point of contact (SPOC) for each company or legal entity. Companies are encouraged to adopt a change@companyname.com e-mail format that will be insulated from individuals leaving a company and vacating the SPOC role or not being available at the time of an emergency notification. This should not preclude interpersonal communication, but rather should allow for traceable and timely formal transfer of documentation.

The workflow in Fig. 2 presumes a high-impact change is being managed, and therefore contains pre-change notification and a full complement of feedback steps. Changes of lesser impact may naturally not need the same level of attention to two-way communication. The process begins at T0, the date on which a supplier SPOC issues a pre-change notification to the customer SPOC. The supplier SPOC will then receive feedback from one or more customers, which should focus on clarity of the pre-change notification, concerns about timing of notification and implementation, and expected content of the qualification plan and report. When warranted, the suppliers will address concerns and reissue the pre-change notification.

Figure 2: *Workflow of a Level 3 change*



After an agreed-upon time following the pre-change notification, the supplier SPOC will issue the change notification, the date of which is termed T1. Following receipt of the notification, it is incumbent upon the customer to review materials and to respond to the supplier in a timely manner to allow enough time to amend data sets or otherwise clarify questions. The customer will then go on to qualify and prepare to implement the change. If the qualification reveals an issue, the customer must again communicate with the supplier in a timely manner to allow resolution. Barring issues, the supplier will ultimately implement the change, the date of which is termed T2. Shortly thereafter, the customer will begin implementation. Once again, should problems arise, the customer is encouraged to engage in timely communication with the supplier (through the SPOC) to rectify the issue.

Legend: the figure represents a generic change notification workflow. Red lines indicate steps that are commonly associated with ineffective change management, which suppliers and customers should strive to avoid.

FEEDBACK

Continued and high-quality dialog between supplier and customer help to ensure alignment to the process and to each parties' expectations. Customers adopt communication strategies that vary with respect to resource intensiveness and quality of communication (Table 3).

Table 3: *Feedback mechanism to support effective change-notification practices*

MECHANISM OPTION	RESOURCE ALLOCATION	COMMUNICATION EFFECTIVENESS
Transactional relationship	Low	Low: feedback is absent or reactionary
Quality questionnaire	Medium	Medium: one-way feedback; no feedback to supplier
SPOC interaction	Medium	High: real time, bidirectional, supports individual change cases
Business review meetings	High	High: encourages bidirectional process-effectiveness dialog

Strategic relationships or those that are otherwise deemed highly important to both parties are often supported by business review meetings. The resource intensiveness of managing such relationships precludes such a communication mechanism from being implemented with all suppliers. With respect to change notification, business review meetings may be well served by adoption of key performance indicators, which may include one or more of the following:

1. classification agreement
    - frequency of alignment between supplier and customer
2. documentation quality
    - fraction of notifications per time period that did and did not include all of the information required by the customer
3. lead tme
    - actual pre-change notification to change notification lead time versus commitments
    - actual change notification to implementation lead time versus commitments
4. number of changes
    - notification volume per time period and with trending
5. change drivers
    - what were the most common triggers for notifications?

Establishing a supplier and customer feedback strategy will contribute to identifying opportunities for improvement that is meaningful to both parties. Changes to expectations or need, as well as process misalignment and pain points, should be topics for ongoing discussion.

CONCLUSION

The team created this Practice for industry to help themselves and the industry to manage change notifications with efficiency and rigor. The industry will be best served if all biopharmaceutical companies and their supply chain adopt the tools and philosophy of this Practice. Moreover, regulators should welcome this collaborative industry effort to improve upon processes that relate to compliance and to continued patient safety. When widely adopted, we anticipate that better-calibrated and better-educated suppliers will manage, but not notify on, non-notifiable changes; notify only on notifiable changes; and provide notifications only to their customers and not to their customers' customers. We further anticipate that the quality and timeliness of communication will be substantially improved, allowing people to focus more on value-added tasks that contribute either directly or indirectly to documented patient safety.

Specific actions that one can take are:

1. download the Change Notification Template and Instruction and assemble a team to compare it to your current practices. What is similar? What is different? How could it be implemented?
2. introduce the Practice to senior management with the authority to agree to implement it
3. develop a training and implementation plan for use of the Template and the associated workflow
4. implement a SPOC
5. request that your suppliers use the Template and workflow
6. cite this Practice in your contractual agreements (contracts, quality agreements)
7. strive for higher-quality communication with your suppliers to effect better change notification quality over time.

As a support mechanism to the industry, both BPOG and BPSA commit to housing and maintaining the requisite tools and materials, and to administering a discussion board. We will also respond to questions through e-mail and hold several online informational sessions. Lastly, we will house a series of case studies that may be used to calibrate one to the nature of the various levels of change and to the documentation one may use to support the change notification.

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DEFINITIONS

Change: An alteration to legal, business, technical, quality, regulatory or supply chain practices related to a product, which may impact the customer of that product.

T0: The date on which a supplier issues a pre-change notification.

T1: The date on which a supplier issues a change notification.

T2: The date on which a supplier implements a change.

Level 0 change: A change that has an effect on a supplier's operations, but which is very unlikely to have customer impact. It is expected to be documented within the supplier's quality management system (QMS) and become available to customers when required. It does not require a formal notification to the customer.

Level 1 change: A change that does not require pre-change notification and that requires at least three (3) months between T1 and T2.

Level 2 change: A change most likely to warrant a pre-change notification and that requires at least six (6) months between T1 and T2.

Level 3 change: A change that requires at least six (6) months between T0 and T1, and at least twelve (12) months between T1 and T2.

Emergency change: A change for which a supplier is forced to accelerate qualification and implementation, the effects of which are translated to one or more customers. This type of change is expected to be the exception and mainly triggered by force majeure events.

Pre-change notification: A formal document, which follows GDP practices (in accordance with cGMP principles), that is issued by a supplier to a customer to make a customer aware of a potential change.

Change notification: A formal document, which follows GDP practices (in accordance with cGMP principles), that is issued by a supplier to a customer. It provides the customer with qualification material and all other information needed for the customer to proceed with the implementation of the change.

Change implementation: The process of ceasing the pre-change state and moving to the newly qualified state.

Change level: A designation issued by the supplier to indicate the supplier's estimate of relative customer impact. The change level does not have regulatory significance.

Supplier: The party providing a good or service and communicating a change to a customer

Customer: The party receiving a good or service and receiving formal change notification correspondence. Given supply chain dynamics, one party may assume the role of customer and of supplier in cases where a party receives a change from a supplier that instigates the need for that party to issue a change notification to a customer. 'Customer' is not always synonymous with 'end-user' or 'drug manufacturer'.

Data package: A set of one or more qualification reports generated and provided by the supplier to support the customer's understanding and impact/risk assessment of the change.

Process contact surface: As per ASME BPE 2016, a surface under design operating conditions that is in contact with, or has the potential to be in contact with, raw materials, in-process materials, APIs, clean utilities (e.g. WFI, CIP, pure steam, process gases) or components (e.g. stoppers) and where there is a potential for the surface to affect product safety, quality, identity, strength or purity.

Product contact surface: As per ASME BPE 2016, a process contact surface that is in contact with, or has the potential to be in contact with, a product, where product is defined by the owner/user. Examples of product contact surfaces may include the interior surfaces of bioreactors, transfer tubing, chromatography columns, vessels and recirculating segments of CIP systems.

APPENDIX 1:
EXAMPLES OF CHANGES AND ASSIGNED CHANGE LEVELS

CHANGE NAME	DESCRIPTION	ASSIGNED LEVEL	RATIONALE	ADDITIONAL CONSIDERATIONS
Movement of injection molding machine	Injection molding machine was moved 3ft (0.91m) within cleanroom, because of a safety audit, to allow better operator access and improved ergonomics	0	No change to part attributes. Long-term effects on air flow distribution in cleanroom will be monitored	
Change from 10 units to 5 units of connectors per bag	Same connector will now be packaged 5 per pack versus 10 per pack. No other change is associated with this	1	Package size effects on customer, packaging number effects on customer are expected to be minor	Risk analysis may still require supplier qualification, such as new shipping/packaging qualification
Acquisition of company that sells Part X	The legal entity of the plant/company manufacturing Part X will change to reflect the acquisition	1	There is no action to be taken by the customer because the change will not impact the customer	Future changes that occur following the acquisition need to be handled on their own merits
Straight connector grip physical change	Changing the grip area from 10- point round to 6 points and 4 flats to improve molding	1	There is no customer qualification needed. Effect is small	Risk assessment should confirm usability of the grip
Product documentation update due to acquisition	Supplier X has acquired Supplier Y and product documentation will be updated accordingly	2	Acquisition implies that the number of affected parts will be large	Documentation change complexity can vary based on the number of customer parts and systems impacted (e.g. ERP, GMP documentation, business systems)
Part number or part name change	Changes allow implementation of new ERP system by supplier	2	Pre-notification can allow time to assess impact. Part usage in licensed drug manufacture could mean protracted times to inform health authorities	In some respects, a larger number of parts included in such a change will scale the end-user impact, such as the need to update drawings
Component change	Change from one check valve to a different check valve from the same manufacturer. New material of construction.	2	Drawing changes, action of the new part to be confirmed. Extractables risk assessment to be done	Thoroughness of supplier qualification and data package can reduce end-user qualification burden

CHANGE NAME	DESCRIPTION	ASSIGNED LEVEL	RATIONALE	ADDITIONAL CONSIDERATIONS
Hose barb configuration change	Adding 0.05 inches to inner diameter and increased length by 0.5 inches	2	Customer (assembly integrator) will need to confirm effects on system integrity for all tubes and closures, and possibly update assembly instructions and training.	Assembly integrator's change qualification is likely to be more work than the end-user change qualification
Movement of injection molding machine	Injection molding machine was moved from facility A to facility B, which has the same room layout and operational environment	2	In this scenario, level 2 is assigned to account for the possibility of end-users' audits or requests for sample parts	Possible need for inventory management at supplier during the time between notification and implementation
Film replacement in single-use bags	New film has been developed. It has better properties than the original film	3	May require HA notification. Likely to require substantial end-user qualification for a large number of licensed drugs	Large surface area component leads to high risk categorization and subsequent need for extensive qualification
Tubing discontinuation and connector change	Tubing change due to sub-supplier raw material discontinuation. Connector change is needed to assure effective tube-hose barb interface.	3	Two changes that both may require end-user qualification such as extractables and connector performance	Supplier qualification data quality may reduce the end-user qualification effort
Movement of injection molding machine and procurement of new resin	Machine is moved from facility 1 to facility 2. Facility 2 procures a like-for-like resin to make the molded parts. It does not have an animal origin-free claim	3	Two changes in one. The facility change is level 2, but the resin change makes the change level 3 due to the likely need for customers to risk assess, requalify, sample and possibly audit	Change to the animal origin-free claim may mean that this change cannot be accepted

APPENDIX 2:
CHANGE NOTIFICATION TEMPLATE

Insert
Supplier Company
Logo Here

Click Here to Choose a Title

Date of Correspondence	Original Date of Change Implementation	Target Date of Change Implementation
Select a date	Select a date	Select a date
Supplier Change Notification Number	**Sub-Supplier Change Notification Number (if available)**	
Click to enter number	Click to enter number	

1. Product(s) Affected (Purchased by Customer)

Item Number (Model/Part #):	Item Description:
Click to enter number	Click to enter description

Change Description *(enter a brief Description of Change and Pass-Through (50 words or less))*:
Click to enter description

Change Summary *(enter a brief Reason for Change (50 words or less))*:
Click to enter summary

2. Change Level Category

Select a degree of change below based on the following: impact on the system, complexity of the implementation, qualification/equivalence, and/or potential exposure to the patient. Only the selected change level will be listed on final customer notification.

☐ Level 0	☐ Level 1	☐ Level 2	☐ Level 3	☐ Emergency

3. Change Type

Select all change types that apply, only selected change types will be listed on final customer notification.

☐	Chemical Properties	☐	Physical Properties	☐	Manufacturing Process
☐	Functionality	☐	Raw Material	☐	Specification
☐	Equipment	☐	Manufacturing Site	☐	Scale of Manufacturing
☐	Configuration	☐	Contact Packaging	☐	Labeling
☐	Documentation	☐	Test Method	☐	Supply Chain
☐	Discontinuation	☐	Other *(please specify)*: Click to enter other Change Type		

4. Information to Support the Change (add attachments, if necessary)

Click to enter information

5. Information Access

Name of Single Point of Contact	Email Address of Single Point of Contact
Click to enter name	Click to enter email address

If you would like more information about this change notification or have feedback regarding this change, please contact us via quality@supplier.com or go to our website to find the phone number of your local office at www.companyname.com.

Company Name and Address
Controlled Document Number

Page 1 of 1

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