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Standard for Cytiva Change Control and Notification process for Designated products

For External Use

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1. INTRODUCTION

A process for change control is required for suppliers to the biopharmaceutical industry.

As a supplier of products often used in a in a regulated environment such as e.g. GMP environment, Cytiva acknowledges that change control is a critical process in the quality management system and necessary to fulfil the obligations to supply products with a consistent quality to our customers.

Cytiva has adopted the principles of change notification best practices for single-use products, as described in BioPhorum/BPSA papers, and the ASME-BPE standard. Cytiva applies similar principles to all product categories that are used in GMP environments, in a manner befitting the specific characteristics of the various product categories.

Changes to confidential unit operations will be informed of in a way that will not disclose IP or business critical information. More detailed information may be shared during audits.

2. PURPOSE

The purpose of this document is to provide an overview of the change control process and the notifications for designated products within Cytiva.

Detailed procedures and instructions that are in compliance with this document are used at the local Cytiva sites and can be reviewed during audits.

This document may be used to introduce the Cytiva change control process and notifications to customers or other external organizations or individuals.

3. SCOPE

This standard applies to all products intended for use in a regulated environment such as e.g. GMP environments that are available for subscription to change control notifications and thus are listed on the web page: www.cytiva.com/rsf.

Notification for products not available for subscription on the Regulatory Support web site, will be considered and sent through sales channels.

Cytiva products within a FlexFactory™ platform are supported with change control notifications through individual product subscriptions, e.g. for Xcellerex™ bioreactor bags, ReadyCircuit™ assemblies, etc.

The ReadyToProcess columns packed with chromatography resins are supported with change control notifications through product subscriptions to the ReadyToProcess column **and** the included chromatography resin.

4. DEFINITIONS

Change control: Management of all planned changes associated with the design or manufacturing of marketed products.

Product quality: The product characteristics that are listed in the product specification.

Critical subcontractor: Contract manufacturer of critical raw material, product or process.

Design changes: Any modification to a product that may impact design form, fit or function.

Product/process Contact Material (PCM): The finished good that is in contact with the process fluid containing the medical product; also called wetted part.

Form: The unique and relevant physical characteristics of a part, defining the" look" of the part or item, e.g. shape, size, dimensions, colour, mass and/or other visual parameters which uniquely characterize and distinguish the part.

Fit: Fits intended application; The ability of a part to physically interface, connect with, or become an integral part of another part or assembly, includes for example tolerances. Whether the physical dimensions of a part fit into the product it was designed to go into. It must adhere to the specifications set by engineering in the design phase.

Function: The action(s) that an item is designed to perform, what the product actually does, product performance.

5. STEERING PRINCIPLES

Each manufacturing unit has a change control board with relevant representatives from functions or sites concerned with proposed changes. The representatives must be on an organizational level that gives authority to take decisions.

The board is responsible for:

- assessing all aspects of proposed changes
- assessing the output from risk management
- deciding on the extent of verification/validation
- deciding if a customer notification is required, see 7. Customer notification
- reviewing and approving design and manufacturing changes

6. RISK MANAGEMENT OF CHANGE

Changes are evaluated regarding product quality and customer impact from a risk perspective. The magnitude of this evaluation, proportionate with the magnitude or complexity of the change, may range from a brief discussion/handling to a full and comprehensive risk assessment. The risk assessment/customer impact assessment is documented.

When a potential risk is identified, measures are taken to reduce the risk to an acceptable level. Preventive measures are taken to minimize the potential impact on product quality/customer impact. Residual risk evaluation and overall risk acceptance are performed. Customer impact assessment will factor in heavily to the categorization of the change. Residual risk evaluation or overall risk acceptance may cause a proposed change to be abandoned.

7. CUSTOMER NOTIFICATION

For changes listed below in points 7.2-11, customers are always notified. For changes not listed in these sections, a notification may still be provided if the result of the risk assessment indicates an elevated risk (medium or high risk) associated with the change.

The listed points reflect customer input over many years, through many types of interactions (e.g. interaction regarding quality agreements, customer audits, customer feedback to notifications, interactions through industry organizations etc.), and are adopted to fit the different product area characteristics and needs.

For variation of the changes below, the nature of the change and result of the risk assessment will guide change categorization and any notification timeframe (e.g. change in a wetted part form vs a non-wetted part form). Customer impact and criticality of a change is considered, and notification times may be adjusted to fit the nature and complexity of the change.

An additional pre-notification is considered for significant changes.

For changes not listed in points 7.3-12, the result of the risk assessment will determine whether a notification is sent out. The decisions are taken by the change control boards.

Notification time frames are based on the type of the change and the associated risks/customer impact. When the risk assessment and risk control process result is no-risk or low-risk impact on the quality of the product and customer impact, customers need not be notified of the change as an outcome of the risk assessment, and a notification of the change is only sent if the change is listed in sections 7.2-12.

7.1. Changes subject to customer notification, and time frames

Notification is given for products available for subscription to change control notifications listed on the web page www.cytiva.com/rsf, according to this Standard.

The time frames in sections 7.2 through 7.12 are an estimate that Cytiva aims to fulfil. However, there may be extraordinary situations where Cytiva may have to inform with shorter notice, and Cytiva reserves the right to inform with shorter notice than described below.

7.2. Notification of changes concerning all product lines

Notification for the following changes will be sent minimum 3 months prior to implementation:

- New edition of this change control standard (in the unlikely event of Cytiva reducing the stringency laid out in this document, a new edition of this change control standard will be notified minimum 6 months prior to implementation)
- Change of company name or legal entity
- Change of warehouse and/or distribution route

7.3. BioProcess chromatography resins, ReadyToProcess columns, Density gradient media and Microcarriers

Changes for which Cytiva will always send a notification are listed below. In addition to the listed changes, notifications are sent if the result of the risk assessment indicates an elevated risk.

Note that the ReadyToProcess columns packed with chromatography resins are supported with change control notifications through product subscriptions to the ReadyToProcess column and the included chromatography resin. To ensure full coverage changes, please subscribe to both the ReadyToProcess Column and the resin of interest.

Changes for which notification is typically given 1 month prior to implementation:

- Change in label and primary packaging material or other change impacting incoming inspection
- Change concerning shelf life
- Change concerning storage conditions
- New edition of analytical specification, editorial changes (For ReadyToProcess columns the addition of code number for new columns size, resulting in new edition of analytical specification is not notified)
- Discontinuation of product package size when alternative pack size is available

Changes for which notification is typically given a minimum of 6 months prior to implementation:

- Change of product code number
- Change of critical subcontractor
- Change of analytical specification limit within current limits
- Addition of a new test method
- Change regarding animal origin of raw material or product claim/standards status that impacts product quality
- Introduction of new manufacturing facility on site (final product)
- Change of manufacturing site (ReadyToProcess column)
- Change in design or dimension for a product/process contact material (wetted part) the results in alteration of the product quality, including form, fit, function (ReadyToProcess column)

Changes for which notification is typically given a minimum of 9 months prior to implementation.

- Change to a different test method
- Change of analytical specification limit outside current limits
- Elimination of test method
- Change of manufacturing site
- Change to a different raw material
- Change in material of a product/process contact part (wetted part) that alters product quality including form/fit/function (ReadyToProcess column)
- Change to sterilization process - significant changes e.g. gamma to moist heat, or change to validated dose range
- Change to manufacturing equipment or process – significant changes (that impacts product quality /performance or form/fit/function) *

* If parallel manufacturing is not possible (pre/after-change), supporting data will be provided no later than at the time of implementation.

7.4. Cell culture products

Changes for which Cytiva will always send a notification are listed below. In addition to the listed changes, notifications are sent if the result of the risk assessment indicates an elevated risk.

Note that some material is considered proprietary. For such material not all details are disclosed. If product formulation is Cytiva proprietary, Cytiva confidentiality of proprietary information takes precedence over custom product transparency.

Changes for which notification is given 1 month prior to implementation:

- Changes in packaging
- Change concerning shelf life – if extending shelf life
- Change concerning storage conditions – if within currently validated range

Changes for which notification is given 3 months prior to implementation:

- Change to label and certificate content (removal of information)
- Change in product contact surface during manufacturing process
- Addition of new raw material manufacturer, except for proprietary formulations
- Change in specific product release testing
- Change of content to finished product specifications which affects the form, fit or function of finished products
- Discontinuation of product package size when alternative pack size is available

Changes for which notification is given a minimum of 6 months prior to implementation:

- Change of critical subcontractor (manufacturing, finished product release testing, irradiation contractor)
- Change of test method for finished product release test
- Change of animal origin status, BSE/TSE risk
- Addition of manufacturing site – like for like equipment and processes
- Change in raw material grade – if down grading or removing requirement
- Change regarding shelf life – shortening current shelf life

Changes for which notification is given a minimum of 9 months prior to implementation:

- Change in formula, content, or make-up of a given standard liquid, powder or serum product, except for proprietary information
- Significant manufacturing changes (equipment and process)
- Change of manufacturing environment (reduction in classification)
- Change of product storage conditions – if outside of currently validated range
- Change in product contact material of primary packaging that could impact product stability

Changes for which notification is given a minimum of 1 year prior to implementation:

- Addition of manufacturing site – not like for like
- Significant change to quality product release procedure

7.5. BioProcess Single-Use disposable products

Changes for which Cytiva will always send a notification are listed below. In addition to the listed changes, notifications are sent if the result of the risk assessment indicates an elevated risk. For variation of the changes below, the nature of the change and result of the risk assessment will guide change categorization and any notification timeframe (e.g. change in a wetted part vs a non-wetted part).

For custom products, notifications will be provided according to the following when changes are prompted by Cytiva. For changes prompted by the customer, a formal notification will not be provided.

Changes for which notification is typically given 3 months prior to implementation:

- Change to the certificate and labelling, editorial changes
- Change in specification/addition of claim, shelf-life or storage - product improvement
- Change in packaging or packaging material
- Change to release testing/inspection procedures
- Change in appearance impacting incoming or fit for use inspection, no change to form/fit/function
- Change to dimension or design for a product/process contact part (wetted part), that has no impact to form/fit/function
- Change/addition of new manufacturer for fluid path components or raw materials w/out a change to resin grade, specification, form/fit/function

Changes for which notification is typically given a minimum of 6 months prior to implementation:

- Change to the following product documentation/labelling- Certificate (content), product name, catalogue/part number, label
- Change to product specification/removal of product claim/standards status that impacts product quality
- Change of shelf-life or storage conditions
- Change/addition of irradiation provider, release testing provider or other critical subcontractor
- Change in design or dimension for a product/process contact material (wetted part) that results in alteration of the product quality, including form/fit/function
- Change of manufacturing site location for final product or selected critical subassemblies/components (film, fiber, impeller, bag chambers)

Changes for which notification is typically given a minimum of 12 months prior to implementation:

- Change to manufacturing equipment – significant changes (that impacts product specification or form, fit and function)
- Change to manufacturing process - significant changes (that impacts product specification or form, fit and function)
- Change to sterilization process - significant changes (e.g. gamma to moist heat, or change to validated dose range)
- Change in material/resin of a product/process contact part (wetted part) that results in alteration of the product quality

7.6. BioProcess equipment spare parts and accessories

BioProcess equipment include systems, instruments, and columns.

Changes for which notification is typically given prior to implementation:

- Change of code numbers for spare parts and accessories

Changes for which notification is typically given a minimum of 6 months prior to implementation:

- Change in product/process contact material (wetted part) that results in:
  - Alteration of the product quality (form, fit and function)
  - Change to specification, including change of material type
  - Change to regulatory or compliance status

7.7. Software

New software versions

No change is made to a launched version of a software. Changes/updates are introduced via new versions. For new versions of a software, notifications are sent out. The notification can include descriptive information on the change or refer to information letters and change description documents published on software product pages on Cytiva web site. The information letters contain descriptions of different scenarios that can occur when the software is used. Actions to avoid or correct problems resulting from the described scenarios are suggested. The change description documents describe major implemented changes and improvements in the new version of the software compared to older versions.

Handling software issues

For critical software matters, such as operating system security updates and vulnerability issues, notifications are sent, describing work-arounds, availability of patches, etc.

7.8. Aseptic filling workcells

For aseptic filling workcells (e.g. SA25 Aseptic Filling Workcell-042 and Microcell Vial Filler-043) CCN are provided per product revisions. A product revision scheme is a process where multiple changes to a product are released simultaneously under a new revision of that product. Product revisions can include major/minor hardware, major/minor software changes and design document changes. A release can include a combination of the above changes or only one of the above.

To receive CCN for product revisions for aseptic filling workcells, subscribe by product category for equipment.

7.9. Cell and gene therapy Single-Use disposable products

Changes for which notification is typically given 3 months prior to implementation:

- Change to the certificate and labelling, editorial changes
- Change in specification
- Change in shelf-life or storage - product improvement
- Change in packaging or packaging material
- Change to release testing procedures
- Change of manufacturing site location (that does not impact product specification or form, fit and function)

Changes for which notification is typically given a minimum of 6 months prior to implementation:

- Change regarding certificate (content) – product name, labelling, catalogue number
- Change to compliance/standards status
- Change of critical subcontractor
- Change in product/process contact material (wetted part) that results in alteration of the product quality, including form, fit or function (including raw material)
- Change of manufacturing site location (that impacts product specification or form, fit and function)
- Change to manufacturing equipment – significant changes (that impacts product specification or form, fit and function)
- Change to manufacturing process - significant changes (that impacts product specification or form, fit and function)

- Change to sterilization procedures - significant changes (e.g. gamma to moist heat, or change to validated range of operation)
- Change to product specification (design changes) for functional attributes

7.10. Cell and gene therapy equipment and accessories

Changes for which notification is typically given prior to implementation:

- Change of code numbers for spare parts

Changes for which notification is typically given a minimum of 3 months prior to implementation:

- Change in product/process contact material (wetted part) that results in alteration of the product quality (form, fit and function)
- Change to specification
- Change to regulatory or compliance status

7.11. Biacore consumables

Changes for which notification is made prior to implementation:

- Change in label and/or packaging material
- Change concerning storage condition
- Change of critical information in Instructions For Use (IFU)

Changes for which notification is made a minimum of 3 months prior to implementation:

- Change of critical subcontractor
- New edition of an analytical specification (editorial changes may have a shorter notice period)
- Change of analytical specification limit outside current limits
- Change of manufacturing site
- Change to a different raw material

7.12. Biacore instruments, spare parts & accessories

Changes for which notification is made prior to implementation:

- Change of code numbers for spare parts
- Changes in critical dimensions and material changes on wetted parts, excluding consumables
- Change in spare parts that after exchange require the system to operate with specified software versions
- Change in components that result in alteration of the technical specification.

7.13. Discontinuation Policy

Should Cytiva decide to discontinue any:

- Bulk chromatography resin product, (including ReadyToProcess™ chromatography resins) customers registered for Change Control Notifications for that product shall be notified at least 3 years in advance.
- BioProcess and Cell & Gene therapy products single-use disposable products, the notification period for discontinuation will be minimum 1 year in advance.
- BioProcess, Biacore and Cell & Gene Therapy equipment, the Change Control Notification will be sent out when production of the equipment is discontinued. An End-of-Service notification will be sent to out one year before the service support period ends.
- Standard cell culture product, customers registered for Change Control Notifications for that product shall be notified at least 1 year in advance.
- Designated Biacore consumables product, the notification period is minimum 1 year.

However, there may be extraordinary situations due to external or internal factors where Cytiva may have to inform of a discontinuation with shorter notice. Cytiva reserves the right to inform with shorter notice than described in situations when non-standard events occur.

The “Policy for Discontinuation of BioProcess Chromatography media and single-use products” applies only to products for which subscription to change control notification is available on the web page www.cytiva.com/rsf.

8. SUBSCRIPTION TO CHANGE NOTIFICATION

Products subject to change control notification are listed on www.cytiva.com/rsf. Registration at the Regulatory Support web page is required for notification. To receive change control notifications, customers need to register at this web site and subscribe to CCN for the product they buy. Each product for which notification is required must be selected.

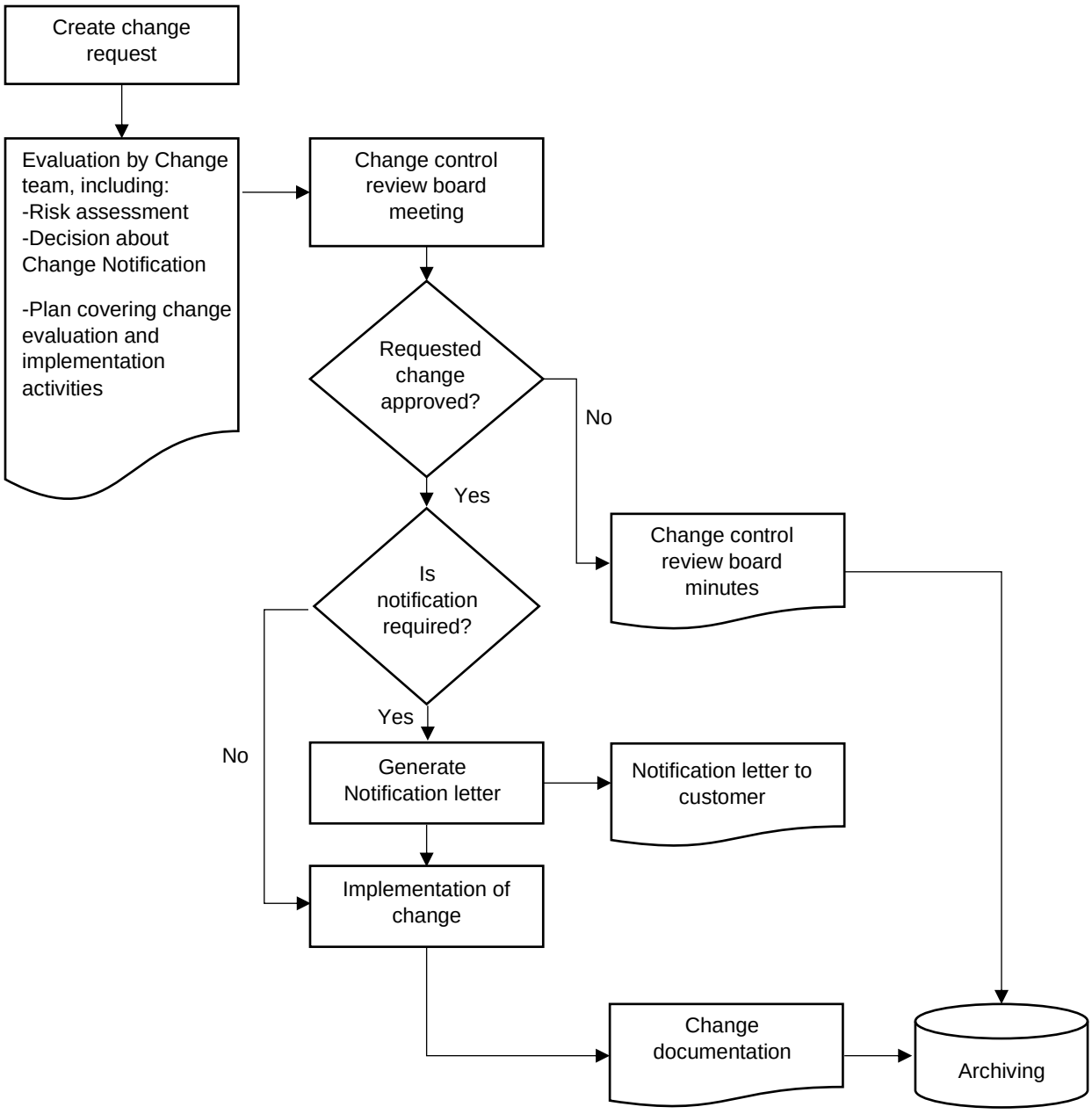
8.1. Notification Content

The notification contains the following information:

- identity of product (product name, article/code number)
- description of the change
- reason for change
- impact of change
- supporting data (when applicable)
- updated specification when applicable
- timeline for the change

9. FLOW CHART

Flowchart for the change control procedure.



10. DOCUMENT OWNER

Customer Regulatory Support Director

11. REVISION HISTORY

Revision Number	Section(s) Changed	Changes	Updated by
7.0	**7.5**	Editorial error, missed the word "function" in 7.5	Henrik Norberg
6.0	1,2,3,7,8	Title of document updated to include "notification". 1 "regulated environment" added. 2 "QMS" replaced with "change control process". 3 Scope updated to include Biacore products. Info added about CCN for products not available on RS web. 7 Paragraph on variation of changes added. 7.3 Info about RTP columns added. Bullet points rephrased re. change in label, ned edition of AS, animal origin, animal origin of raw materials Bullet points added re. discont. of product package, product code number, manuf. facility, manuf. site, change in design 7.4 Header updated Bullet points rephrased re. raw mtrl manufacturer, change in formula Bullet point added re. discont. of product package Text re. agreements removed. 7.5 Info re. RTP columns removed Bullet points rephrased re. specification, product documentation, critical subcontractor, contact material (under 6 months), material/resin (under 12 months) Bullet points added re. appearance, contact material (under 3 months) Bullet points removed re. prod. spec (under 12 months) 7.6 Header updated Bullet point rephrased re. spec. 7.7 New section 7.8 New section 7.9 Bullet point added re. manuf. site (under 3 months)	Ondina Åsberg

		7.10 Header updated 7.11 New section 7.12 New section 7.13 Bullet points list updated 8. “product they buy” added	
05	All	New template - Change from GE Healthcare Life Sciences to Cytiva	Anna Lindgren
04	Section 3 Section 7.6 Section 7.7 Section 7.8-7.9 Section 7.10	- Cell and gene therapy products are included - ”Change to pressure holding part” is removed. It is already covered by “Change to regulatory or compliance status” - Text on software made general to include additional software - Cell and gene therapy products included in the standard - - Editorial changes to the text	Ondina Åsberg
03	All	- Warehouse and distribution changes added - Significant manufacturing changes added to chromatography resins - Single-use products aligned with BPOG thoughts principle - Instruments and columns aligned with the change management part in ASME-BPE 2016 - Cell culture media catalogue products included - Editorial changes to the text	Ondina Åsberg
02	- Entire document - Section 7 - Section 7.2	- Editorial change to the text - Clarifying sentence added: Time frames are based on the type of the change. - 7.2 Notification points have been clarified: o primary packaging material o editorial changes of analytical specification without implementation delay o addition of new test method - 7.3: o Xcellerex single-use products are added	Ondina Åsberg

	- Section 7.3 - Section 8.1	○ Change of manufacturing site have been moved to 6 months ○ Notification points have been clarified ▪ Primary packaging material ▪ Vocabulary/nomenclature has been adjusted to clarify and better reflect the use of the terms in the Single-Use area, e.g.: • Certificate of Quality • Product release criteria • Release testing procedures • Sterilization procedure • Product specification • Part (form, fit and function) - 8.1 Notification content: Time line for the change have been added	
01		*- This document replaces "Standard for GEHC Life Sciences Change Control process for designated products" 70-5032-65 (last edition: AE) and "Standard for GEHC Life Sciences Change Control process for BioProcess columns and instruments" 70-5053-56 (last edition: AA).* *- The two documents have been merged to one, and the document has been moved to another document system and therefore has a new number.* *- No changes to "Standard for GEHC Life Sciences Change Control process for BioProcess columns and instruments" 70-5053-56 (last edition: AA).* *- Changes to "Standard for GEHC Life Sciences Change Control process for designated products" 70-5032-65 (last edition: AE) are mainly:* • *ReadyToProcess products and Wave products added* • *Time for which notification is given prior to implementation is prolonged from 3 to 6 months and from 6 to 9 months* • *Changes concerning shelf life, storage conditions and animal origin of raw material are added*	*Ondina Åsberg*

End of Document