European Federation of Pharmaceutical Industries and Associations

Annex VI to Clinical Trial Regulation 536/2014
Risk assessment-based concept of an interim* solution on expiry date labelling of the immediate packaging of Investigational Medicinal Products (IMPs)

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Executive summary

While the current EU Good Manufacturing Practice (GMP) Annex 13 allows for the expiry date to be omitted from immediate packaging in certain circumstances, Investigational Medicinal Products that will be supplied for clinical trials operating under the Clinical Trial Regulation 536/2014 (CTR) will no longer have this option, since Annex VI requires the expiry date to be labelled on the immediate packaging without exception.

For IMP expiry date updates, which often become necessary in clinical trials, EFPIA identified potential risks associated with the new requirement, especially for vials, syringes, and kit packs with inner and outer carton labels as follows:

1. Risks associated with updating the expiry date of the inner packs at the investigational site
2. Risks associated with a higher frequency of re-supply
3. Risks associated with consistency of IMP supply to patients

While EFPIA believes that the most feasible long-term solution will be to change the Annex VI requirements to eliminate the expiry date from the immediate packaging in certain circumstances as allowed for in Annex 13, an interim solution has been developed to address the main challenges of Annex VI and to mitigate the risks described above. The interim solution is underpinned by a comprehensive Risk Assessment that was applied to firstly identify packaging configurations susceptible to issues associated with the expiry update labeling of the immediate packaging, and to secondly elaborate the solution with the least risk amongst feasible solutions that avoid expiry update labeling on the immediate packaging.

Amongst solutions assessed as not being feasible now were digital approaches like QR-code or e-label technologies. Use of these technologies for the labelling of IMPs offers potential to help advance the digital transformation of health and care set out in the European Commission's 'Pharmaceutical Strategy for Europe'[1], but their use is severely limited by the current wording of Annex VI.

[1] https://ec.europa.eu/health/sites/health/files/human-use/docs/pharma-strategy_report_en.pdf

*: interim solution until Annex VI would be revised/amended by the Commission.

Of all solutions that were assessed feasible two solutions with low SOD (Severity x Occurrence x Detectability) risk scores resulted from Risk Assessment Part 2. Of those two the labelling solution to print the initial expiry date together with a statement like '*For most current expiry update see outer packaging of immediate container*' on the immediate container label is recommended as interim solution.

This work has been undertaken to mitigate some of the instantaneous consequences of Annex VI. It does not dilute the unanimous opinion within the Pharmaceutical Industry that Annex VI should be changed to better represent the wider best interest of patients as soon as legally possible.

1. Introduction/Background

Annex 13[1] has been proven over many years to set appropriate GMP standards that ensure patient safety while providing the flexibility needed for the timely and consistent supply of innovative Investigational Medicinal Products (IMP) to patients. It allows for the expiry date to be omitted from immediate packaging in certain circumstances which is generally beneficial, where the expiry date is subject to extension due to limited stability data in clinical trials especially where IMPs consist of kits with several packaging layers, and where the label text is of a rather small font size difficult to over-label. The difficulty is even greater for special storage conditions and in most cases the risk of having an inner expiry date with the complications it brings far outweighs the risk of not having one on inner packing.

When the Clinical Trial Regulation (EU) No 536/2014[2] (CTR) comes into application (currently anticipated around end 2021), its Annex VI on 'Labelling of Investigational Medicinal Products and Auxiliary Medicinal Products' will supersede the Annex 13 labelling guidelines. Annex VI requires the 'period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity' to appear on the labels of both the immediate (primary) and the outer (secondary) packaging. In contrast with Annex 13, the omission of this date from any label is specifically prevented by paragraph 9 of CTR Annex VI.

2. Problem statement

Pharma Companies' current practice is to omit the expiry date from the immediate container label where justified according to Annex 13 to the EU GMP guide[1]. Investigational sites may update the expiry date of medication sitting at site according to and in compliance with procedures and controls described in Annex 13, limited to the outer container in case of the exceptions provided in Annex 13.

With Annex VI becoming applicable, IMPs at the Pharma Company, depot and/or investigational site that need an expiry update would require both, the immediate and the outer container labels to be updated. For certain packaging configurations this may only be done by impairing the integrity of the IMP (e.g., breaking tamper evident seals, disassembling the multilayer kit) and adding significant complexity to the expiry updating process (e.g., instructions, handling very small expiry update labels,

documentation, reconciliation, reassembling, keeping the blind). These additional IMP handling steps are associated with an elevated risk for failures especially at depot and investigational site with impact on appearance, product stability, availability, and patient acceptability of IMP kits.

As an alternative the Pharma Company could resupply new IMP kits before the IMP kits at the investigational site or depot expire, thus creating an additional burden on stock and product availability and increasing the risk of treatment delay or interruption due to delay in IMP re-supply (drug supply can be very limited due to limited API and evolving formulations). This burden may be such that some treatments for rare diseases become too resource intensive to be developed or shift the development to other geographical regions where standards are maintained without the limitations of Annex VI.

3. Purpose and scope

The purpose of this work was to use risk assessments to firstly identify packaging configurations that are susceptible to the changed expiry-labelling requirement of Annex VI (Part 1), and secondly to conclude on the best solution to mitigate the challenges for identified susceptible packaging configurations (Part 2).

The detailed Part 1 risk assessment to determine the level of risk associated with expiry update labeling of the immediate and outer packaging of usual IMP packaging types/configurations is described under 4.1 Part 1 Risk Assessment (Part 1 RA).

Based on the results of Part 1 RA the second risk assessment (Part 2 RA) was performed to determine those amongst potential solutions avoiding expiry labeling and/or expiry update labeling of the immediate packaging with the lowest risk as to feasibility/effectiveness, patient safety, and GMP compliance. The solutions assessed encompass technological solutions, packaging alternatives and labelling alternatives. The detailed risk assessment Part 2 RA is described under 4.2 Part 2 Risk Assessment.

The planned and expected outcomes of the two risk assessments were:

- Determination of the most challenging packaging configurations
- Evaluation of the level of risk and compliance by using technology, packaging and alternative labeling solutions with most challenging packaging configurations
- Decision on mitigation, remediation, and potential solutions for all packaging configurations
- Definition and documentation of the acceptable level of risk and justification of partial compliance or formal non-compliance
- Documentation of conclusions

4. Risk Assessments

4.1 Part 1 Risk Assessment

For Part 1 RA a risk assessment table was completed for the following packaging configurations:

- Syringes in cartons
- Vials in cartons
- Multiple blister cards within a pack (Kits)
- Individual blister cards
- Oral Dosage Forms in Bottles

Prior to use of this Risk Assessment tool, Risk Categories were determined around characteristics of the packaging configuration which would prove difficult in site compliance with relabeling activities for the immediate and outer container. The following is a table of the Risk Categories that were analyzed along with the rationale for the concern for each. For each Risk Category a Relative Priority Level or Risk Ranking was given (High = 5, Medium = 3, or Low =1) and a multiplier for relative importance (Weighting Factor) was used based on the importance of the Risk Category (High =3, Medium =2, Low=1). This Risk Assessment tool was preapproved for use by the Risk Assessment team prior to scoring.

Table 1: Risk categories for assessment of risks associated with different packaging configurations

Risk Category	Reason for Concern	Weighting Factor
Size of Immediate Container	• Compliance: Limited space on small containers to apply additional label; increased waste if impractical to re-label	3
Complexity of packaging configuration	• Compliance: Additional difficulty in relabeling immediate pack, limited space on small containers, training of staff on re-assembly	3
Sealing of Outer Container	• Product Quality / Integrity: broken tamper evident seals may cause concern to patients if not correctly replaced; may give negative impression to patients or investigator sites • Product Quality: Secondary pack seal integrity may be critical to product stability • Compliance: documentation issues, training of staff on proper re-sealing	3
Temperature sensitive product	• Product Quality / Integrity and Patient Safety: potential for product impact if out of temperature range or out of refrigerator/freezer for too long • Compliance: documentation issues, training of staff	2
Light Sensitivity	• Product Quality / Integrity and Patient Safety: potential for product impact if exposed • Compliance: documentation issues, training of staff	2
Font Size	• Compliance: Limited space on small containers to apply additional label; increased waste if impractical to re-label	2

Risk Category	Reason for Concern	Weighting Factor
Label type	• Integrity: concern to patients if label not correctly replaced; may give negative impression to patients or investigator sites • Compliance: documentation issues, training of staff on proper re-labeling	1
Packaging contains carton insert / cutout	• Product Quality / Integrity: Damage to carton or product • Compliance: Additional difficulty in re-labeling, training of staff on re-assembly	2
Material Location	• Patient Safety: Greater risk of mix-up or re-labeling issues if material is out of Pharma Company's control • Compliance: documentation issues, training of staff on proper re-labeling	2
Blinding	• Patient Safety: High risk of mix-up of blinded supplies during manual re-labeling	3

The Total Score was used to determine the overall comprehensive risk per packaging configuration, which was used to decide the need for additional level of control or mitigation. This Total Score was a summation of the scoring of each Risk Category x Weighting Factor.

Total Score of >/= 88 is a HIGH risk, additional actions should be taken (relabeling this configuration would provide unnecessary additional risk);
Total Score of 45-87 is a MEDIUM risk, additional action should be considered;
Total Score of </= 44 is a LOW risk, no additional action is required.

Results of Part 1 RA

The specific scores will depend on product characteristics, packaging design and supply chain. So, it is not possible to provide a comprehensive risk assessment taking into consideration all the factors in Table 1 on a generic basis. However, with reference to the specific examples exemplified in Appendix A, it is possible to see a typical gradation of risk level according to packaging consideration as follows:

Packaging configuration	Risk score	Overall risk level
Syringe in cartons	106	High
Vials in cartons	106	High
Multiple blister cards within pack (Kit)	68	Medium
Individual Blister Cards	38	Low
Oral Dosage Forms in Bottles	38	Low

It is evident from the pre-filled syringe and vial examples that the risk is unacceptably high if the expiry date is printed on the label of the immediate packaging and the shelf-life needs to be extended. Yet shelf-life extensions are a common feature of clinical trials with studies being conducted in parallel with stability testing. The EFPIA preferred option is for Annex VI to be amended in-line with Annex 13, but is it possible to mitigate this risk in compliance with the current wording? The possible options were explored as Part 2 RA of this exercise.

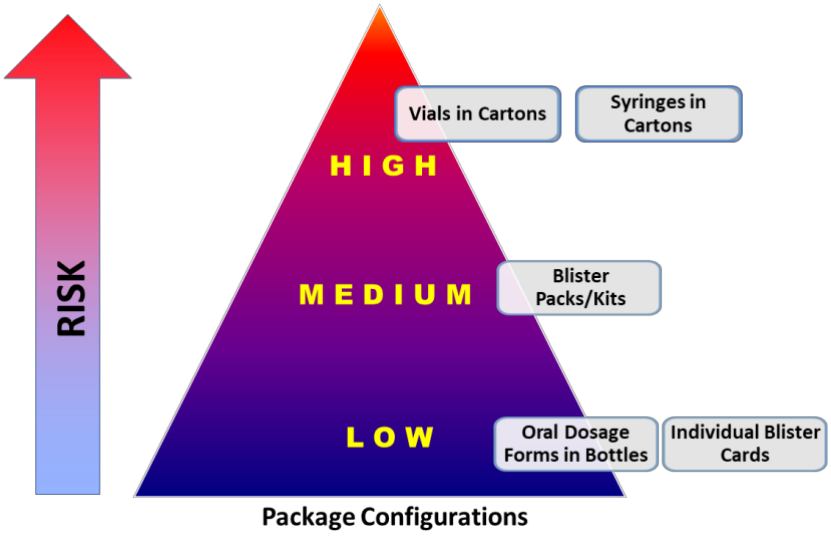

Figure 1: Risk level for different packaging configurations

Acknowledging that the selected packaging configurations are not exhaustive they provide a good basis for assessing packaging configurations not described here. There may be circumstances where the risks described are increased.

A detailed Risk Assessment for Part 1 for the above-mentioned packaging configurations is provided in Appendix A.

4.2 Part 2 Risk Assessment

In the Part 2 RA several if not all theoretically and practically available mitigation solutions for the high-risk packaging configurations were assessed, covering a variety of labeling, packaging and technological solutions as follows:

Technology solutions

- IRT alone
- Combination of IRT with basic label and QR code
- QR code
- Commercially available electronic label solutions (e.g., Faubel Med®Label)

Packaging solutions (some pictorial examples are shown at the end of this document)

- Label with external tail
- External plastic holder
- Large vial with integrated low volume inserts (allowing expiry update labelling)
- External sealed foil or plastic overwrap
- Large “unit dose” rigid blister pack
- Large window through outer packaging
- More frequent and/or smaller packaging campaigns
- Just-in-time (JIT) / On-demand-labelling (ODL) /On-demand-packaging (ODP) either onsite or at depot
- Destroy expired material vs performing expiry update in the field.

Alternative Labelling solutions

- No expiry date printed on immediate packaging. Print expiry date only on outer container. (Annex 13 but not Annex VI compliant for certain packaging configurations)
- No expiry date printed on immediate container but ‘For expiry date see outer packaging’.
- Print expiry date on immediate container and additionally state ‘For most current expiry update see outer packaging of immediate container’.

One initial element of the risk assessment was to assess the **feasibility** of each solution to decide whether the given approach can realistically be performed at Pharma/Sponsor Companies, depots, or investigator sites. Only for the solutions assessed feasible under the terms described above the risks for patient safety (related to supply and treatment stability/consistency) and for Annex VI compliance were assessed. Depending on the risk level resulting, potential mitigations or controls were identified to help develop each alternative solution to full robustness. The final alternative solution would be selected based on given feasibility, the lowest patient safety risk score and maximum compliance with Annex VI requirements.

Result of Part 2 RA

The details of the assessments are given in Appendix B.
The summary of preferred options is given in Table 2.

Table 2: Risk scores and solution decisions for the packaging configurations investigated.

Packaging Configuration	Risk Score	Overall Risk Level	Solution Decision	Rationale
Syringe in Cartons	**106**	**High**	Print initial expiry date on immediate container and additionally state "For most current expiry update see outer packaging of immediate container" on country specific label. Continue including statement: "Keep (immediate container) in outer carton"	Per the risk assessment this presents the lowest risk to patient safety, while maintaining a compliant solution that best mitigates the overall risk score presented by the packaging configuration represented.
Vials in Cartons	**106**	**High**	Print initial expiry date on immediate container and additionally state "For most current expiry update see outer packaging of immediate container" on country specific label. Continue including statement: " Keep (immediate container) in outer carton"	Per the risk assessment this presents the lowest risk to patient safety, while maintaining a compliant solution that best mitigates the overall risk score presented by the packaging configuration represented.
Multiple blister cards within pack (Kit)	**68**	**Medium**	Print initial expiry date on immediate container and additionally state "For most current expiry update see outer packaging of immediate container" on country specific label.	Blister Cards that are kitted within a carton as a pack have greater risk than individual Blister Cards because they would also have to be disassembled, re-labeled and repacked with adherence of a tamper evident seal. These have more surface area for applying expiry update labels and this option is feasible, the overall level of risk of disassembly is enough to warrant a consistent approach to the syringe and vial kit updates.

Packaging Configuration	Risk Score	Overall Risk Level	Solution Decision	Rationale
Oral Dosage Forms in Bottle, Individual Blister Cards	**38**	**Low**	Relabeling activities will continue as per current process, as necessary.	This has been assessed as a low-risk activity and changes are not necessary to the current process to comply with Annex VI.

Of all solutions that were assessed feasible and subjected to the risk assessment process, the lowest low SOD risk score of Part 2 RA was received for one of the alternative labelling solutions, i.e., printing the initial expiry date on the immediate container plus a statement like "*For most current expiry update see outer packaging of immediate container*" (final SOD risk score: 3). All other solutions revealed higher risk scores or were assessed as not applicable to clinical trials with a large amount of investigational medicinal products.
The detailed Part 2 RA for evaluation of the alternative solutions is found in Appendix B.

5. Conclusion / Discussion

For the packaging configurations with high and medium risk scores resulting from Part 1 of the Risk Assessment, an alternative interim solution avoiding expiry update (re-)labeling of immediate containers is considered necessary. The proposed alternative solution resulting from Part 2 of the Risk Assessment is to print the initial expiry date on the immediate container label and additionally "*For most current expiry update see outer packaging of the immediate container*". For an additional level of control, it is recommended to add on the outer container the statement: "Keep (immediate container) in outer carton".

The described alternative interim solution is well supported by the following rationales:

- ✓ Annex VI is complied with as an expiry date is printed on the immediate container.
- ✓ The patient is instructed to check the label of the outer carton for any expiry updates, so only the outer carton needs to be updated (a much lower risk activity).
- ✓ Disassembling of multilayer kits is avoided for expiry updating immediate container labels thus avoiding a serious risk for mix-up or confusion during re-labelling activities of dis-assembled subparts.
- ✓ The ability to limit expiry update labelling to the outer container reduces the need for resupply, which reduces product/material demands (often key for early phase studies) and the risks of delays due to product/material availability issues (reducing risk of harm to patients or to trial integrity due to trial disruption).
- ✓ Finally, the interim solution reduces environmental impacts resulting from wastage and additional transportation.

Overall, this interim alternative solution provides the safest and most feasible approach for Pharma/Sponsor Companies maintaining compliance with Annex VI, enabling risk reduction to an acceptable level.

For packaging configurations with low-risk scores resulting from Part 1 of the Risk Assessment (e.g., oral dosage form in bottle), Annex VI is an added challenge, but can be more readily addressed in expiry process and may not require an alternative interim solution.

References

Reference 1: The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use - Annex 13 Investigational Medicinal Products
LINK: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf

Reference 2: REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/E
LINK: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

Acknowledgement:

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Appendices

Appendix A (see pages following Appendix C): Risk Assessment of Packaging Configurations (Syringe in carton / Vial in carton / Blister Cards within packs/kits / Bottle/Blister Card)

Appendix B (see pages following Appendix C): Risk Assessment of Potential Alternative Solutions

Appendix C: Pictorial examples for alternative packaging solutions described in 4.2 Part 2 RA:

- Label with blank tail

Source: http://www.superiorlabels.com/box-instructions.html

- External holder

Source: http://ambimedinc.com/

- Carton with window

Appendix A: Bottle / Blister Card

Risk Assessment Tool For Packaging Configurations as a part of EU CTR Annex VI for labelling of IMP for expiry date

Packaging Configurations: Tablets in Induction sealed HDPE Bottles or Large Blister Cards

Individual Risk Score
1-4 low
5-9 med
10-15 high

		Relative Priority Level								Mitigation Evaluation		Mitigation Risk Perspectives		
Risk Category	Reasons for Concern	High 5 pts	Medium 3 pts	Low 1 pt	Initial Score	Multiplier using Relative Category Importance 3 High; 2 Medium; 1 Low	Final Category Score	Reason for Scoring	Potential Impact	Mitigation Plan	Benefits	Additional Risks (Risks of Non-Compliance)	Patient Safety Risk	Compliance/ Regulatory Authority	Effectiveness
STATIC: highlights the reason for evaluation of the Risk Category	*STATIC: highlights the reason for evaluation of the Risk Category*	*Choose Score for this Packaging Configuration and record in the column to the right--->*			*Choose Score for this Pkg config*	*STATIC: do not change - indicates importance of this risk category*	*Final Category Score*	*Describe the justification for scoring level given to this risk category for THIS SPECIFIC packaging configuration you are evaluating above*	*Describe the result of the risk / potential quality , safety or compliance impact / what could happen if the risk is not mitigated?*	*Provide a detailed description proposed risk mitigation plan - there may be multiple actions associated with the mitigation plan*	*Describe the benefits the mitigation will provide on the risk category*	*Describe any additional risks the proposed mitigation could cause*	*H, M, L*	*H, M, L*	*H, M, L*
Size of Primary Container	Compliance: Limited space on small containers to apply additional label; increased waste if impractical to relabel	Small primary container - Space extremely limited on primary container	Moderately sized primary Container - space for labeling is retricted - size /text considerations	Large primary Container -Enough space on primary container for additional extension label	1	3	3	Booklet label is positioned on front and variable text is positioned high on bottle or card on back enabling position of additional expiry label underneath when needed, Enough space on Bottles and Blister Cards to allow activity to occur.	No impact.	If necessary, will start at 6-12 month shelf life and relabelling would continue as planned. No expiry extensions or relabelling for shelf life should be needed for this product when it is at maximum.	N/A	N/A	Low	Low	Low
Complexity of packaging configuration	Compliance: Additional difficulty in relabeling primary pack, limited space on small containers, training of staff on re-assembly	Multiple primary units within a secondary container	One primary unit within a secondary container	Single primary unit with no secondary container OR is fully integrated with the secondary container	1	3	3	Simple packaging configuration. Single Primary unit with no secondary container.	No impact.	Relabelling activities would continue as planned, if necessary.	N/A	N/A	Low	Low	Low
Sealing of Secondary Container	Product Quality / Integrity: broken tamper evident seals may cause concern to patients if not correctly replaced; gives bad impression Compliance: documentation issues, training of staff on proper re-sealing	Tamper Evident Seals	The packaging contains seals, but they are not tamper evident seals	No special sealing; Not applicable - no secondary container	1	3	3	Not Applicable - Primary container only	No impact.	Relabelling activities would continue as planned, if necessary.	N/A	N/A	Low	Low	Low
Temperature sensitive product	Product Quality / Integrity and Patient Safety: potential for product impact if out of temperature range or out of refridgerator/freezer for too long. Compliance: documentation issues, training of staff	Refrigerated or Frozen conditions	Other special storage conditions	No special storage; Ambient Conditions	1	2	2	Storage conditions are 15-25 C, no special storage conditions for consideration in relabelling activities.	No impact.	Relabelling activities would continue as planned, if necessary.	N/A	N/A	Low	Low	Low
Light Sensitivity	Product Quality / Integrity and Patient Safety: potential for product impact if exposed. Compliance: documentation issues, training of staff	Exposure to light can cause degredation of the product if removed from outer container.	Exposure to light is controlled through primary pack and labelling; re-labelling should not effect.	Product is not light sensitive	1	2	2	Product is not light sensitive and primary packaging protects from light (HDPE Bottles/ Blister cards)	No impact.	Relabelling activities would continue as planned, if necessary.	N/A	N/A	Low	Low	Low
Font Size	Compliance: Limited space on small containers to apply additional label; increased waste if impractical to relabel	Smallest font allowed by regulations is already printed on primary pack.	Medium-size font on primary container, limited space for additional auxillary	Large font on primary container with additional room for smaller font auxillary label.	1	2	2	Bottle / blister card is labelled with adequate font size to ensure relabelling is effective.	No impact.	Relabelling activities would continue as planned.	N/A	N/A	Low	Low	Low

Appendix A: Bottle / Blister Card

Packaging Configurations: Tablets in Induction sealed HDPE Bottles or Large Blister Cards

Individual Risk Score
1-4 low
5-9 med
10-15 high

		Relative Priority Level									Mitigation Evaluation		Mitigation Risk Perspectives		
Risk Category	Reasons for Concern	High 5 pts	Medium 3 pts	Low 1 pt	Initial Score	Multiplier using Relative Category Importance 3 High; 2 Medium; 1 Low	Final Category Score	Reason for Scoring	Potential Impact	Mitigation Plan	Benefits	Additional Risks (Risks of Non-Compliance)	Patient Safety Risk	Compliance/ Regulatory Authority	Effectiveness
Label type	Integrity: concern to patients if label not correctly replaced; gives bad impression Compliance: documentation issues, training of staff on proper re-labeling	Label must be opened and reclosed / manipulated (i.e.- booklet or flag)	Complex labeling but no manipulation of original label required.	Non-complex; Single panel label	1	2	2	Booklet label may be on the primary pack, however, for variable text and extension labelling, and additional ancillary label is used.	No impact.	Relabelling activities would continue as planned, if necessary.	N/A	N/A	Low	Low	Low
Packaging contains carton insert / cutout	Product Quality / Integrity: Damage to carton or product Compliance: Additional difficulty in re-labeling, training of staff on re-assembly	Insert present - must remove primary container and replace	Carton without insert	No carton	1	1	1	No carton, insert or cutout is present.	No impact.	Relabelling activities would continue as planned, if necessary.	N/A	N/A	Low	Low	Low
Material Location	Patient Safety: Greater risk of mix-up or re-labeling issues if material is out of sponsor company control Compliance: documentation issues, training of staff on proper re-labeling	Site *(must have TQA (Technical Quality Agreement) in place with site for relabeling actvities)*	Depot / Vendor	Sponsor company control	5	2	10	Historically relabelling has been done in all three locations for these packaging types.	Documentation issues - recovering paperwork from sites, greater risk of relabeling mixup	Proper GMP contols. Training is provided to sites prior to expiry update activity.	Continue to use material at sites. Training provided should be sufficient for site relabelling.	Auditing risk - documentation for inspection; missing, incomplete, incorrect.	Low	Medium compliance risk due to location and potential for documentation compliance issues.	Low
Blinding	Patient Safety: High risk of mix-up of blinded supplies during manual re-labeling	Double-Blinded	Blinded	Open label	5	2	10	Assume that the material is used in a Double-Blinded clinical trial for conservative scoring. If open label, this is lower risk	Potential impact if there is a discernable difference in label placement between treatment arms.	Proper GMP contols. Batch record for labelling will make it evident where to place auxillary label along with instuctions and photograph. Need a blindness check for treatment arms after enrichment period. All blinded labels need to be applied the same way. Active and Placebo labeled with the same date.	Verification of the label placement.	Risk of potential bias vs. actual unblinding	Low	Medium compliance risk due to blinding and potential for documentation compliance issues.	Low
Any additional?					0		0								
						Total Score:	38	Low Risk							

Total Score is used to determine the comprehensive risk the site and the supplied starting materials have, which is used to make a determination of the need for additional oversight activities. Total Score of >/= 88 is a HIGH risk, additional action should be taken; 45-87 is a MEDIUM risk, additional action should be considered </= 44 is a LOW risk, additional action is not required

Risk Priority Level (indicate one): **LOW**

Comments: (*Blank indicates none)*

Appendix A: Blister cards within packs/kits

Risk Assessment Tool For Packaging Configurations as a part of EU CTR Annex VI for labelling of IMP for expiry date

Packaging Configuration: Blister Cards within packs/kits

Individual Risk Score
1-4 low
5-9 med
10-15 high

		Relative Priority Level									Mitigation Evaluation		Mitigation Risk Perspectives		
Risk Category	Reasons for Concern	High 5 pts	Medium 3 pts	Low 1 pt	Initial Score	Multiplier using Relative Category Importance 3 High; 2 Medium; 1 Low	Final Category Score	Reason for Scoring	Potential Impact	Mitigation Plan	Benefits	Additional Risks (Risks of Non-Compliance)	Patient Safety Risk	Compliance/ Regulatory Authority	Effectiveness
STATIC: highlights the reason for evaluation of the Risk Category	*STATIC: highlights the reason for evaluation of the Risk Category*	*Choose Score for this Packaging Configuration and record in the column to the right--->*			*Choose Score for this Pkg config*	*STATIC: do not change - indicates importance of this risk category*	*Final Category Score*	*Describe the justification for scoring level given to this risk category for THIS SPECIFIC packaging configuration you are evaluating above*	*Describe the result of the risk / potential quality , safety or compliance impact / what could happen if the risk is not mitigated?*	*Provide a detailed description proposed risk mitigation plan - there may be multiple actions associated with the mitigation plan*	*Describe the benefits the mitigation will provide on the risk category*	*Describe any additional risks the proposed mitigation could cause*	*H, M, L*	*H, M, L*	*H, M, L*
Size of Primary Container	Compliance: Limited space on small containers to apply additional label; increased waste if impractical to relabel	Small primary container - Space extremely limited on primary container	Moderately sized primary Container - space for labeling is retricted - size /text considerations	Large primary Container - Enough space on primary container for additional extension label	3	3	9	Size of primary container is blister cards within the packs, typically enough space for relabeling activities as the cards are larger.	No impact.	If necessary, relabelling would continue as planned.	N/A	N/A	Low	Low	Low
Complexity of packaging configuration	Compliance: Additional difficulty in relabeling primary pack, limited space on small containers, training of staff on re-assembly	Multiple primary units within a secondary container	One primary unit within a secondary container	Single primary unit with no secondary container OR is fully integrated with the secondary container	3	3	9	Multiple blister cards may be contained within a pack but would not be an overly complicated task to relabel both cards and packs	Potential for impact to materials.	Need visual second person checks to ensure that card numbers match blister packs. Keep activity in house where possible, limit the amount of material that is at sites and sub-depots.	Proper GMP controls, minimize amount of study disruption and reduce impact to subject dosing.	Requires good coordination with Clinical Operations to ensure that enrollment is managed.	Potential for Study disruption	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue, accountability issues.
Sealing of Secondary Container	Product Quality / Integrity: broken tamper evident seals may cause concern to patients if not correctly replaced; gives bad impression Compliance: documentation issues, training of staff on proper re-sealing	Tamper Evident Seals	The packaging contains seals, but they are not tamper evident seals	No special sealing; Not applicable - no secondary container	5	3	15	Blister card or pack has to have a tamper evident seal and removing poses a GMP risk.	May not know what has been done to material once seal has been removed; cold form blisters could be difficult to handle to prevent deformation and/or product damage.	Possible removal and replacement of the tamper evident seals and careful handling of material warrants that this be done under sponsor control. Would provide second TE seal for the depot / sites to use as well as oversight and documentation.	Second seal applied under GMP controls would be compliant. (eg. QP on site, GMP license in EU)	Patient/site personnel perspective - may not look good, product compliants. Management of TE seals may not be realistic - documentation issues, strict accountability.	Appearance to patient. Potential for Study disruption. Unclear what was done with the material when initial seal was broken.	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue, accountability issues.
Temperature sensitive product	Product Quality / Integrity and Patient Safety: potential for product impact if out of temperature range or out of refridgerator/freezer for too long. Compliance: documentation issues, training of staff	Refrigerated or Frozen conditions	Other special storage conditions	No special storage; Ambient Conditions	1	2	2	Storage conditions are typically less/equal 25 or 30 deg C, no special storage conditions for consideration in relabelling activities.	No impact.	Relabelling activities would continue as planned, if necessary.	N/A	N/A	Low	Low	Low
Light Sensitivity	Product Quality / Integrity and Patient Safety: potential for product impact if exposed. Compliance: documentation issues, training of staff	Exposure to light can cause degredation of the product if removed from outer container.	Exposure to light is controlled through primary pack and labelling; re-labelling should not effect.	Product is not light sensitive	1	2	2	Product is assumed to be not light sensitive and primary packaging protects from light (Blister Cards/Packs)	No impact.	Relabelling activities would continue as planned, if necessary.	N/A	N/A	Low	Low	Low
Font Size	Compliance: Limited space on small containers to apply additional label; increased waste if impractical to relabel	Smallest font allowed by regulations is already printed on primary pack.	Medium-size font on primary container, limited space for additional auxillary label.	Large font on primary container with additional room for smaller font auxillary label.	3	2	6	Cards/Packs are typically labelled with adequate font size to ensure relabelling is effective. **See also line 10 for size of primary container.**	No impact.	Relabelling activities would continue as planned.	N/A	N/A	Low	Low	Low
Label type	Integrity: concern to patients if label not correctly replaced; gives bad impression Compliance: documentation issues, training of staff on proper re-labeling	Label must be opened and reclosed / manipulated (i.e.- booklet or flag)	Complex labeling but no manipulation of original label required.	Non-complex; Single panel label	1	2	2	Booklet label may be on the primary pack, however for variable text and extension labelling, and additional ancillary label is used.	No impact.	Relabelling activities would continue as planned, if necessary.	N/A	N/A	Low	Low	Low

Appendix A: Blister cards within packs/kits

Packaging Configuration: Blister Cards within packs/kits

Individual Risk Score
1-4 low
5-9 med
10-15 high

		Relative Priority Level								Mitigation Evaluation		Mitigation Risk Perspectives		
Risk Category	Reasons for Concern	High 5 pts	Medium 3 pts	Low 1 pt	Initial Score	Multiplier using Relative Category Importance 3 High; 2 Medium; 1 Low	Final Category Score	Reason for Scoring	Potential Impact	Mitigation Plan	Benefits	Additional Risks (Risks of Non-Compliance)	Patient Safety Risk	Compliance/ Regulatory Authority	Effectiveness
Packaging contains carton insert / cutout	Product Quality / Integrity: Damage to carton or product Compliance: Additional difficulty in re-labeling, training of staff on re-assembly	Insert present - must remove primary container and replace	Carton without insert	No carton	3	1	3	Typically no carton insert for blister cards/packs. Adequate separation.	No impact.	Relabelling activities would continue as planned, if necessary.	N/A	N/A	Low	Low	Low
Material Location	Patient Safety: Greater risk of mix-up or re-labeling issues if material is out of sponsor company control Compliance: documentation issues, training of staff on proper re-labeling	Site *(must have TQA in place with site for relabeling actvities)*	Depot / Vendor	Sponsor company control	5	2	10	Historically relabelling has been done in all three locations for these packaging types.	Documentation issues - recovering paperwork from sites, greater risk of relabeling mixup	Proper GMP contols. Training is provided to sites prior to expiry update activity.	Continue to use material at sites. Training provided should be sufficient for site relabelling.	Auditing risk - documentation for inspection; missing, incomplete, incorrect.	Low	Medium compliance risk due to location and potential for documentation compliance issues.	Low
Blinding	Patient Safety: High risk of mix-up of blinded supplies during manual re-labeling	Double-Blinded	Blinded	Open label	5	2	10	Assume that the material is used in a Double-Blinded clinical trial for conservative scoring. If open label, this is lower risk	Potential impact if there is a discernable difference in label placement between treatment arms.	Proper GMP contols. Batch record for labelling will make it evident where to place auxillary label along with instuctions and photograph. Need a blindness check for treatment arms after enrichement period. All blinded labels need to be the applied the same way. Active and Placebo labeled with the same date.	Verification of the label placement.	Risk of potential bias vs. actual unblinding	Low	Medium compliance risk due to blinding and potential for documentation compliance issues.	Low
Any additional?					0		0								
						Total Score:	68	Medium Risk							

Total Score is used to determine the comprehensive risk the site and the supplied starting materials have, which is used to make a determination of the need for additional oversight activities.
Total Score of >/= 88 is a HIGH risk, additional action should be taken; 45-87 is a MEDIUM risk, additional action should be considered </= 44 is a LOW risk, additional action is not required

Risk Priority Level (indicate one): MEDIUM

Comments: (*Blank indicates none)*

Appendix A: Syringe in carton

Risk Assessment Tool For Packaging Configurations as a part of EU CTR Annex VI for labelling of IMP for expiry date

Packaging Configuration: Syringe in Carton

Individual Risk Score
1-4 low
5-9 med
10-15 high

		Relative Priority Level							Mitigation Evaluation		Mitigation Risk Perspectives		
Risk Category	**Reasons for Concern**	**High 5 pts**	**Medium 3 pts**	**Low 1 pt**	**Initial Score**	**Multiplier using Relative Category Importance 3 High; 2 Medium; 1 Low**	**Final Category Score**	**Reason for Scoring**	**Potential Impact**	**Mitigation Plan Options**	**Benefits**	**Additional Risks (Risks of Non-Compliance)**	**Patient Safety Risk**	**Compliance/ Regulatory Authority**	**Effectiveness**
STATIC: highlights the reason for evaluation of the Risk Category	*STATIC: highlights the reason for evaluation of the Risk Category*	*Choose Score for this Packaging Configuration and record in the column to the right--->*			*Choose Score for this Pkg config*	*STATIC: do not change - indicates importance of this risk category*	*Final Category Score*	*Describe the justification for scoring level given to this risk category for THIS SPECIFIC packaging configuration you are evaluating above*	*Describe the result of the risk / potential quality , safety or compliance impact / what could happen if the risk is not mitigated?*	*Provide a detailed description proposed risk mitigation plan - there may be multiple actions associated with the mitigation plan*	*Describe the benefits the mitigation will provide on the risk category*	*Describe any additional risks the proposed mitigation could cause*	*H, M, L*	*H, M, L*	*H, M, L*
Size of Primary Container	Compliance: Limited space on small containers to apply additional label	Small primary container - Space extremely limited on primary container	Moderately sized primary Container - space for labeling is retricted - size /text considerations	Large primary Container -Enough space on primary container for additional extension label	5	3	15	Very limited space on primary container (Syringe). Size of syringe already dictates label text has minimum required info or is a wrapped label.	Very limited space makes it very difficult to perform this activity effectively.	Would need GMP controls, visual second person checks to ensure that vials are labeled effectively. Instructions and training at sites. Keep activity in house where possible, and limit the amount of material that is at sites and sub-depots	Proper GMP controls, minimize amount of study disruption and reduce impact to subject dosing. Sites following up with patients.	Unpacking and relabling presents a risk to product, pack or label damage, mix-up, repacking confusion, and documentation issues at depots/sites.	Manpulation of product - plunger rod, stopper could cause sterilty issues. Appearance of label. Appearance to patient. Study disruption	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor company control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue with reassembly, accountability issues.
Complexity of packaging configuration	Compliance: Additional difficulty in relabeling primary pack, limited space on small containers, training of staff on re-assembly	Multiple primary units within a secondary container	One primary unit within a secondary container	Single primary unit with no secondary container OR is fully integrated with the secondary container	5	3	15	Multiple units within a carton presents more complexity for this operation in removing the syringes and relabeling, not significantly higher risk than one.	Potential for breakage and damage to materials, carton, etc. Putting syringes back in the carton in the same manner to protect the blinding of the study.	Would need GMP controls, visual second person checks to ensure that vials are labeled effectively. Instructions and training at sites. Keep activity in house where possible, and limit the amount of material that is at sites and sub-depots	Proper GMP controls, minimize amount of study disruption and reduce impact to subject dosing.	Requires good coordination with Clinical Operations to ensure that enrollment is managed.	Manpulation of product - plunger rod, stopper could cause sterilty issues. Appearance of label. Appearance to patient. Study disruption	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor company control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue with reassembly, accountability issues.
Sealing of Secondary Container	Product Quality / Integrity: broken tamper evident seals may cause concern to patients if not correctly replaced; gives bad impression Compliance: documentation issues, training of staff on proper re-sealing	Tamper Evident Seals	The packaging contains seals, but they are not tamper evident seals	No special sealing	5	3	15	Syringe cartons have tamper evident seals which will need to be replaced after relabeling activity on cassettes. Removing poses a GMP risk.	Presents a GMP risk, need 100% accountability of tamper seals, need to apply correctly for appearance to patients.	Documentation records for replacement of TE seals, second person check to ensure that placement of seal is correct. If possible, in-house, would use a new carton.	Second seal applied under GMP controls would be compliant. (eg. QP on site, GMP license in EU). If allowed, would prevent study disruption.	Patient/site personnel perspective - may not look good, product compliants. Management of TE seals may not be realistic - documentation issues, strict accountability.	Appearance to patient. Potential for Study disruption. Unclear what was done with the material when initial seal was broken	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor company control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue with reassembly, accountability issues.
Temperature sensitive product	Product Quality / Integrity and Patient Safety: potential for product impact if out of temperature range or out of refridgerator/freezer for too long. Compliance: documentation issues, training of staff	Refrigerated or Frozen conditions	Other special storage conditions	No special storage; Ambient Conditions	5	2	10	Syringe is usually biologic which is cold chain storage	Impact is relabeling material and having to manage time out of refrigerated unit, presents more complexity, potential loss of product/waste material	Documented start and stop time - relabeling instructions, reconciliation, should be controlled tightly and in-house where possible.	Proper GMP controls over temperature sensitive products. Maintain tight Control over activity.	Need to understand instructions clearly or potential impact to product	Temperature excursions, Loss of material, stopping of study	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor company control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue, accountability issues.
Light Sensitivity	Product Quality / Integrity and Patient Safety: potential for product impact if exposed. Compliance: documentation issues, training of staff	Exposure to light can cause degredation of the product if removed from outer container.	Exposure to light is controlled through primary pack and labelling; re-labelling should not affect.	Product is not light sensitive	3	2	6	Primary pack would protect from light. If expiry update needed on these types of materials and would require light sensitive controls would be in-house and under GMP control	The light expose impact would be to the product if it was light sensitive. The re-label activity would need to be performed in-house and under special light conditions.	N/A - None needed - Primary pack would protect from light. If expiry update needed on these types of materials and would require light sensitive controls under GMP control.	Proper GMP controls, minimize amount exposre of product to light.	Need to understand instructions clearly or potential impact to product	Loss of material, stopping of study	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor company control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue with reassembly, accountability issues.
Font Size	Compliance: Limited space on small containers to apply additional label; increased waste if impractical to relabel	Smallest font allowed by regulations is already printed on primary pack.	Medium-size font on primary container, limited space for additional auxillary label.	Large font on primary container with additional room for smaller font auxillary label.	5	2	10	**See line 10 of Risk Assessment for Primary Container size**							

Appendix A: Syringe in carton

Packaging Configuration: Syringe in Carton

Individual Risk Score
1-4 low
5-9 med
10-15 high

		Relative Priority Level							Mitigation Evaluation		Mitigation Risk Perspectives		
Risk Category	Reasons for Concern	High 5 pts	Medium 3 pts	Low 1 pt	Initial Score	Multiplier using Relative Category Importance 3 High; 2 Medium; 1 Low	Final Category Score	Reason for Scoring	Potential Impact	Mitigation Plan Options	Benefits	Additional Risks (Risks of Non-Compliance)	Patient Safety Risk	Compliance/ Regulatory Authority	Effectiveness
Label type	Integrity: concern to patients if label not correctly replaced; gives bad impression Compliance: documentation issues, training of staff on proper re-labeling	Label must be opened and reclosed / manipulated (i.e.- booklet or flag)	Complex labeling but no manipulation of original label required.	Non-complex; Single panel label	5	2	10	Current label design does not account for relabeling. Would obscure the label in some way. Original expiry date cannot be obscured in some countries (South America). Complex re-labling activties: label would have to be unwrapped and closed or removed from syringe after syringe is removed from carton.	Have to remove the syringe from carton to relabel, danger in plunger rod impact. Cannot remove the original label, need to include batch number again during the expriy update. Limited space for ancillary label.	Would need to develop a new label design to give physical room to apply expiry date label with batch number. - change in label design.	Ability to relabel using a new label design.	Would encounter the same risks with removal of syringe from carton - potenial for damage to product as label.	Manpulation of product - plunger rod, stopper could impact sterilty. Appearance of label.	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor company control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue with reassembly, accountability issues.
Packaging contains carton insert / cutout	Product Quality / Integrity: Damage to carton or product Compliance: Additional difficulty in re-labeling, training of staff on re-assembly	Insert present - must remove primary container and replace	Carton without insert	No carton	5	1	5	**See line 12 of Risk Assessment for Complexity of Packaging Configuration**							
Material Location	Patient Safety: Greater risk of mix-up or re-labeling issues if material is out of sponsor company control Compliance: documentation issues, training of staff on proper re-labeling	Site	Depot / Vendor	Sponsor company control	5	2	10	Re-labeling activities may have to be performed in all 3 locations.	Additional risk as the product gets further away from sponsor company control, operation has the potential to damage product or impact blinding without sponsor company knowledge.	Proper GMP controls. Agree on Batch Record before the operation occurs, additional training of sites, second person verification. Labelling and documentation.	Potential to have this activity occur in specific sites as needed for this relabeling activity, EU sites may have GMP controls for this.	Since this is still a complex configuration the residual risk is high for appearance and potential damage. Auditing risk - documentation for inspection; missing, incomplete, incorrect.	Appearance to patient. Potential for damage. Potential for Study disruption.	Medium compliance risk due to location and potential for documentation compliance issues.	Potential feasibility issue, accountability issues.
Blinding	Patient Safety: High risk of mix-up of blinded supplies during manual re-labeling	Double-Blinded	Blinded	Open label	5	2	10	Assume that the material is used in a Double-Blinded clinical trial for conservative scoring. If open label, this is lower risk	Potential impact if there is a discernable difference in label placement between treatment arms.	Proper GMP contols. Batch record for labelling will make it evident where to place auxillary label along with instuctions and photograph. Need a blindness check for treatment arms after enrichment period. All blinded labels need to be the applied the same way. Active and Placebo labeled with the same date.	Verification of the label placement.	Risk of potential bias vs. actual unblinding	Low	Medium compliance risk due to blinding and potential for documentation compliance issues.	Low
Any additional?					0		0								
						Total Score:	106	High Risk							

Total Score is used to determine the comprehensive risk the site and the supplied starting materials have, which is used to make a determination of the need for additional oversight activities. Total Score of >/= 88 is a HIGH risk, additional action should be taken; 45-87 is a MEDIUM risk, additional action should be considered </= 44 is a LOW risk, additional action is not required

Risk Priority Level (indicate one): **HIGH**

Comments: (*Blank indicates none)*

Appendix A: Vial in carton

Risk Assessment Tool For Packaging Configurations as a part of EU CTR Annex VI for labelling of IMP for expiry date

Packaging Configuration: Vial in Carton

Individual Risk Score
1-4 low
5-9 med
10-15 high

		Relative Priority Level								Mitigation Evaluation		Mitigation Risk Perspectives		
Risk Category	**Reasons for Concern**	**High 5 pts**	**Medium 3 pts**	**Low 1 pt**	**Initial Score**	**Multiplier using Relative Category Importance 3 High; 2 Medium; 1 Low**	**Final Category Score**	**Reason for Scoring**	**Potential Impact**	**Mitigation to comply**	**Benefits**	**Additional Risks (Risks of Non-Compliance)**	**Patient Safety Risk**	**Compliance/ Regulatory Authority**	**Effectiveness**
STATIC: highlights the reason for evaluation of the Risk Category	*STATIC: highlights the reason for evaluation of the Risk Category*	*Choose Score for this Packaging Configuration and record in the column to the right--->*			*Choose Score for this Pkg config*	*STATIC: do not change - indicates importance of this risk category*	*Final Category Score*	*Describe the justification for scoring level given to this risk category for THIS SPECIFIC packaging configuration you are evaluating above*	*Describe the result of the risk / potential quality , safety or compliance impact / what could happen if the risk is not mitigated?*	*Provide a detailed description proposed risk mitigation plan - there may be multiple actions associated with the mitigation plan*	*Describe the benefits the mitigation will provide on the risk category*	*Describe any additional risks the proposed mitigation could cause*	*H, M, L*	*H, M, L*	*H, M, L*
Size of Primary Container	Compliance: Limited space on small containers to apply additional label	Small primary container - Space extremely limited on primary container	Moderately sized primary Container - space for labeling is retricted - size /text considerations	Large primary Container -Enough space on primary container for additional extension label	5	3	15	Limited space and small labels on primary container (vial) to apply update label. Size of vial already dictates label text has minimum required info or is a wrapped label.	Limited space makes it very difficult to perform this activity effectively.	Would need GMP controls, visual second person checks to ensure that vials are labeled effectively. Instructions and training at sites. Keep activity in house where possible, and limit the amount of material that is at sites and sub-depots	Proper GMP controls, minimize amount of study disruption and reduce impact to subject dosing. Sites follow up with patients.	**Not a feasible mitigation as sites would not be able to re-label vials due to space contraints. Need to consider alternative solutions.** Unpacking and relabling presents a risk to product, pack or label damage, mix-up, repacking confusion, and documentation issues at depots/sites.	Appearance to patient, appearance of label. Potential for damage. Potential for Study disruption.	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor company control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue with reassembly, accountability issues.
Complexity of packaging configuration	Compliance: Additional difficulty in relabeling primary pack, limited space on small containers, training of staff on re-assembly	Multiple primary units within a secondary container	One primary unit within a secondary container	Single primary unit with no secondary container OR is fully integrated with the secondary container	5	3	15	Multiple units within a carton presents more complexity for this operation in removing the vials and relabeling, not significantly higher risk than one.	Potential for breakage and damage to materials, carton, etc. Putting vials back in the carton in the same manner to protect the blinding of the study.	Would need GMP controls, visual second person checks to ensure that vials are labeled effectively. Instructions and training at sites. Keep activity in house where possible, and limit the amount of material that is at sites and sub-depots	Proper GMP controls, minimize amount of study disruption and reduce impact to subject dosing.	Requires good coordination with Clinical Operations to ensure that enrollment is managed.	Appearance to patient, appearance of label. Potential for damage. Potential for Study disruption.	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor company control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue with reassembly, accountability issues.
Sealing of Secondary Container	Product Quality / Integrity: broken tamper evident seals may cause concern to patients if not correctly replaced; gives bad impression Compliance: documentation issues, training of staff on proper re-sealing	Tamper Evident Seals	The packaging contains seals, but they are not tamper evident seals	No special sealing	5	3	15	Vial cartons have tamper evident seals which will need to be replaced after relabeling activity. Removing poses a GMP risk.	Presents a GMP risk, need 100% accountability of tamper seals, need to apply correctly for appearance to patients.	Documentation records for replacement of TE seals, second person check to ensure that placement of seal is correct.	Second seal applied under GMP controls would be compliant. (eg. QP on site, GMP license in EU). If allowed, would prevent study disruption.	Patient/site personnel perspective - may not look good, product compliants. Management of TE seals may not be realistic - documentation issues, strict accountability.	Appearance to patient. Potential for Study disruption. Unclear what was done with the material when initial seal was broken.	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor company control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue, accountability issues.
Temperature sensitive product	Product Quality / Integrity and Patient Safety: potential for product impact if out of temperature range or out of refridgerator/freezer for too long. Compliance: documentation issues, training of staff	Refrigerated or Frozen conditions	Other special storage conditions	No special storage; Ambient Conditions	5	2	10	Usually biologic, which is cold chain storage.	Impact is relabeling material and having to manage time out of refrigerated unit, presents more complexity, potential loss of product/waste material	Documented start and stop time - relabeling instructions, reconciliation, should be controlled tightly and in-house where possible.	Proper GMP controls over temperature sensitive products. Maintain tight Control over activity.	Need to understand instructions clearly or potential impact to product	Temperature excursions, Loss of material, stopping of study	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor company control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue, accountability issues.
Light Sensitivity	Product Quality / Integrity and Patient Safety: potential for product impact if exposed. Compliance: documentation issues, training of staff	Exposure to light can cause degredation of the product if removed from outer container.	Exposure to light is controlled through primary pack and labelling; re-labelling should not effect.	Product is not light sensitive	3	2	6	Primary pack would protect from light. If expiry update needed on these types of materials and would require light sensitive controls would be in-house and under GMP control	The light expose impact would be to the product if it was light sensitive. The re-label activity would need to be performed in-house and under special light conditions.	N/A - None needed - Primary pack would protect from light. If expiry update needed on these types of materials and would require light sensitive controls would be in-house and under GMP control	Proper GMP controls, minimize amount exposre of product to light.	Need to understand instructions clearly or potential impact to product	Loss of material, stopping of study	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor company control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue, accountability issues.

Appendix A: Vial in carton

Packaging Configuration: Vial in Carton

Individual Risk Score
1-4 low
5-9 med
10-15 high

		Relative Priority Level								Mitigation Evaluation		Mitigation Risk Perspectives		
Risk Category	Reasons for Concern	High 5 pts	Medium 3 pts	Low 1 pt	Initial Score	Multiplier using Relative Category Importance 3 High; 2 Medium; 1 Low	Final Category Score	Reason for Scoring	Potential Impact	Mitigation to comply	Benefits	Additional Risks (Risks of Non-Compliance)	Patient Safety Risk	Compliance/ Regulatory Authority	Effectiveness
Font Size	Compliance: Limited space on small containers to apply additional label; increased waste if impractical to relabel	Smallest font allowed by regulations is already printed on primary pack.	Medium-size font on primary container, limited space for additional auxillary label.	Large font on primary container with additional room for smaller font auxillary label.	5	2	10	**See line 10 of Risk Assessment for Primary Container size**							
Label type	Integrity: concern to patients if label not correctly replaced; gives bad impression Compliance: documentation issues, training of staff on proper re-labeling	Label must be opened and reclosed / manipulated (i.e.- booklet or flag)	Complex labeling but no manipulation of original label required.	Non-complex; Single panel label	5	2	10	Current label design does not account for relabeling. Would obscure the label in some way. Original expiry date cannot be obscured in some countries (South America). Complex re-labling activties: label may have to be unwrapped and closed after vial is removed from carton.	Cannot remove the original label, need to include batch number again during the expiry update. Limited space for ancillary label.	Would need to develop a new label design to give physical room to apply expiry date label with batch number. - change in label design.	Ability to relabel using a new label design.	Would encounter the same risks with removal of vial from carton - potenial for damage to product as label.	Appearance to patient, appearance of label. Potential for damage. Potential for Study disruption.	Would be compliant if done under GMP; however, sites may find it difficult to apply correct GMP control (the further away from sponsor company control the bigger the risk). Potential for Documentation issues.	Potential feasibility issue with reassembly, accountability issues.
Packaging contains carton insert / cutout	Product Quality / Integrity: Damage to carton or product Compliance: Additional difficulty in re-labeling, training of staff on re-assembly	Insert present - must remove primary container and replace	Carton without insert	No carton	5	1	5	**See line 12 of Risk Assessment for Complexity of Packaging Configuration**							
Material Location	Patient Safety: Greater risk of mix-up or re-labeling issues if material is out of sponsor company control Compliance: documentation issues, training of staff on proper re-labeling	Site	Depot / Vendor	Sponsor company control	5	2	10	Re-labeling activitiesmay have to be performed in all 3 locations.	Additional risk as the product gets further from sponsor company control, operation has the potential to damage product or impact blinding without sponsor company knowledge.	Proper GMP controls. Agree on Batch Record before the operation occurs, additional training of sites, second person verification. Labelling and documentation.	Potential to have this activity occur in specific sites as needed for this relabeling activity, EU sites may have GMP controls for this.	Since this is still a complex configuration the residual risk is high for appearance and potential damage. Auditing risk - documentation for inspection; missing, incomplete, incorrect.	Appearance to patient. Potential for damage. Potential for Study disruption.	Medium compliance risk due to location and potential for documentation compliance issues.	Potential feasibility issue, accountability issues.
Blinding	Patient Safety: High risk of mix-up of blinded supplies during manual re-labeling	Double-Blinded	Blinded	Open label	5	2	10	Assume that the material is used in a Double-Blinded clinical trial for conservative scoring. If open label, this is lower risk	Potential impact if there is a discernable difference in label placement between treatment arms.	Proper GMP contols. Batch record for labelling will make it evident where to place auxillary label along with instuctions and photograph. Need a blindness check for treatment arms after enrichement period. All blinded labels need to be the applied the same way. Active and Placebo labeled with the same date.	Verification of the label placement.	Risk of potential bias vs. actual unblinding	Low	Medium compliance risk due to blinding and potential for documentation compliance issues.	Low
Any additional?					0		0								
						Total Score:	106	High Risk							

Total Score is used to determine the comprehensive risk the site and the supplied starting materials have, which is used to make a determination of the need for additional oversight activities. Total Score of >/= 88 is a HIGH risk, additional action should be taken; 45-87 is a MEDIUM risk, additional action should be considered </= 44 is a LOW risk, additional action is not required

Risk Priority Level (indicate one): **HIGH**

Comments: (*Blank indicates none*)

APPENDIX B

Annex VI – *Potential alternative solutions and risk assessment*

Risk levels: S/O: high = 5; medium = 3; low = 1
D: high = 1; medium = 3; low = 5

Alternative Solutions	Feasible option	Patient safety risk	S	O	D	Risk score	Potential mitigation / control	Compliance risk	Comment/consideration
No expiry date printed on primary container. Instead print expiry date only on secondary container.	Yes – for most configurations	Patient could remove the primary container from the carton and not have an expiry date	5	1	3	15	Statement needed on outer container that the primary container must remain together with the secondary package; sponsor/site monitors expiry dates of packs in use and ensures dispensed packs are likely to be used before this date and actively contacts trial subjects if extension is not possible	Non-compliant with EU Annex VI as no expiry date labelled on primary packaging	Some situations such as – 80° C storage remain difficult
No expiry date printed on primary container. Instead print 'For expiry date see outer packaging'	Yes – for most configurations	Patient could remove the primary container from the carton and not have an expiry date	5	1	3	15	Statement needed on outer container that the primary container must remain together with the secondary package; sponsor/site monitors expiry dates of packs in use and ensures dispensed packs are likely to be used before this date and actively contacts trial subjects if extension is not possible	Partially compliant with Annex VI: no expiry date labelled on primary packaging but reference to expiry date on the outer packaging.	Some situations such as – 80° C storage remain difficult
Initial expiry date printed on primary container label and additionally state 'For most current expiry update see outer packaging of primary container'	Yes – for most configurations	Patient could remove the primary container from the carton and not have the updated expiry date; severity reduced as is an expiry date and most updates are extensions (and reductions will be subject to more active communication); only little potential for confusion due to reference to outer packaging	3	1	1	3	Statement on outer container that the primary container shall remain together with the outer packaging	Considered compliant with Annex VI as expiry date labelled on primary packaging with additional reference to updated expiry date on outer container	Greater detectability as initial expiry date is printed on label of primary container. Some situations such as – 80° C storage remain difficult.
E-ink based technology	No – not yet ready for implementation and potential conflict with Annex VI chapter D	No assessment as not a feasible solution at the moment						Different EU countries have different opinions if this meets the regulations.	E-Ink is not currently ready to be implemented - would require validation, etc. High cost is another issue, although certainly a viable option for the future
JIT/ODL/ODP labelling either onsite or at depot	Not for every study, due to increase in number of labelling runs required – time, cost and personnel factor	Low patient risk	1	1	1	1	Must be undertaken in GMP conditions as a manufacturing step	Not well suited to large numbers of packs and too high a load on the capacity could increase the compliance risk	**Not a generally acceptable solution**: while solution allows to apply the most recent expiry date multilayer kits and larger numbers of packs create serious logistic, QA and QP challenges.

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Alternative Solutions	Feasible option	Patient safety risk	S	O	D	Risk score	Potential mitigation / control	Compliance risk	Comment/consideration
QR code to manage expiry date for labels on small primary containers (i.e., syringes) • 2D QR code can be printed onto clip attachment • Detachable – could be removed at time of use so it would not interfere with dose administration	No – refer to current e-labelling discussions on products with EMA	No assessment as not a feasible solution at the moment						Conflict with Annex VI chapter D. QR codes are not yet accepted by regulatory authorities.	Risk of being detached (deliberately or accidentally) before administration
QR code applied on the bottom of a bottle or vial • Potential application for vials where label would wrap around and obscure the code • Could contain the same information as standard variable text labels • Consider making it easy to peel off at time of use for product visibility	No – refer to current e-labelling discussions on products with EMA	No assessment as not a feasible solution at the moment						Conflict with Annex VI chapter D. QR codes are not yet accepted by regulatory authorities.	Viable option for the future
Use of IRT	Yes, however still needing printed expiry date	Not assessed as currently not an option to implement						Conflict with Annex VI chapter D. Use of IRT does not help to meet new regulation as still requires printed expiry date on the label.	Other Geographical regions use this and will have increased use in the future
Combination of IRT with basic label and QR code • Allows central update of expiry date if encoded on QR code • no physical re-labeling of primary container required • use traditional label to update outer carton	No – refer to current e-labelling discussions on products with EMA	Not assessed as currently not an option to implement						Conflict with Annex VI chapter D. Use of IRT does not help to meet new regulation as still requires printed expiry date on the label.	
Label on primary container with long, blank "tail" that could extend outside of the carton to allow room to apply expiry date labels. • "Tail" could be completely blank and held in place with light adhesive tab (e.g., as with booklet label cover pages) • Multiple expiry update labels could be applied to "tail"	Feasible for some configurations	Tail could be torn off by patient/study personnel or label be damaged	3	3	3	27	Choose another solution for control	Technically compliant unless tail is torn off or damaged which would turn it non-compliant	Little practical experience given with little guarantee to work consistently

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Alternative Solutions	Feasible option	Patient safety risk	S	O	D	Risk score	Potential mitigation / control	Compliance risk	Comment/consideration
Small vials could be placed into an **external plastic holder** which could provide more space to apply expiry date labels	No (conceptional solution yet)	Not assessed as currently not an option to implement						Holder is technically not primary packaging; holder and vial would need to be inseparable => not compliant	Ways to increase surface area on packaging but will not add much space and is technically very challenging
Larger vials with integrated "low volume insert" – larger surface area for labeling	Possible	No assessment of Patient Safety as this is currently not an option to implement as it is not technically feasible.						Not assessed	Increase in surface area may not be sufficient to allow Annex VI labelling and increasing vial size may have significant manufacturing and packaging challenges resulting in it being unviable in most cases
Small vials could be placed into an **external sealed foil** or **plastic overwrap** (e.g., as with albuterol or saline, etc.), or large "unit dose" rigid blister pack, which could provide more space to apply expiry date labels. • Overwrap / blister would remain sealed until time of use (Outer carton would provide protection against breakage)	Possible	No assessment of Patient Safety as this is currently not an option to implement as it is not technically feasible.						Regulatory authorities may not accept labelling pouch/overwrap as 'primary container' in lieu of the vial itself and therefore not accept as Annex VI compliant.	Ways to increase surface area on packaging but will not add much space and is technically not feasible. Would need to define minimum labelling for vial itself.
Large window through secondary packaging to allow for expiry updates	Unlikely	Could damage product more easily with large window	5	3	3	45	Choose another solution for control	Not assessed	Window would have to be large to allow for any updates and does not protect product adequately, risk of product being manipulated in other ways.
More frequent and/or smaller packaging campaigns	Possible	Could cause disruption of supplies and impact subjects/study	5	5	1	25	Choose another solution for control for larger quantities of patient packs		Eliminates the need for expiry updates and may be viable in some smaller IMP needs
Destruction of expired material in the field. Expiry update only on material in sponsor's possession.	Per study basis and availability of material	Could cause disruption of supplies and impact subjects/study. Early phase studies may have limited IMP stock with a risk for treatment interruption.	5	5	1	25	Choose another solution for control	Does not fully address stronger assurance of GMP-compliant label updating but may still have issues with size of primary container and other pack design elements making this unfeasible.	If applied, risk to not comply with continued IMP supply and subject/patient treatment.

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Risk Assessment Evaluation Criteria

Category (Value)	Severity (S): Patient Impact	Severity: Process Impact
Low (1)	Possibly patient inconvenience. Product functionality is intact. Cosmetic risks.	No
Medium (3)	Potential for modest discomfort or low safety risk issue. Drug functionality is affected. Failure is not expected. No medically significant impact on patient safety or health.	Re-process or re-work needed; process can be completed alternatively.
High (5)	Potential for injury, disability. Drug functionality is affected. Failure will directly or indirectly result in temporary or reversible injury or irreversible disability.	Failed batch, Out-of-stock, Regulatory impact

Category (Value)	Occurrence (O) Description
Low (1)	The failure is unlikely or will not occur under specified operating conditions.
Possible (3)	Failure will likely occur infrequently.
Frequent (5)	Failure will likely occur in significant magnitude.

Category (Value)	Detectability (D) Description
High/Likely (1)	Check/controls will almost certainly detect a failure mode.
Possible (3)	Controls may detect a failure. Failure is easy to identify and checked regularly.
Rare (5)	Controls probably will not detect failure. Failure is not easy to identify.

Risk Level Evaluation and Consequences

SOD Value	Risk Level	Evaluation and Consequences
SOD > 27	High	Risk is unacceptable and must be remediated. If additional control measures are implemented to remediate the risk, the SO and SOD values of the Risk Assessment must be reassessed.
15 ≤ SOD ≤ 27	Medium	Risk may be acceptable. If additional control measures are implemented to remediate the risk, the SO and SOD values of the Risk Assessment must be reassessed.
SOD < 15	Low	The identified Risk can be accepted; no further actions or measures are required.