18 February 2014
EMA/INS/GCP/100058/2012
Good Clinical Practice Inspectors Working Group (GCP IWG)

Overview of comments received on 'Reflection paper on the use of interactive response technologies (interactive voice/web response systems) in clinical trials' (EMA/INS/GCP/600788/2011)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	eClinical Forum
2	International Federation of Associations of Pharmaceutical Physicians (IFAPP)
3	Association of the European Self- Medication Industry (AESGP)
4	Perceptive Informatics, a business unit of PAREXEL
5	Novo Nordisk
6	Verdacom, Inc.
7	Geronimo Consultancy
8	Janssen Pharmaceutical Companies of Johnson & Johnson
9	GlaxoSmithKline R&D
10	The European CRO Federation (EUCROF)
11	Pharmaceutical Quality Group (PQG) of the Chartered Quality Institute (CQI)
12	Biomedical Data Management association (DMB)
13	Cenduit LLC
14	Celgene Europe Ltd
15	AstraZeneca
16	European Federation of Pharmaceutical Industries and Associations (EFPIA)

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	1) Will the EMA be working with ICH partners to develop a guideline that will more uniformly address the use of these computerized systems?	There is no proposal at the level of ICH at this time.
	2)We support the modification of Annex 13 to permit the absence of all expiry dating on IMPs, and rely on a risk-based approach to using these systems. This will bring the EMA's requirements more in line with other global requirements.	Noted. Annex 13 is not being modified at this time.
	3) Other regulatory authorities (e.g. US FDA and Japan PMDA) do not require expiry dating on IMPs that are dispensed for subject self administration. We ask that the EMA consider expanding this proposal for the omission of expiry dates to products dispensed to and self-administered by subjects. Since unused IMP must be returned to the clinical site at each visit, this self-policing will help ensure that only IMP that are of acceptable quality/stability and within their expiration date requirements will be available to subjects.	The paper presents the current consensus.
	4) There are other systems in use today that are not specifically identified as IV/IWRS applications but these systems keep track of randomisation/product shipment/expiry information. It would be helpful to more generically categorize these applications so that the principles required by this paper might apply to all computer systems that perform these functions.	The scope of the paper is to provide guidance on what National Competent Authorities expect from IRT systems and in particular their use for handling of the expiry date of the Investigational Medicinal Product. It is not intended to address all tracking systems.
	5) Does the EMA have specific recommendations as to the	No

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	information about these computerized systems that should be included in study protocols, or market applications? 6) This reflection paper stresses the importance of drug accountability when using IV/IWRS systems. Might it be useful to include a statement in the introduction that makes the point that drug accountability is an important component of drug management (see line 54) for automated systems to track? Also, will this paper include guidance on how information should be tracked in the IV/IWRS and/or the EDC system at the clinical site? For example, will this paper suggest that these systems need to be interoperable, and that any systems validation efforts needs to challenge algorithms/procedures that account for the IMP?	The importance of drug accountability is inherent in the legislation and is covered by GCP. The guide cannot be so prescriptive with all the different systems in use.
2	Well prepared guideline, addressing an important issue. IFAPP agrees with its contents and has no special comment to submit. The document provides a detailed and useful analysis on the overall aspects of quality in clinical trials. In IFAPP opinion however too much emphasis is given to sponsored clinical trials only, while more attention should be paid to Investigators' activated trials. Recent data suggest that up to 35% of clinical trails belong to the category of "Investigators' activated trials" and experience suggest that many of these trails are still – after almost 20 years of GCP implementation - of low and unacceptable quality, exposing patients to unnecessary risks. IFAPP recommends that some parts of this guideline are devoted to this category of trials, with clear recommendations to Ethics	All trials have a sponsor as per EU legislation.

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	Committees to supervise the overall organisation of these studies, and to approve them only when a clear indication of management structure and monitoring plan is provided.	
4	This is a conservative document which does not follow the thrust of the ISPE document that is referenced within the guidance. The ISPE document essentially advocated the expansion of the use of technology in removing use-by-date dates from labels. The ISPE document mentioned some of the problems that can occur with relabelling and some of these could apply when a pharmacist adds the use-by-date on the label. We would consider a risk based approach to each particular trial to be more appropriate. This risk based approach is being applied in other guidances e.g. EMA reflection paper on risk based quality management in clinical trials. The risk based approach for use-by date labels would depend on the particular medication/treatment and the chances of the subject not returning the medication. We note that it is an expectation that the subject returns all the trial materials.	The paper presents the current consensus.
4	The document mentions the situation in U.S and Japan that currently applies to use-by date labelling. Whilst it is clearly not appropriate to criticise other regulatory authorities, it would be good to see discussion of why the same approach is not being taken in the E.U. A common approach would seem to be more consistent with the philosophy of I.C.H. and the philosophy of harmonising procedures for sponsors so they can devote more resources to the development of new treatments.	The paper presents the current consensus.
4	The title does not reflect the content of the paper which is concentrated primarily on the use of such systems to handle use-by	The paper has been restructured taking this into account.

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	date labels. The title might lead the reader to expect many more topics to be addressed including, but not limited to, matters arising from the usual separation of the randomisation and dispensing steps where any pack of the appropriate treatment can be dispensed to any patient e.g. pooling of medication across studies, scrambling of kit lists to maintain the blind, what to do in case of supply failures etc.	
5	Please be consistent in using IVRS/IWRS in the document or even better to change to “IRT system” which is used in the title of this reflection paper	Accepted IRT will be used throughout.
6	From my understanding this document began as a way to justify removing the expiry dates from labels in the EU as put forward by ISPE. The document as titled here seems to have much larger scope. My concern is this - do other regulated technical systems used in EU clinical trials subject to detailed regulation and have similar documents listing vendor, sponsor, quality, sdlc requirements? Wouldn't it be sufficient for this doc to reference GCMP, GAMP, SOX and other relevant guidelines? We reviewed this draft several months ago and felt we were in compliance, but the idea that the sponsor/vendor relationship are being 'reflected on' seems troubling. Vendors know what the requirements are; any sponsor QA group would know the risks involved with using systems for inventory management and randomisation and take appropriate safeguards.. I would like to see this document limited to guidance about expiry date labelling or generalised to recommendations on managing all software development vendors involved in managing submission related data: electronic data collection, patient recruitment, inventory supply chain, patient reported outcome systems, etc.	The paper has been restructured to give more emphasis to IRT.

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7	The reflection paper title is Interactive Response Technologies, this is generally abbreviated as IRT; the abbreviation used in the paper is IVRS. This is an old abbreviation, not in line with the current standard (IRT) and the terminology used by the ISPE.	IRT to be used.
8	Overall, we found section 2.2 of the document to be confusing, particularly section 2.2.2 regarding P2 – P4 studies. It would be easier for the reader if the recommendations outlined in the document were structured under clear sections, e.g. Guidance to sponsor, Guidance to IVR/IWR Providers.	The paper has been restructured for clarification.
9	This recognition by EMA of the importance of IVRS/IWRS technology to the conduct of clinical trials is welcome. In particular, it is appreciated that there is acceptance of the fact that such systems might, in certain circumstances, be used to justify the removal of expiry dates from Investigational Medicinal Product (IMP) labels and thus overcome challenges with expiry date extensions in the field.	-
9	It is disappointing that the paper's perspective is that "There is currently no justification… for omission of labelling of use-by date … if the IMP is handed out to trial subjects for use at home" (lines 119-121). This is much more restrictive than in other countries, such as the US, and significantly limits the potential benefits that may be derived from such systems. The only reason given for this position is "Patients not returning kits and then utilising them past their expiry date" (line 125). Given the requirements for IMP accountability, it should be possible to address this scenario and it should not fundamentally be a reason for needing use-by dates on labels. We suggest that if a company was able to demonstrate a robust system for ensuring materials did not remain with trial subjects past their expiry date, then there could be a justification for omitting the use-	The paper presents the current consensus.

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	by date from the labels of IMPs taken home by subjects.	
9	Given the perspective requiring use-by date labelling of IMPs that are to be taken home, it would be beneficial if EU regulations could be updated to facilitate the addition of this information at the point of dispensing. Currently, the labelling of IMPs is governed by Directive 2001/20/EC in the majority of cases and requires Manufacturing Authorisation and QP certification, preventing this being undertaken by a pharmacist at an investigator site. The exceptions of Directive 2005/28/EC, Article 9, Paragraph 2, are limited to reconstitution and 'non commercial' institution-led trials.	The paper presents the current consensus.
9	The document reads as though it was originally intended to address the specific circumstances where the removal of expiry dates could be justified (2.2 with 2.1 providing a legal preamble to this) and that a number of more general aspects, such as specification, standards, validation, etc. were added on subsequently (2.3). It would be beneficial to restructure the document to address general requirements first.	The paper has been restructured.
9	The document is mainly written with the assumption that the IVRS/IWRS service is provided by a party other than the Sponsor. This is not always the case; IRSs may be managed by the Sponsor directly as an in-house activity. The document would benefit from revision to better reflect this possibility.	The paper has been restructured. This has been made clearer.
9	The document also considers IR systems as 'stand alone' and does not address the fact that they may be integrated with other systems, from which data regarding expiry dates may be sourced. Greater integration of IR technology within broader clinical supply chain and data management systems is likely to be seen in future. This document should be written to recognise such trends and to ensure	The paper has been restructured.

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	that future advances are not restrained in any way.	
9	There are specific challenges associated with expiry date extensions through systems interfaces, especially where there are different ranges of containers. The document does not clearly cover such scenarios currently.	Not clear what suggestion is.
9	The document mentions the delivery of documents or printouts with use-by date information in a number of places. Where blinded clinical supplies are concerned, it is important that information in these does not result in unblinding, e.g. as a consequence of different treatment arms having different technical shelf-lives. It is suggested that this is stated explicitly within the document.	This has been considered in the revised version of the paper.
9	Also relating to documents and printouts, the possibility of clinic staff having on-line access to data within a controlled system should be allowed for, rather than specifically requiring paper documents.	This has been considered in the revised version of the paper.
9	Section 2.3.1.1 should clearly specify the accountability of the Sponsor for URS, UAT and formal acceptance of the system for use.	This has been considered in the revised version of the paper.
9	Further detail within Section 2.3.3 would be useful to clarify what the regulatory expectations are for items such as emergency unblinding, disaster recovery, currency of data, etc.	This has been considered in the revised version of the paper.
9	In addition to the specifics relating to updates to the system in Section 2.3.5, it should be clear that the sponsor needs to be able to demonstrate a full chain of control regarding expiry date information which goes beyond the IRT itself, i.e., there needs to be control over the feed-ins to the system.	This has been considered in the revised version of the paper.
9	The Annex I QP declaration appears to be added bureaucracy with unclear value. It is agreed that the certifying QP should ensure that if an IVRS/IWRS is used to control expiry dates then it is fit for purpose and there is traceability back to appropriate audits.	This has been considered in the revised version of the paper.

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	However, the audit/validation traceability could be addressed through an internal control and the needs of those downstream covered by the QP's certification of the batch. To create and maintain a form in every Product Specification File and Trial Master File (ref. line 135) is unnecessary bureaucracy. Furthermore, what is the objective of listing assembly and distribution sites and including them within this? Should the declaration be retained, then the focus should be on the IRS itself, not specific locations within the supply chain.	
9	Should the requirement for the Annex 1 QP declaration be retained, guidance notes on its completion will be required. For example, what is meant by the 'date of last audit (completion)'? Is this the last day of fieldwork; date of report issue; date of Corrective Action Plan acceptance; date of closure of all actions arising from the audit?	This has been considered in the revised version of the paper.
	In addition to having confidence in the IVRS/IWRS itself, the QP should have confidence that appropriate control processes (procedures) are in place regarding its configuration, use and maintenance.	This has been considered in the revised version of the paper.
10	EUCROF is very much in favour of the document you provided, especially regarding the attempt to clarify expiry date administration and providing requirements when using IxRS vendors. However, we do feel that the text is not written in a uniform style and uniform level of clarity. Some parts of the document provide full text blocks, others are limited to bullet points only. Some abbreviations are not explained, references are missing and some sentences are not correct. Although we understand that this is a draft text only and does not have to be 100% perfect, we do think that appropriate quality control should be applied before posting a document into the	This has been considered in the revised version of the paper.

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	public domain in order to ease the review process.	
10	Section 26 of Annex 13 states "The following information should be included on labels, unless its absence can be justified, e.g. use of a centralised electronic randomisation system:" It would be very welcome to learn about clear expectations as to which of the items a – k of section 26 of Annex 13 can be omitted on the label if they are fully represented and administered by the use of a centralised electronic interactive voice/web system.	This has been considered in the revised version of the paper.
11	This recognition by EMA of the importance of IVRS/IWRS technology to the conduct of clinical trials is welcome. In particular, it is appreciated that there is acceptance of the fact that such systems might, in certain circumstances, be used to justify the removal of expiry dates from Investigational Medicinal Product (IMP) labels and thus overcome challenges with expiry date extensions in the field. IVR and IWR technology is likely to become more integrated into clinical supply chain and data management systems in future and there is concern that this document is written in a manner that may constrain technological advances. This document should be written with a focus on the fundamentals, e.g. the need for relevant persons to have ready access to confirmation of the expiration date, without stipulating how this must be achieved, e.g. the delivery of documents or printouts. That way there is flexibility to allow for direct reference to and recording within the system itself without the need for additional paper records.	This has been considered in the revised version of the paper.
14	First of all, we would like to applaud the agency's consideration of using Interactive Response Technology (IRT) to manage expiry date which should lead to the removal of expiry dates from IMP labels as	This has been considered in the revised version of the paper.

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	currently practiced in the United States and Canada. Validated IRS has proven to be very useful and effective in facilitation of this function. Furthermore, the ability to avoid logistical issues related to re-labelling of the use-by-date permits resources to be better utilised; as well as, serve as a central source of control. It is noted that a uniform approach to processes and validation of such systems in regards to this function is vital and warranted. It is also recognised that a central movement to an electronic record system has many advantages as well. Validated IRS' can be utilised to efficiently and effectively manage the expiration dating in a manner to mitigate patient safety risk justifying the absence of expiry dating on labels.	
15	Within Annex 1 of the reflection paper, there is a requirement for the QP to declare compliance with GCP and GMP requirements. However, EudraLex Annex 13 and Directive 2001/20/EG does not state compliance with GCP to be a QP responsibility, but a sponsor responsibility. We suggest splitting Annex 1 into two annexes: Annex 1 to be signed by the QP providing assurance of GMP compliance; Annex 2 to be signed by the sponsor providing assurance of GCP compliance.	This has been considered in the revised version of the paper.
	The reflection paper is very clear in defining the conditions required to support removal of expiry dates from labels. However, the conditions defined are limiting and do not reflect our recent experiences in which regulatory authorities have accepted expiry date removal from labels for studies in which patients took the study medications home. We would like to ensure that the reflection paper	This has been considered in the revised version of the paper.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	does not restrict such approaches in future. Provided patients have received assurance that the study medication is within its expiry date, we believe they could take home medication without the expiry date on the label. This assurance could be either via the investigator or through a print-out from the IRT system. This should be sufficient for patient assurance and carries less risk than that associated with the pharmacist adding the expiry date onto the label. With proper management of supplies, returns and accountability we do not believe that there is a risk of patients retaining medication beyond its expiry date and therefore taking it in these circumstances. The AstraZeneca IRT system has a fully validated clinical drug accountability module that records and tracks all drug returns, so this would ensure there is no risk of patients retaining medication beyond its expiry date.	
16	Robust IRT (interactive response technology) systems are very effective in managing expiry dating. These systems are fully validated and in compliance with GAMP. As a result, the use of the system is more robust than a manual paper or stickering systems that are subject to human error and longer lead teams to make adjustments to expiry data. It seems in general that the reflection paper deviates from the guidance provided in the Annex 13, which is open for the possibility of omitting expiry dates from labels for take-home study medication if its absence can be justified by use of a centralised electronic randomisation system. The conditions defined in the reflection paper are limiting and do not reflect the industry experiences with regulatory authorities regarding the removal of the expiry date from the label including for studies in which the patients	This has been considered in the revised version of the paper.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	took the study medications home. It is recommended that the reflection paper be updated to include the use of IRT as the source of expiry dating management in both in patient and at home studies. This recommendation is supported by the following data, which was submitted by several members of EFPIA: • An internal review of our data has shown that >95% of the cases where expired material has been given to a patient occurred in non-IVRS studies where manual systems were used, mainly expiry dating on the label. In the <5% where the expired material was given to a patient despite an IVRS system, it was a training error at the site level and would have happened regardless of a system (manual or automated). **In summary, the data denotes that the use of a qualified, validated IVRS system is superior to a manual system for ensuring patients do not receive expired drug.** • Use of visual means via the label to maintain the expiry dating of CT Material inherently has risks. Key risks include updating of the date requires sites to be compliant in administering the procedure to update the expiry dating as often as every 3-6 months. Sites can take weeks to a few months to update all packages at the site and complete reconciliation/accountability process for verification is completed appropriately. Additionally, if the expiry dating is on the inner container, the primary tamper seal must be broken for each update and the material removed to be updated followed by re-tamper sealing. This type of operation is usually performed by a qualified CMO (contract manufacturer vs. a clinical site that does not have the appropriate facilities, processes and procedures to ensure the kits are repacked appropriately, no misplacement occurs and that the label is still legible and appropriate in compliance with all applicable laws and regulations. This further underscores the reason why we should avoid this process. This was further supported in the White Paper by the	

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	ISPE/PDA Expiry Date Task Force reg. Use of IVRS to manage IMP retest dates (2009), the use of an IVRS for managing expiry dates presents an overall lower risk compared to manual re-labelling of IMP. **In conclusion, use of visual means is associated with risks. Rather a robust, validated, GMP compliant IRT system is effective and should be used in place of a visual dating on the label.** Other ICH Regions rely on internal procedures and controls to control the elimination of the date on the drug supplies. The reflection paper is a significant departure from other regions and would continue to make additional distinctions with regards to clinical research in the EU versus rest of world. It is recommended to align the reflection paper with the ICH regions, which if implemented the EU would be a more desirable place to conduct studies in. This would further reinforce and support other initiatives to attract more research in the EU. (Reference Article – Applied Clinical Trials, November 10, 2011 – indicating that Clinical Trials in EU are down by 17%) http://blog.appliedclinicaltrialsonline.com/2011/11/10/europes-ct-drain-gathers-pace/	
16	The reflection paper is inconsistent in the use of IVRS, IWRS. We would suggest the use of IRT (Interactive Response Technology), which is inclusive of both IVRS and IWRS and would create consistency for the intended audience. Additionally, it is recommended that the language be consistent to use either expiry date (recommended) or use by date. The current reflection paper uses a mix of these terms, which can be confusing for the intended audience.	This has been considered in the revised version of the paper.
16	Within the reflection there are several references to the role of the QP with regard to expiry dating and IRT. Moreover, the references cover topics that span both GCP and GMP. EudraLex Annex 13 and Directive 2001/20/EG does not state compliance with GCP to be a QP	This has been considered in the revised version of the paper.

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	responsibility, but a sponsor responsibility. It is recommended that the reflection paper be updated to remove the references to the QP obligations as this is covered in regulations and directives. However, if it is left within the document, the paper must be updated to ensure the QP references are only with regard to GMP matters and are in accordance with regulations, laws and directives. Finally, sufficient guidance and standards already exist for the traditional uses of IRT as well as other GCP and GMP computer systems that are intrinsic to patient safety and data integrity. Thus, it is recommended that the reflection paper not cover these points and narrow the scope to the specific points of expiry dating, including eliminating specific references to individual validation or quality steps unless they differ from recommendations in GAMP & other existing guidance. The existing reference to GAMP is sufficient. Highlighting only certain validation and quality steps is unnecessary and may be confusing since other critical steps are not equally referenced.	
16	IRT enables the sponsor to leverage the system capabilities to effectively manage each study medication used in clinical trials. This flexibility is essential and includes: • Use of electronic means to maintain the expiry data for CT Material is very effective if the system is robust with flexibility to program in various stability algorithms based on the stability program for the product, the system is validated and GMP compliant. Additional effort to standardise the IVRS specifications and invest in the capability industry wide is essential. • All relevant packs can be updated instantly without the logistic challenges derived from multiple re-labelling operations at multiple locations, including clinical sites. It reduces the risk of manual errors and improves the documentation of the expiry updates. It also opens for the possibility of better control of who is authorised to perform expiry updates. Designed to limit dispensing of IMP to specific periods i.e. it gives a	This has been considered in the revised version of the paper.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	much better control over IMP which is due to expire.	
16	Visit windows at the end of the expiry dating period must be robustly managed using procedures and a tracking program to ensure the patients are moved to appropriately dated material prior to the time of expiry of the current material. The IVRS system takes into account the visit window and only dispenses material with suitable dating.	This has been considered in the revised version of the paper.
16	Should removal of the retest date from the clinical trial material label be deemed unacceptable from a local regulatory perspective or similar, we would propose to place use the target expiration date on the clinical trial material label as supported by the ongoing stability program (described in the Retest Ext. Proposal within IMPD) and use the IVRS to manage the use of material (i.e. quarantine and remove material from sites that is trending out of specification).	This has been considered in the revised version of the paper.
16	Please clarify the following within the reflection paper: • Distinction between Sponsor and Service Provider responsibilities Differentiate in expectations between the vendor's core IRT system and a sponsor's protocol specific configuration. The reflection paper refers to 'system' without such differentiation, yet sponsor and vendor roles may differ considerably.	This has been considered in the revised version of the paper.

2. Specific comments on text

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Title	12	The title of this paper is not coherent with its content : its content is mainly focussed on "expiry dates management" whereas in general IVRS applications encompass a lot of goals which are not detailed here, especially centralised randomisation. Either the title should be changed or the content adjusted to cover all aspects of IRT systems (i.e. process and tasks to be done by sponsor/CRO regarding randomisation list generation, validation and implementation)	Partly accepted. The paper has been restructured to give a more generic emphasis on the use of IRT.
Across the document	5	Please use one term – expiry date or use-by-date Currently there is a mix of terms.	Accepted. The Annex 13 definition uses all variants; the reflection paper will use expiry date.
4-6	10	The title of the document is not fully disclosing what this document is actually covering. We suggest that the title includes a reference to the IMP expiry date management or re-labelling, since this is one of the most prominent topics that this document is addressing. Proposed change (if any): The title of the paper should read: 'Reflection paper on the Use of Interactive Response Technologies (IV/WRS) in Clinical Trials and Management of IMP Expiry Date '	Partly accepted. The paper has been restructured to give a more generic emphasis on the use of IRT.
32-34	14	Comment: Suggestion to integrate commonly-used terms, see below.	Accepted. Interactive Response Technology (IRT) has been used throughout.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Over the last 15 years there has been an increasing utilisation of telephone based interactive voice response systems (IVRS) utilising telephones. Such systems have been developed further into internet based interactive web based response systems (IWRS) utilising the internet.	
33-34	10	Comment: With “interactive web based systems (IWRS)” the abbreviation is used here for the first time, but IWRS is not explained properly (“interactive web based systems”).The title of the document refers correctly to “interactive web response systems”. Proposed change (if any): Change the text to: “interactive web response systems (IWRS)”	Accepted. Interactive Response Technology has been used throughout.
34	16	…developed initially to optimize drug …. Please change to …developed initially to randomise subjects…..	Not accepted. Terms are semantics therefore have used original terms.
Line 34-35	4	Comment: We believe IVRS were initially developed to handle randomisation methods as much as optimising drug availability. Code breaking was a relatively early piece of additional functionality Proposed change (if any): These systems were developed initially to handle centralised randomisation methods, medication dispensing and secure emergency code-breaking in multicentre trials.	Not accepted. Terms are semantics therefore have used original terms.

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34	5	…developed initially to optimize drug …. Please change to …developed initially to randomise subjects…..	Not accepted. Terms are semantics therefore have used original terms.
Line 35,55	4	Comment: unblinding is a little vague Proposed change (if any): ”emergency unblinding” as used on line 172 is preferable. Or “emergency code-breaking” is perhaps a more widely used term.	Not accepted. Unblinding is universally accepted and is used in Annex 13 and ICH GCP.
Lines 35, 54-55	4	Comment: It would be more correct to say that IVRS has expanded into other areas such as dose titration, collecting patient reported outcomes and expiry date updating. Proposed change (if any):	Not accepted. Introduction gives a flavour for the areas now encompassed by IRT, not necessarily all of them.
40	10	Proposed change (if any): “… systems and in particular their use in expiry date updating.”	Accepted.
Line 43	16	Comment: For consistency throughout the document please use “Investigational Medicinal Product” (IMP) instead of “study medication” Proposed change (if any): “… to omit the use-by date on ~~study medication~~ IMP in case of IVRS/IWRS use.”	Accepted.
48-49	15	AstraZeneca have built an IVRS / IWRS system consisting of a series of pre-validated modules. A	Not accepted. This is also in the ISPE white paper. Although training in IRT

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		comprehensive set of training guides has been created and used to ensure that all relevant staff are fully trained, therefore removing the risk of a sponsor having insufficient knowledge to use the IVRS/IWRS appropriately.	has been seen on inspection, nevertheless issues have resulted in expired medication being taken.
48-50	16	We would suggest removing lines 48-50 and replacing with the quote from the White Paper by the ISPE/PDA Expiry Date Task Force on page 8, 3rd paragraph that states "with appropriate controls in place, the use of an IVR/IWR system for managing expiry/retest dates presents an overall lower risk," Training guides can and have been prepared for IVRS/IWRS systems removing the risk of insufficient knowledge Recommend reviewing the US processes for managing expiry dates.	Not accepted. Inspectors have seen expired medication being used by trial subjects when the expiry date was under the control of an IRT.
51-53	15	AstraZeneca submit a letter of intent with the regulatory submissions that documents in detail the manner in which the IVRS/IWRS technology controls the expiry date of medication.	Accepted. Change text to "is usually……."
51-53	16	The current form (EuraCT) currently only refers to when IVRS is used in the randomisation scheme and specifically when this task is outsourced. The form could be modified to collect additional information. Additionally some companies submit a letter of intent with the regulatory submission that documents in detail the manner in which the IVRS/IWRS technology controls the expiry date.	Partly accepted. The CTS form is not open for revision at the present time.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
51-53	15	This refers to the EuraCT form, however the form currently only refers to where IVRS is used in randomisation schemes and specifically where this task is outsourced. It does not contain any sections on where IVRS is used generally. This, however, may be an option to highlight to agencies where it is used, and also whether supporting information for its use is contained in the CTA dossier.	Partly accepted. The CTS form is not open for revision at the present time.
Lines 54-57	16	In terms of utilisation of IVRS for dose titration - IVRS is sometimes the only source to hold the unblinding data/values that are used to determine the dose for the subject. In these types of protocol designs, IVRS is the source to determine appropriate dose and there is no "second review" of the data because all other parties are blinded. **Proposed change (if any):** To mitigate this potential risk, Sponsors can have a separate unblinding group creating the dosing algorithm independently from the IVRS and periodically run the actual study data against their algorithm to ensure accuracy.	Not accepted. Comment not understood in relation to the text.
58	8	Comment: It is stated that “The potential for the revision of Annex 13, when it is next reviewed is also considered. It is not clear however where in the document this has been captured.	Accepted. Determined as outside of the scope of the paper.
58	10	Comment: As Annex 13 is an annex to the GMP Guide (EudraLex Volume 4), Annex 13 should be referenced as such.	Accepted. Determined as outside of the scope of the paper.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): "Annex 13, Investigational Medicinal Products, of Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use"	
58	9	States that the potential for the revision of Annex 13 "is also considered", but there does not appear to be any further consideration of this later in the document.	Accepted. Determined as outside of the scope of the paper.
62-63	16	Comment: The preamble on line 62-63 (considering the need for expiry dating on labels): it would be a real positive for Industry to eliminate the pain point of an inconsistency reference requiring the re-eval date on investigational labels. It would be beneficial for Industry to have one harmonized global approach of the re-eval date not being required on the label when dispensed to patients, and the Sponsor incorporating controls into their processes and IVRS/IWRS systems	Not accepted. No response. Conflicts with current position of the group.
68		It would be useful to make available for reference, e.g., via EMA website, the Member States where national law overrules Annex 13.	Partly accepted. The paper is being restricted to give the emphasis to IRT.
Lines 69-71	7	Comment: the reference to the German Ordinance makes the document restricted in value over time Proposed change (if any): delete (line 69) for example … … 9line 71) conditions	Partly accepted. The paper is being restricted to give the emphasis to IRT.
72 - 117	5	With the system requirements and validation in place according to this reflection paper we see no need for	Not accepted. The paper presents the current consensus.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		not allowing removal of expiry date on labels for all trial phase regardless where the trial is being conducted. As mentioned in section 2.1 this has been and is the current practice in the US and in Japan and in Germany under certain circumstances. The IVRS/IWRS maintain the control of expiry date including processes around extending the expiry date, the investigator and/or site staff responsible for dispensing IMP can and will be notified of the expiry date of the allocated IMP, and it will be easy also to include this information to the subject at time of dispensing. Section 2.2 should be changed to allow removal of expiry date on labels justified by using an IVRS/IWRS regardless where the subject is treated by dividing the section into home treatment and Hospital/Clinic treatment because even in clinical trials phase 2, 3, and 4 subjects could be treated only at hospitals/clinics.	
72-86	16	Implementing IVRS, across all study phases, reduces the opportunity for human error and improves investigational product management (e.g., expiry, assignment, etc.). With the system requirements and validation in place according to this reflection paper we see no need for not allowing removal of expiry date on labels for all trial phases. As mentioned in section 2.1 this has been and is the current practice in the US and	Not accepted. The paper presents the current consensus.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		in Japan and in Germany under certain circumstances. The IVRS/IWRS system maintains the control of expiry date including processes around extending the expiry date, the investigator and/or site staff responsible for dispensing IMP can and will be notified of the expiry date of the allocated IMP, and it will be easy also to include this information to the subject at time of dispensing. Additionally, Section 2.2 should be changed to allow removal of expiry date on labels justified by using an IVRS/IWRS regardless where the subject is treated. The IT systems (IVRS/IWRS) need to be built and validated accordingly. Comment: For the example quoted, i.e. a Phase I unit and on-site dosing only, it would seem to be redundant to utilize IVRS as several of the pre-requisites could potentially be designed / adapted to put a manual system in place to allow the site pharmacist to have enough control to manage the supplies without a use by date on the label. Please adjust the header type to be the same header type	
72 and 118	5	Please adjust the header type to be the same header type	Not accepted. Header line 72 and line 118 match.
73	12	We do not think that the difference between Phase I and II/III regarding TU delivery justifies acceptance of different processes	Not accepted. Phase I in a very well controlled setting.
73	13	Comment: Although Phase I has been considered	Not accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		separately from Phases II – IV the reflection or recommendations appear to be the same for all phases. Proposed change (if any): If the recommendations are to be the same then just include them all together in one section	Phase I in more well controlled and therefore the recommendations are slightly different.
73-86	8	Comment: Section 2.2.1 does not address where the final responsibility resides. We propose that the standard for a Phase I study should not differ from Phase II – IV. Proposed change: Add text similar to Lines 117 - "The final responsibility resides with the investigator".	Accepted.
78-79	1	Comment: Since other regulatory authorities permit the dispensing of products to subjects for self-administration without a use-by-date, it would be useful to try to globally standardize this issue. Proposed change (if any): remove restrictions with regard to products that are to be self-dispensed by the subject. There are adequate protections within the GCPs , such as the need for subjects/site staff to account for/return unused IMP at each visit, to prevent the subject from using expired product. These protections make the restriction to products administered by study personnel unnecessary.	Not accepted. The paper presents the current consensus.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
78-86	14	Comment: It is not clear if all three conditions in 2.2.1 need to be true in order for it to be justified. Proposed change (if any): … Under the prerequisites that the clinical setting in the phase I Unit is highly controlled, the investigator and the trial personnel are well-trained and familiar with the study protocol, the omission of the labelling of the use-by date could be justified under one or more of the following conditions…	Accepted.
79	3	Comment: It is common for IMP to be taken home by patients between site visits during clinical trials. Proposed change: The IMP is administered by study personnel in the Phase I Unit and the subjects do not take IMP out of the clinic for dosing between visits.	Not accepted. It is not usual that in Phase I studies medication is taken home.
Lines 80 - 86	16	Comment: A clear definition of "use-by date" , “do not dispense” and "expiry date" should be included in the document ….for each allocated kit… Please change to …. for allocated kits per batch…. As multiple kits can be allocated from the same batch	Accepted. Annex 13 uses all variants; this paper uses the term expiry date.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		with the same expiry date at the same dispensing visit. The report requirement is not relevant to Phase I Trials only.	
Lines 80-84	7	Comment: use all type of release documentation not only a limited number of options Proposed change (if any): add Certificate of Compliance or add “or equivalent’	Not accepted. Examples are only incuded and are not limited to.
80-84	14	Comment: Is there a method to make this a cleaner process for when expiry is updated? Example: General form goes with the shipment or is available online for review? Would electronic web reports and version be acceptable?	Not accepted. The paper states A copy, but not necessarily a paper copy. This is not specified.
80-86 and 96-103	9	The current level of detail is potentially restrictive to full use of electronic technologies. Personnel responsible for dispensing should have access to controlled, human readable, expiry date information at the time of dispensing and should confirm this within study records. However, this could conceivably be achieved through the system itself without the need for paper certificates and printouts. It is suggested that the wording is updated to stipulate the fundamental requirement and remove the detail regarding certificates and printouts.	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
82	10	Comment: As Phase I unit is used in singular, it should be “Principal Investigator” and NOT “Principal Investigators”. To have more than one PI at a Phase I unit is the exception. Proposed change (if any): See comment.	Accepted.
84	10	Comment: Specify, like in line 103, that the documentation should be filed with the investigator site file. Proposed change (if any): See comment.	Accepted.
85-86	14	Comment: What frequency is the agency requesting for this print out? Is the agency requiring delivery of the document prior to dispensation? Would an electronic report for end users be sufficient?	Accepted.
85	3	Comment: since the IVRS/IWRS is a fully validated and GMP compliant electronic information system, the additional requirement of a 'printout' assignment report is unnecessary for risk mitigation. Proposed change: IVRS/IWRS shall deliver a printout (‘assignment report’) contain information for each allocated kit with information on trial subject, individual kit identifier and use-by date.	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
85	1	Comment: what does “deliver a printout” mean? May the printout be electronic or must it be a paper printout? Proposed change (if any): include clarification that printout can be electronic or paper	Accepted.
85	5	….for each allocated kit… Please change to …. for allocated kits per batch…. As multiple kits can be allocated from the same batch with the same expiry date at the same dispensing visit.	Not accepted. The paper means per patient packet not on a batch level.
85 - 86	13	Comment: Electronic ‘assignment report’ should also be suitable rather than just a hardcopy printout Proposed change (if any): Allow both printout or Email / other electronic assignment reports to be produced. This also applies to lines 96 - 97	Accepted.
85-86	8	Comment: Unlike Section 2.2.2 (Conduct of Phase II to Phase IV clinical trials), Section 2.2.1 (Conduct of Phase I clinical trials in Phase I Units) does not address disposition/retention of the printed assignment report. We propose that the standard for a Phase I study should not differ from Phase II - IV.	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change: Add text similar to Lines 102/103 - "The printed assignment report should be checked, dated, and signed by the investigator or delegated person administering the IMP and filed with the investigator site file".	
88-125	4	Comment: This section requires very careful reading. We suggest it would be clearer to re-organise and use sub-headings to differentiate the situations where medication is given to the patient for use at home and the situation where the medication is administered by dedicated staff at the facility. Proposed change (if any):	Accepted.
88-125	4	Comment: The situation regarding the dispensing of multiple packs to last for a scheduled duration should be discussed. For instance if 4 packs each containing one weeks supply of medication are dispensed for a 4 week period, under what circumstances is it permitted to have some packs with earlier expiry than the full 4 week period? Proposed change (if any):	Not accepted. Outside the scope of this paper.
90	1	Comment: same comment as for line 78-79. This restriction seems unnecessary, given current controls and best practice for IMP to be accounted for each subject visit.	Not accepted. The paper presents the current consensus.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Delete restriction related to IMP that will be self-administered by the subject.	
90-93	16	It should also be possible to use IVRS/IWRS and omit the use-by date in an outpatient setting where patients take their IMP home. A common practice is that patients do take home IMP, but should deliver back empty packs and left over IMP to the investigator at next visit and therefore no additional IMP will be retained by the patient. This approach should be acceptable provided that IVRS/IWRS is designed and validated to ensure that when allocating IMP to the patient, this IMP is not expired and has sufficient shelf life left to cover the period until next visit. Proposed change (if any): Please consider adding the possibility of using IVRS in the above stated case and that IMP is administered by dedicated trial staff, who is qualified in that Member State to perform such duties.	Not accepted. The paper presents the current consensus.
90-91	3	Comment: It is common for IMP to be taken home by patients between site visits during clinical trials. Proposed change: IMP is administered by dedicated trial staff, who is qualified in that Member State to perform such duties, and no additional IMP is retained by the patient.	Not accepted. The paper presents the current consensus.
Lines 94-	4	Comment: The most common consideration in	Not accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
101		determining an adequate buffer is the use of permitted visit windows to allow the investigator and patient more flexibility. For example the visit scheduled might be 4 weekly but an allowable window of ±3 days is permitted to allow for early and late dispensing visits. We suggest it would be useful to include this term. Proposed change (if any): append to sentence that ends on line 95 “including allowance for permitted windows to cover flexible scheduling”.	This is considered already in the paper.
Line 94-95	16	Comment: This may be interpreted as if the authorities expect assignment of individual, limited shelf life per pack at the time of allocation and handout to the patient. This would not be feasible, and is anyway not the intention. Proposed change (if any): It should be specified that there is no requirement for limiting the already approved shelf life for the batch on individual IMP packs to assure unambiguity.	Accepted.
94/97	9	Some trials may include open-label elements and where open-label supplies are made, the allocation may be of a batch/lot number rather than an individual kit identifier.	Not accepted. A batch in not allocated but some quantity. Out of the scope of this paper.
94	10	Comment: “a suitable expiry to cover the period between visits” is not sufficient to guarantee patient safety.	Not accepted. This has been explained.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Adapt to the description of the timeframe in line 110-112: “IMP kits per visit with a use-by-date valid beyond the planned administration with adequate additional buffer in case delays as defined in the protocol and/or IMP handling procedures”.	
Line 96-97	7	Comment: add the time of printing (at dispensing or assignment) to avoid manipulation in time Proposed change (if any): (line 97 end of sentence)….at the moment of dispensing or assigning.	Accepted.
96	15	The AstraZeneca IRT system does not currently provide a printout with the expiry date of the kit and this facility has to be built in to the system as a bespoke element. This section of the paper implies it is essential which is contrary to AstraZeneca current usage.	Partly accepted. Electronic records are acceptable to document this fact.
96	16	Comment: since the IVRS/IWRS is a fully validated and GMP compliant electronic information system, the additional requirement of a 'printout' assignment report is not necessary for risk mitigation. Proposed change: IVRS/IWRS shall for each allocated kit include information on trial subject, individual kit identifier and use-by date. The requirement to have a printed report at the site adds a logistical as well as a procedural burden and also does not sit well with the IVRS / IWRS concept, i.e. an IT process requiring a	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		paper-based control.	
96	3	Comment: since the IVRS/IWRS is a fully validated and GMP compliant electronic information system, the additional requirement of a 'printout' assignment report is not necessary for risk mitigation Proposed change: IVRS/IWRS shall deliver a printout ('assignment report') for each allocated kit with include information on trial subject, individual kit identifier and use-by date.	Accepted.
96	14	Comment: Clarify delivery of a printout "assignment report" throughout - could this be via email/fax or online? Would a dispensing report for site staff to confirm use by date and additional data be sufficient?	Accepted.
96-99	4	Comment: The assignment report should contain the expiry time as 00:00:00 and 23:59:59 are different and sponsors adopt different conventions to deal with multiple time zones.	Not accepted. Time down to this level is not discussed in the paper.
96	1	Comment: what does "deliver a printout" mean? May the printout be electronic or must it be a paper printout? Proposed change (if any): include clarification that printout can be electronic or paper.	Accepted. See above. The paper includes the possibility for this to be paper or electronic.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
98-99	14	Comment: Would the agency provide their definition of what they assume is adequate additional days on the expiry?	Not accepted. Examples are given in the paper.
102-103 107-108 110-112	14	Comment: Is there any requirement or guideline regarding confirmation of the signatures on the assignment reports required by sponsors? Proposed change: Assignment confirmations must be made available to site personnel in an electronic or paper form for confirmation of the IMP and expiration date. Movement away from paper based records. IRT systems could allow this by stating the expiration date of the medication assigned for dispensation and also provide information in and email, fax or web report.	Accepted. As per page 33 comments.
Lines 102-103	16	Comment: Since the IVRS/IWRS is a fully validated and GMP compliant electronic information system, the additional requirement of a 'printout' assignment report is not necessary for risk mitigation. Proposed change: omit "~~The printed assignment report should be checked, dated, and signed by the investigator, or delegated person administering the IMP and filed with the investigator site file~~"	Accepted. See page 33 response.
102	3	Comment: since the IVRS/IWRS is a fully validated and GMP compliant electronic information system, the	Accepted. See page 33 response.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		additional requirement of a 'printout' assignment report is not necessary for risk mitigation. Proposed change: omit "The printed assignment report should be checked, dated, and signed by the investigator, or delegated person administering the IMP and filed with the investigator site file".	
102	15	The requirement for the investigator to check, date and sign the printed assignment report would have to be agreed and then built into the randomisation and dispensation report.	Partly accepted. See answer page 32.
Line 102-103	7	Comment: IRT is used to support the operations and work as a CFR 21 part 11 compliant system. Hence there is no need to sign and keep a paper trail when this can be done by electronic signature. Proposed change (if any): (end line 103) ….. either via hardcopy or electronic signature.	Accepted. See page 33 response.
102-3	4	Comment: These lines request the printed assignment report is checked, signed & dated but this seems unnecessary in the modern world. It should be possible to use an electronic signature to approve a declaration statement about the checking rather than retaining paper records which may get lost or mis-filed by the site.	Accepted. See page 33 response.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Providing a mechanism either within the IVR (Pin Number) or IWB (User name and password) with suitable declaration statements should be enough to satisfy this.	
102	9	"The printed assignment report should be checked, dated and signed by the investigator... "should be updated to "The assignment report should be checked, dated, and signed by the investigator.." These changes in wording will permit the work to be performed electronically.	Accepted. See page 33 response.
102	10	Comment: In the section on Phase I, the term "principal investigator" is used, whereas here "investigator" is used. Terminology should be consistent in order not to confuse the reader. According to the definition (2001/20/EC, Article 2f), an investigator may be called principal investigator, if he/she is leading a team of individuals, i.e. these terms are synonyms and should be used consistently. Proposed change (if any): Replace "investigator" by "principal investigator".	Accepted.
102	10	Comment: It should be specified more explicitly against which other document or information the investigator should check the printout. If the check refers to control whether the expiry date has already or will be shortly be passed then it should be said here. If the check should address other items, they	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		should be listed. Proposed change (if any): Give more explicit guidance.	
104	10	Comment: "For the pharmacist to re-label …" In this sentence "or other person legally authorized" is missing. Proposed change (if any): Change sentence: "For the pharmacist or other person legally authorized to re-label …"	Accepted.
104-116	5	The section should only remain if a pharmacist is involved in dispensing and if expiry date on labels can not be removed. The check should be, that medication will not expiry before the next scheduled visit.	Partly accepted. Addressed by adding a subheading.
Lines 104-116	16	Comment: Since the IVRS/IWRS is a fully validated and GMP compliant electronic information system, and is considered superior to a manual system for ensuring patients do not receive expired drug, there is no reason to include expiry dating on the label. Given this, there is no need to define parameters under which a pharmacist can re-label IMP. Proposed change: omit lines 104-116. ~~For the pharmacist to re-label for its own establishment in accordance with article 9 paragraph 2 of directive 2005/28/EC: A pharmacist or other person legally authorised may manually add the use-by date on the label with a placeholder for this information when all the following conditions are met:~~	Not accepted. The paper presents the current consensus.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		~~The pharmacist has access to IVRS/IWRS and the system delivers a printout ('assignment report') 107 for each allocated kit with information on trial subject, individual kit identifier and use-by date~~ ~~The kit allocation information should be stored at the trial file in the pharmacy~~ ~~The pharmacist should ensure that the use-by date of the study medication is valid beyond the 110 planned administration with adequate additional buffer in case of delays as defined in the protocol and/or IMP handling procedures~~ ~~The labeling process should be described in a Standard Operating Procedure and adequate 113 documentation should be maintained and filed to evidence the process~~ ~~The process should clearly be defined in the protocol. This alternative is currently already possible 115 within the scope of the effective regulations Directive 2005/28/EC.~~ However, if section is retained, the following change is proposed throughout as not all clinical trial sites are staffed with a pharmacist: "pharmacist" should be expanded to "pharmacist or other person legally authorised"	
107	1	Comment: what does "deliver a printout" mean? May the printout be electronic or must it be a paper printout?	Accepted. See page 33 answer.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): include clarification that printout can be electronic or paper	
107-108	3	Comment: since the IVRS/IWRS is a fully validated and GMP compliant electronic information system, the additional requirement of a 'printout' assignment report is not necessary for risk mitigation. A pharmacist is not always available at a clinical trial site, as they would be in a large teaching hospital. Proposed change: The pharmacist or other person legally authorized has access to IVRS/IWRS and the system delivers a printout ('assignment report') for each allocated kit with information on trial subject, individual kit identifier and use-by date	Accepted. See page 33 answer.
107-108	14	Comment: It is not typical for the pharmacist to have direct access to the IVRS/IWRS. This would be a change in the administration of the IVRS/IWRS. The additional bullets in this section expand the role of the Pharmacist. Proposed change (if any): The pharmacist person legally authorised to has access to IVRS/IWRS and the system delivers a printout ('assignment report') for each allocated kit with	Accepted. Sub headings included to clarify this point.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		information on trial subject, individual kit identifier and use-by date…	
109	1	Comment: it would be helpful to explain whether a copy of the IMP label prepared by the pharmacist must be retained in the trial file in the pharmacy. Proposed change (if any): include clarification as to the specific information the EMA expects the pharmacist to retain. Is it only accountability information, or is there also an expectation that a copy of the IMP label be preserved by the pharmacist. If a copy is needed, must it be a paper copy or can it be an electronic copy? Must this information be incorporated into the IV/IWRS application?	Accepted.
109	3	Comment: since the IVRS/IWRS is a fully validated and GMP compliant electronic information system, the additional requirement of a 'printout' assignment report is not always necessary for risk mitigation. It is recognized that in the case of emergency there are many sites around the world that do not have ready access to the internet – in an emergency situation the pharmacist in that type of situation would want kit allocation information. Proposed change: omit "The kit allocation information should be stored at the trial file in the pharmacy"	Accepted. See page 33 answer.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Line 109	7	Comment: Same as above, try to avoid paper Proposed change (if any): If not available as report within IRT the kit allocation information……	Accepted. See page 33 answer.
110	10	Comment: The text demands that the pharmacist should ensure that the use-by date of the medication is valid, but the use-by date is pre-defined by the IxRS. The pharmacist can only check if the use-by-date defined by the IxRS will cover a period “beyond the planned administration with adequate buffer”. ”Valid” is an ambiguous term in this context as it suggests that the pharmacist is able to check its correctness, which is beyond her/his capacities. Proposed change (if any): Re-formulate the text to make it less ambiguous.	Accepted.
113	5	Please specify if the SOP referred to here is a site or sponsor SOP	Not accepted. Could be either site of sponsor provided (with training)
113-114	14	Comment: It is not clear as to whose SOP the text is referring to. Please elaborate as appropriate.	Not accepted. Could be either site of sponsor provided (with training)
114 and other lines10		Comment: Here and in other lines the text should be more explicit.	Not accepted. This is clear in the document and GCP principles and the purpose of an expiry date.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Add here something like: "No product should be administered to a patient beyond its expiry date. The person administering an investigational product must check the expiry date (from the product label, the certificate of analysis or IxRS assignment report). Product should not be administered to the patient when this date is unavailable or not known."	
114	10	Comment: Specify, like in line 103, where the documentation should be filed. Proposed change (if any): See comment.	Accepted.
115	10	Comment: The protocol might not be the appropriate document to define the re-labelling process when the re-labelling is actually done by the pharmacist. The protocol is rather a text for the investigator and the sponsor. Moreover, during the development of the protocol it might not be known that re-labelling will become necessary. Therefore, as suggested in line 113, it is more appropriate to describe the procedure for re-labelling in an SOP. The conditions to be met to allow re-labelling should be described in the IMPD. Proposed change (if any): Delete "The process should clearly be defined in the protocol."	Accepted.
115	5	Please add after the sentence "…clearly defined in the protocol" "or in a protocol referenced document"	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
115-116	14	Comment: "The process should clearly be defined in the protocol. This alternative is currently already possible within the scope of the effective regulations Directive 2005/28/EC." This is an important point. This is not universally done at this point.	Accepted.
115-116	4	Comment: This sentence is quite general. Could more specific recommendations be made? For instance how should a pharmacist document the fact that they have handwritten something on a label?	Not Accepted. Not for us to make specific recommendation.
116	10	"… within the scope of the effective regulations Directive 2005/28/EC" In the context of EU legislation the word "regulation" has a specific meaning and should not be used when referencing a directive. Proposed change (if any): Change to "… within the scope of the effective Directive 2005/28/EC"	Accepted.
117	10	Comment: "The final responsibility resides with the investigator." We think that this sentence is misleading as the final responsibility for re-labelling actually is with the GMP QP. The intention is probably to express that IMP handling on-site is within the responsibility of	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		the investigator as opposed to the pharmacist, i.e. a pharmacist would be a designated person by the investigator for whose activities the investigator is responsible. Proposed change (if any): Give more explanation as to what is really meant here	
118	10	Comment: In the title of section 2.2.3., "Circumstances when this is not currently appropriate", is not a proper heading of a chapter. It looks rather strange in a table of content. Proposed change: The title of the section should be "Circumstances when removal of expiry date is not appropriate"	Accepted.
118	5	Justification does exist: to avoid the manual re-labelling of medication currently allowed in Annex 13. The procedure if causing many findings and not properly done by sites making this very difficult for the subject to get a proper overview if the extension/change of use-by-date is done multiple times. Patients not returning the kits and utilising them after their expiry date is not prohibited by adding a label with use-by-date. Can this be supported by data e.g. from FDA?	Not accepted. The paper presents the current consensus.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
118-125	16	Comment: This paragraph excludes the possibility of omitting the use-by date when IMP is handed for patients use at home. It should be possible to omit the use-by date in the situation where the IMP is handed to patients with a sufficient supply until the following visit. The IVRS is designed to control IMP including expiry dates and expired IMP or IMP due to expire during the period until next visit, cannot be allocated to patients. Investigator instructs the patient in the use of the IMP as does the labels on the IMP. The instruction includes the requirement to return any left-over IMP at next visit. The IMP is clearly marked as for clinical trial use only and thus should only be used in relation to the trial as instructed by the doctor. Justification does exist to allow omission of labelling of use-by date from labelling. Annex 13 provides for this justification. Further, providing a use-by date on the label will not prevent patients from returning the kits and/or utilising them after their expiry date as unfortunately, that practice occurs with the current system which includes use-by dates on labels. Proposed change: omit lines 118-125. ~~There is currently no justification, neither in the context of Phase I nor Phase II to Phase IV clinical trials for omission of labelling of use-by date from labelling if the IMP is handed out to trial subjects for use at home, except when a pharmacy adds the use-by date on the label. This use-by date should be added by a pharmacist in accordance with local law~~ ~~Where there is no possibility to add an additional label~~	Not accepted. The paper presents the current consensus.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		~~the expiry date as provided by the manufacturer should b included on the original label. This is for reasons such as:~~ ~~Patients not returning kits and then utilising them past their expiry date.~~	
119-125	14	Comment: "There is currently no justification, neither in the context of Phase I nor Phase II to Phase IV clinical trials for omission of labelling of use-by date from labelling if the IMP is handed out to trial subjects for use at home, except when a pharmacy adds the use-by date on the label." Very much agreed. Validated IRS have built in control that is confirmed/validated for each study to mitigate the possibility of allocating IMP material that may expire before the next scheduled visit by the patient. Celgene recognizes that use-by dates communicate expiration date; however, it should be noted that this does not offer any control on the patient taking expired IMP or adherence to the study protocol directions. Furthermore, the validated controls within the IRS mitigate the risk of dispensing medication that will expire before the next scheduled visit.	Not accepted. The paper presents the current consensus.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
119-125	15	Comment: As written, this section can be interpreted as saying that if a patient takes study medication home then the Pharmacist must insert the expiry date to the label at the time of dispensing. Some sites may perceive this action as being a manufacturing step and therefore be averse to taking on that responsibility. Proposed change (if any): Consider adding additional text “Unless the reconciliation and return of IMP is controlled by a validated procedure which includes contacting the patient if supplies are unaccounted for after the expiry date, and prompted and recorded by the IVR/IWR system”	Not accepted. Article 9 (2) states that manufacturing authorisation shall not be required for reconstitution or packaging if done by pharmacist or authorised person.
119-125	1	Comment: Since other regulatory authorities permit the dispensing of products to subjects for self-administration without a use-by-date, it would be useful to try to globally standardize this issue. We offer the same comment as for line 78 - 79, namely, this restriction seems unnecessary, given current controls and best practice for IMP to be accounted for each subject visit. Proposed change (if any): remove restrictions with regard to products that are to be self-dispensed by the subject. There are adequate protections within the GCPs, such as the need for subjects/site staff to account for/return unused IMP at each visit, to prevent	Not accepted. The paper presents the current consensus.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		the subject from using expired product. These protections make the restriction to products administered by study personnel unnecessary.	
Line 119-21 and Line 125	11	Comment: "There is currently no justification… for omission of labelling of use-by date … if the IMP is handed out to trial subjects for use at home" (lines 119-121). This is much more restrictive than in other countries, such as the US, and significantly limits the potential benefits that may be derived from such systems. The only reason given for this position is "Patients not returning kits and then utilising them past their expiry date" (line 125). Whilst accepting that it could be a problem if this was to happen, this should not fundamentally be a reason to prevent use of technology in this way. There are already strict GCP requirements for IMP accountability and if a company can demonstrate a robust system for ensuring materials did not remain with trial subjects past their expiry date, then this should be acceptable. Proposed change (if any): Account for the existing GCP requirements and measures in place to manage patient kits at home. This would lead to full utilisation of the technology available without compliance risk	Not accepted. The paper presents the current consensus.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Line 119 - 125	7	Comment: If medication without expiry date can only be used for in-patients, the entire discussion on the previous session is of limited value: the local hospital pharmacy is very well capable of processing the medication expiry date in their normal procedures based on provided certificates and does not need this complicated guidance. Proposed change (if any): allow all patients.	Not accepted. The paper presents the current consensus.
119	10	Comment: The sentence is difficult to understand due to double-negative phrasing: " … there is … no justification … for the omission of…". Proposed change (if any): Rephrase: It is mandatory to have a use-by date on the IMP if the IMP is handed out to trial subjects for use at home. In the event that the use-by date is not provided on the label but in a centralised system, the pharmacist or other person legally authorised to provide the IMP must manually add the used-by date on the IMP in accordance to local law.	Accepted.
119-122	10	Comment: The text is not sufficiently explicit since it is not stated that the used-by date manually added on the IMP must match the used-by date provided by the IxRS.	Not accepted. Rational for request not clear.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Add guidance whether or not it is allowed to change the used-by date manually added to the IMP into an earlier date or whether it must exactly match the used-by date provided by the IxRS.	
120	10	Comment: “for omission of labelling of use-by date from labelling” sounds strange. Proposed change (if any): Change to: “for omission of the use-by date on the IMP label”.	Accepted.
121-122	3	Comment: a pharmacist is not always available at a clinical trial site. Proposed change: There is currently no justification, neither in the context of Phase I nor Phase II to Phase IV clinical trials for omission of labelling of use-by date from labelling if the IMP is handed out to trial subjects for use at home, except when a pharmacy or dedicated trial staff adds the use-by date on the label. This use-by date should be added by a pharmacist in accordance with local law.	Not accepted. States pharmacist or other legally authorised invividual.
Lines 124 - 125	7	Comment: Medication with an expiry date can still be used by patients if not returned. Having an expiry date gives no added guarantee. The expiry date will need to be checked at the moment of dispensing.	Not accepted. Patients are much more aware these days about medication including expiry dates.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		In general, the overwhelming majority of patients will not check expiry date, nor on medication or nor on food. Proposed change (if any):delete reason(s)	
125	13	Comment: Discusses the non – compliance of patients in not returning kits and the risk of retaining them beyond their expiry date. If sites and patients are going to be non compliant in this way it probably doesn't make any difference whether the kit is labelled with current expiry date or not Proposed change (if any):	Accepted.
127-128	10	Comment: The "following prerequisites" makes the reader expect a list of items in this very part of the text, but in fact the prerequisites are described in long subsections, separated from this introduction by sub-heading. This might be confusing. Proposed change (if any): "The prerequisites defined in the following subsections …."	Accepted. This has been revised and has been included at the beginning of the paper.
Lines 127-128	16	Comment: The same practices would apply to any functionality utilised in an IVR/IWR system, not just use-by updates. IVRS/IWRS systems have numerous aspects which individually or collectively represent significant risk if robust systems controls are not implemented.	Accepted. The paper has been revised to reflect that there are other risks associated with IRT usage (when robust systems are not in place), which include expiry dates, but also dose titration

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): The following prerequisites ~~for use-by updates in the IVRS/IWRS~~ are required for the above processes to be acceptable.	etc.
127-128	15	Comment: As written, section 2.3 can be interpreted as saying that section 2.3 must only be followed when the expiry date is not on the label; however, the requirements stated in section 2.3 are valid for an IVRS/IWRS system regardless of whether expiry date text is included on the labels. Proposed change (if any): Suggest rephrasing section 2.3 to stating "The following prerequisites for use-by updates in the IVRS/IWRS are expected of all IVRS/IWRS systems regardless of expiry date labelling processes.	Accepted. As above.
129-139	8	Comment: This section has 'use of GAMP principles' as an expectation (Line 131 - 132) and a requirement (Line 139). However, GAMP is not a legal requirement, so this Reflection Paper should not mandate the use of GAMP. Proposed change: Line 131 – 132 – "It is suggested that GAMP principles would therefore be applied." Proposed change: Line 139 – "Adaptation of Annex 11 for the validation requirements is required. Adaptation	Not accepted. GMP guidances are not deviated from in this paper. There are no differences in the requirements for CSV between GCP/GMP/GLP.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		of the application of GAMP standards should be considered."	
130-132	16	Reference to GAMP problematic 1) as the GAMP is produced by a nongovernmental organisation 2) the GAMP is a guidance 3) New version of the GAMP guidance is not necessary formally announced in forehand 4) Not all vendors follow GAMP as a methodology for software development, testing and release. Is the expectation of the EMA that GAMP specifically be applied and adhered to or are other Software Development Life-cycle (SDLC) concepts acceptable? Please change to reference GAMP guidance as a good practice recommended to be in compliance with.	Partially accepted, have considered other CSV methodologies in general terms. Reference to GAMP removed.
132-135	9	The sentence in lines 132/133 expects the NCA be notified that an IVRS/IVWS will be used by "inclusion of a statement in the protocol". The next sentence then talks about the QP declaration in Annex 1 and the following sentence states that this should be included in the PSF and Trial Master File. From this it is understood that the Annex 1 QP declaration is NOT intended to be submitted to the NCA, since that notification is via the protocol and there is no mention of the QP declaration being included in the protocol. If this is correct, then it is suggested that there is a	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		more obvious separation of these statements. If this is not correct, then the wording requires update to clarify this point.	
130 - 138		Reference to GAMP problematic 5) as the GAMP is produced by a nongovernmental organisation 6) 2) the GAMP is a guidance 7) 3) New version of the GAMP guidance is not necessary formally announced in forehand Please change to just reference GAMP guidance as a good practice recommended to be in compliance with.	Reference to GAMP removed.
133-135	3	Comment: Qualification including auditing of suppliers, in this case IRT suppliers, is integral part of the Quality Management System (ICH Q10) and thus, does not need separate compliance declaration of a QP. It is the senior management's responsibility to assure effectiveness of this Quality Management System. See below 240-264. Proposed change: delete Where the system is used to control expiry dates a QP declaration is required, Annex I. This declaration will be included in the Product Specification File and the Trial Master File.	Not accepted. This is separate since the QP has responsibility for the expiry date which is now part of the IRT system.
133-135	16	Comment: Qualification including auditing of suppliers, in this case IRT suppliers, is integral part of the Quality Management System (ICH Q10) and thus, does not need separate compliance declaration of a QP. It is the senior management's responsibility to assure effectiveness of this Quality Management System. See	Not accepted. This is separate since the QP has responsibility for the expiry date which is now part of the IRT system.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		below 240-264. Proposed change: delete ~~Where the system is used to control expiry dates a QP declaration is required, Annex I. This declaration will be included in the Product Specification File and the Trial Master File.~~	
134	5	It is not quite clear when Annex 1 to the reflection paper should be used. It should be clarified if it is sufficient to file this statement with the validation documentation of the system if expiry control is a standard functionality in all IVRS/IWRS and not per clinical trial TMF.	Not accepted. It is expected to be referenced in the TMF, but not necessarily filed there.
134	10	Comment: Reference is not given in an appropriate way. As there are several references in this document to Annexes deriving from different sources, extreme care should be taken when referencing in order to avoid confusion (see also comment for line 138) Proposed change (if any): replace text with "… required (see Annex I of this document)".	Accepted.
Annex 1 and line 135	11	Comment: The Annex I QP declaration appears to be added bureaucracy with unclear value. It is agreed that the certifying QP should ensure that if an IVRS/IWRS is used to control expiry dates then it is fit for purpose and there is traceability back to appropriate audits. However, the audit/validation traceability could be addressed through internal control	Not accepted. Needs to be referenced in the files, not necessarily filed in each one. QP should have assurance of the system controlling expiry dates.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		processes and the needs of those downstream covered by the QP's certification of the batch. To create and maintain a form in every Product Specification File and Trial Master File (ref. line 135) is unnecessary bureaucracy. Furthermore, what is the objective of listing assembly and distribution sites and including them within this? Proposed change (if any): Use the QP certification of the batch in combination with internal control mechanisms to remove the need for an additional declaration.	
138	10	Comment: For someone who is not familiar with the topic it should be specified which document is annexed by "Annex 11". Proposed change (if any): "Annex 11, Computerized Systems, of Volume 4 , EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use".	Accepted.
138-139	16	The reference to GAMP should be limited to best practice examples. Please remove **application of GAMP standards is required.** We also recommend including only expectations that are not addressed in Annex 11 and GAMP (e.g. specific expectations of the sponsor).	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
139	10	Comment: To have the statement "as a minimum the following should be in place" followed by a single subsection with a separate title produces a confusing structure of the text. Proposed change: Delete the header of the subsection 2.3.1.1. and make the list of line 141 ff. follow directly after line 139.	Accepted.
141 157	1	Comment: This line makes reference to "activities undertaken by the provider..." Line 157 also makes reference to "provider". To what entity is this word, provider, making reference? Is it the clinical site/staff, the technology provider, or the sponsor or CRO that may be providing sites access to an IV/IWRS system?	Accepted.
141	10	Comment: The sentence "Regardless of what clinical research activities are undertaken by the provider then the sponsor ..." is unclear. Proposed change: The sentence might read "... by the provider, the sponsor ..."	Accepted.
141-142	16	Comment: clarify that the provider conducts the validation, not the sponsor Proposed change: Regardless of what clinical research activities are undertaken by the provider the sponsor should assure themselves that the provider has adequately validated the system.	Accepted.
142	3	Comment: clarify that the provider conducts the	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		validation, not the sponsor. Proposed change: Regardless of what clinical research activities are undertaken by the provider then the sponsor should assure themselves that they have the provider has adequately validated the system.	
142	10	Comment: "…they have adequately validated the system." Proposed change (if any): Clarify the reference of "they": Is it the provider or the sponsor or both? Also clarify if the sponsor can create its own system and test it.	Accepted.
144	14	Comment: "User requirements specification (URS) or equivalents should be approved by the sponsor. Any subsequent documents produced by the provider should be mapped back to the URS. This should be down to the level of mapping individual test scripts back to the requirement it tests". Important point. Proposed change: None.	No comment needed.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
144-146	16	Comment: clarify that the provider conducts the validation, not the sponsor. Proposed change: User requirements specification (URS) or equivalents should be approved by the sponsor. Any subsequent documents produced by the provider should be mapped back to the URS by the provider.	Accepted.
144-146	3	Comment: clarify that the provider conducts the validation, not the sponsor. Proposed change: User requirements specification (URS) or equivalents should be approved by the sponsor. Any subsequent documents produced by the provider should be mapped back to the URS by the provider.	Accepted.
147-149	14	Comment: “Client User Acceptance Tests (UAT) are always offered to sponsors. This is an opportunity for the 147 sponsor to test the system and this should be undertaken, preferably with scripts written by the client” Important point. Proposed change: None.	No comment needed.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
147 and 192	16	Inconsistency between the two sections related to UAT. Section 2.3.4.1 UAT is mentioned as 'an opportunity' which 'should be undertaken' and 'The sponsor should assure themselves…' but in section 2.3.5.1 is stated 'The IVRS/IWRS has to be validated and qualified and undergone UAT' This inconsistency could lead in misunderstandings of the requirements for UAT.	Not accepted. Different types of UAT. One is the provider, one is sponsor.
147-149	16	Comment: "Client User Acceptance Tests (UAT) are always offered to sponsors. This is an opportunity for the sponsor to test the system and this should be undertaken, preferably with scripts written by the client" As per ICH GCP 5.5.3, the sponsor is responsible to ensure and document that the system conforms to established requirements for completeness, accuracy, reliability and is fit for intended use. The UAT documentation is the objective evidence used to demonstrate that the event occurred and that there is acceptance of the system prior to it being released into production. Proposed change (if any): The sponsor should document the outcome of UAT (pass/failure of test cases) to provide documented evidence that the UAT occurred and the system was accepted prior to being released into production.	Not accepted. This would appear to be a specific example for in-house.
147	10	Comment: See proposed change.	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Replace “are” by “should be”.	
147-149	10	Comment: “client” and “user” might be too much. Also, in this context, it should be clarified that the sponsor is referred to as the user (and not the investigator, although the system later on will be used by the investigator (as well as by the sponsor). More clarity around this terminology, which comes from the IT arena, would be very helpful. Proposed change (if any): Define terminology and stick to it throughout the whole text.	Accepted.
147-149	4	Comment: We are in agreement and pleased to see the preference that clients write their own UAT scripts but wonder whether this could be strengthened. Proposed change (if any): “the sponsor shall produce their own independent UAT Test Plans and conduct their own testing; Sponsors should not rely upon Vendor testing or Vendor provided test plans as a substitute for their own UAT”	Partly accepted.
147 and 149	5	Client is sponsor? If so please be consistent.	Accepted.
149	16	Comment: Client and Sponsor are used interchangeably. Please use consistent terminology. Proposed change (if any):	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		In line 149, “client” should be replaced by “sponsor”	
148	12	We do not think that the wording "preferably" is appropriate in the context of a clear recommendation ; it remains ambiguous whether or not the scripts should be done by the client.	Not accepted. Different situations may apply.
150	10	Comment: The text is corrupted. Proposed change (if any): Add “should be” after “this”.	Accepted.
150	16	Comment: Per section 13 of Annex 11, all incidents should be reported and assessed. However, a risk-based decision should be allowed to determine whether non-critical incidents must be corrected prior to release. Proposed change (if any): Remove this requirement	Not accepted. The paper clearly states all incidents affecting functionality should be fixed. Minor issues eg typos would not influence functionality.
150	5	“All incidents affecting…… and to enable corrective actions to be taken. Sometimes during UAT an incident is disclosed but not impacting go-live of the system, so this could be solved after go-live. Therefore please change to: Prior to release any incident affecting functionality should preferably be fixed and as a minimum an evaluation and plan for fixing the incident must be in place and agreed upon before release. This must be	Not accepted. As above.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		documented appropriately. A SOP should be established how to record and analyse incidents and to enable actions to be taken.	
150	8	Comment: It is acceptable to release a system with bugs into production as long as there is a documented path forward. Proposed change: Change 'fixed" to "resolved".	Not accepted. As above + Both fixed and resolved. Fixed is preferred.
151-152	8	Comment: We disagree that there needs to be a specific SOP for this. For example, this topic can be addressed as part of a CSV methodology SOP. Proposed change: Procedures to record and analyse incidents and to enable corrective actions to be taken should be established.	Accepted.
153	10	Comment: It is not obvious who should conduct the sign off. Proposed change (if any): Define who should conduct the sign off.	Partly accepted.Clarification has been provided.
153	14	Comment: "There should be a formal sign off prior to use" Important point. Proposed change: None.	No comment required.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
154	10	Comment: it is not clear for whom the audit trail should be readily accessible. Proposed change (if any): Specify whether only the administrator has access or if audit trail should be accessible for all users.	Not accepted. This is an extra level of detail which is defined in many CSV documents.
155	10	Comment: "QC" means "in-process quality control" and therefore is not "independent". Proposed change (if any): Key steps should be subject to review and sign off by the person responsible for QA and/or QC. Proposed change(if any): Delete "(QA/QC)".	Accepted.
155	16	Comment: Quality roles, responsibility, and independence are sufficiently addressed in existing regulations. The sponsor's quality management should be aligned and consistent across all aspects of the clinical trial per existing regulatory requirements Proposed change (if any): Consider eliminating this recommendation without a broader context of overall clinical trial quality considerations.	Accepted. As above
155	10	Comment: It is not fully clear what "key steps" refer to. Do the key steps refer to steps before the release of the system or do they include already critical updates as in line 205. What is exactly meant?	Not accepted. This would need to be defined by the organisation and appropriate for the tasks undertaken.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Please specify what “key steps” refers to.	
155	5	*Key steps should be……and sign off by an independent department (QA/QC) As validation and development can be outsourced it needs to be specified if this QA/QC activity could be done by the vendor/provider of the IVRS/IWRS. Please clarify. This is also applicable for section 2.3.5.1 (line 194)	Not accepted. As above.
157	9	Add text for clarity: “The quality system at the provider of the IVR/IWRS should include:”	Accepted. Clarified by restructure of paper and use of IRT term.
159	10	Comment: Any valid SOP is a formal one. SOP should be part of robust quality system (but this is not addressed by adding the word “formal”). Proposed change (if any): Delete “formal”.	Not accepted. This is considered to be clear.
164-179	8	Comment: Section addresses Disaster Recovery, but not fall-back procedures. Proposed change: Consider adding fall-back procedures.	Accepted.
165	10	Comment: We propose that the qualification should include proper documentation.	Not accepted. This is inherent and self explanatory.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): "Access permissions (personnel with these access rights at the site should be qualified for these delegated activities, including appropriate documentation of qualification)"	
165-179	10	Comment: The language here should be more detailed and clear. Explain the meaning of the statement "personnel with these access rights at the site should be qualified for these delegated activities": A connection between specific access rights and activities appears to be assumed, but it remains unclear how they are connected (e.g. which activity is assumed to be permitted for site staff as compared to some other staff?). Does the meaning of the statement change when it is abbreviated to "personnel at the site should be qualified for this delegated activities"? If not, what information does "with these access rights" add? Proposed change (if any): Add, before line 165, something like: "The system should have the following features." Add, in line 165, as the initial word "differentiated". Add, in line 167, as the last word, "staff". Add, in line 168, some contextualizing qualifier like "of the sponsor" or "of the IVRS service provider". Explain, in line 169, the term "study staff": Is this	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		equivalent to the term “trial staff”, as used by ICH GCP (4.8.3, 5.18.4) i.e. meaning part of the investigator’s team? Or is it a more general term, covering all people involved in the trial (i.e. investigators, CRO employees, sponsor employees, etc.). Is there a difference between “study staff” (line 169) and “site staff” (line 170)? Add, in line 170, “trial” before “site” (cf. ICH GCP, 1.59).	
171	10	Comment: What does “stock” refer to? The term does neither appear in ICH GCP nor in Annex 13 of the EU GMP guideline, it has only one appearance in this text: Here in line 171. Proposed change (if any): Use a qualifier for “stock” or define “stock”.	Accepted.
173	10	Comment: Guidance on “disaster recovery” would be welcome. Proposed change (if any): Add guidance on expectation for disaster recovery.	Not accepted. There is a lot already available on this topic.
176	3	Comment: clarify that the sponsor is responsible for a recall, supported by the IVRS/IWRS system. Proposed change: Location of Recall of product from warehouses and sites to support a sponsor recall.	Not accepted. The system would have this functionality, this has been clarified in the paper.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
176	16	Comment: clarify that the sponsor is responsible for a recall, supported by the IVRS/IWRS system. Proposed change: Location of product from warehouses and sites to support a sponsor recall. It should not be a specific requirement in relation to IVRS as it may be possible and beneficial to use other solutions.	Not accepted. The system would have this functionality, this has been clarified in the paper.
177	16	Comment: It is not clear what is meant by “real time updates” Please clarify how these are defined and how often should updates take place.	Accepted. Some clarification has been provided. The paper cannot provide specific time frames.
178-179	10	Comment: A different wording for “blind breaking” is used in line 172, but to make the text clearer, uniform terminology should be used. Proposed change (if any): Harmonize the wording.	Accepted.
178-179	14	Comment: How should down-time for system updates be handled? What is reasonable downtime? Proposed change: Accessible 24 hours a day where studies are global or where there are other needs for example blind breaking.	Accepted. Cannot give a reasonable downtime, it depends on the details of the trial and needs to be defined in the project. It is beyond the scope of this paper to define specific timeframes.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
181-186	8	Comment: Section does not address sponsor responsibilities for the User Requirements (per Line 144, 'User requirements specification (URS) or equivalents should be approved by the sponsor'). Proposed change: Add 'The sponsor should approve the User requirements specification (URS) or equivalents'.	Accepted.
183	16	Comment: "The Sponsor should clearly define the study access permission requirements." Clarify if the Sponsor should document this in procedures or should the system be designed to control access permissions?	Accepted.
185	10	Comment: It is not clear why this should only be done at the pre-study visits. What is the rationale behind this approach? To check whether the pharmacy would be able to do such activities or is training the point to be made? If so, this should not be limited to pre-study visits, but should be extended to, e.g., investigator meetings and initiation visits. Proposed change (if any): See comment	Accepted.
186	9	Should the document note for studies dispensing multiple containers per study, that the UAT should include a test to ensure that EACH container is assigned with a suitable expiry to cover the entire period between visits?	Partly accepted. This has been clarified.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
187	16	Comment: Expiry dates are data (table values) in the system database. Update of such data are not a system update i.e. does not involve changing the coding of the system.	Accepted.
188 (2.3.5.1.) and 215 (2.3.5.4)	16	Header: Process at the Sponsor for expiry updating resp. Process at the sponsor for the update of the expiry It is very difficult to see the difference in the header but the content is very different – the first covering the expiry date updates is a manual data change process – the second is covering the update of expiry date by a programmed system functionality which should be tested by sponsor during UAT. The difference could be made more clear or move the sections closer to one another.	Accepted.
188 (2.3.5.1.) and 215 (2.3.5.4)	5	Header: Process at the Sponsor for expiry updating resp. Process at the sponsor for the update of the expiry It is very difficult to see the difference in the header but the content is very different – the first covering the expiry date updates is a manual data change process – the second is covering the update of expiry date by a programmed system functionality which should be tested by sponsor during UAT.	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The difference could be made more clear or move the sections closer to one another.	
188	10	Comment: Throughout the document “sponsor” is used instead of “Sponsor” (inconsistency in capital / small letters). Proposed change (if any): Change “Sponsor” into ”sponsor”.	Accepted.
189-191	14	Comment: “When stability data supports an extension to the expiry date this change should be communicated in the form of a revised certificate of analysis or certificate of compliance, which includes the use by date. This extension will have to have been approved by the CTA via an amendment”. This may take some time.	Accepted.
189-191	16	Comment: The Annex 13 QP Batch Certificate requires expiry date and an updated version of this Certificate can be issued by a QP for the sponsor stating the new expiry date that is assigned based on stability data. Stability data supporting a shelf life extension plan stated in an IMPD does not need to result in a new Certificate of Analysis for the released batch. This extension can be based on stability data reports with data in line with specification as per the IMPD and the QP certificate is the revised document stating the new expiry date.	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Perhaps be rephrased to indicate that the shelf life can also be extended based on a CA approved shelf life extension plan, submitted and approved with the original CTA and following normal change control processes.	
190	10	Comment: Certificate of analysis and certificate of compliance was abbreviated earlier in the document: 80-81. Proposed change (if any): Be consistent and use the abbreviation already introduced.	Accepted.
191	10	Comment: The meaning of "CTA" is not clear. This guideline text does not define it and uses the abbreviation only once, in this line 191. The abbreviation is commonly used in the clinical trial context, but with several different meanings: 1. Clinical trial agreement (this meaning is favoured by the CDISC list "Acronyms, Abbreviations, and Initials", by the way). 2. Clinical trial application 3. Clinical trial authorisation (the detailed guidance CT-1, which actually never defines CTA, uses this abbreviation with both of the last two meanings). 4. Clinical trial assistant. The use of "by the CTA" suggests even another meaning of this abbreviation.	Accepted. Abbreviation list has been included.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Either explain the meaning of "CTA" or follow a common rule of medical writing and do not use abbreviations if these abbreviations appear in the text only once.	
191	10	Comment: The sentence in line 191 is difficult to read: "… will have to have been …". Proposed change (if any): Change the wording to: "This extension might represent a substantial amendment and will have to be authorised, in case stability testing plans are lacking in the IMPD".	Accepted. Wording has been changed.
191	10	Comment: Please note that, according to the EU guideline CHMP/QWP/185401/2004, the following is not a substantial amendment requiring authorisation: "Extension of shelf-life and/or extension of the storage conditions on the basis of additional data with unchanged shelf-life specifications, provided proposal for shelf-life extension, defining the criteria based on which the sponsor will extend the shelf-life during an ongoing study, has been submitted with the initial filing of the IMPD and has not been questioned by the competent authority." Proposed change (if any): Add "if expiry date extension plans are not already authorized as part of the IMPD" after "amendment".	Accepted.
191	9	Some Member States allow for shelf life updates without a CTA amendment if the stability programme is detailed in the IMPD. Therefore, text should be	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		amended: “This extension will may have to be…”	
191	15	Increased shelf life does not necessarily need to have been approved by the CTA via an amendment before we can update the shelf life. Some markets are notification only therefore we suggest rewording this statement to that effect. Should perhaps be rephrased to indicate that the shelf life can also be extended based on a CA approved shelf life extension plan, submitted and approved with the original CTA and following normal change control processes	Accepted.
192	5	Updating expiry ….the system must be validated…. and undergone (UAT). As the expiry date in the IVRS/IWRS is a data base setting the changes of expiry date could be done by a programmed functionality by QA/QC (2.3.5.4) it might not be necessary to do a UAT. However this is applicable if this functionality is not covered in the IVRS/IWRS (2.3.5.1). Please make this more clear.	Accepted.
192	10	Comment: Brackets are misplaced. Proposed change (if any): Delete the brackets.	Accepted.
192 - 195	10	Comment: The content of these lines has no relation to the header in line 188.	Partly accepted. Clarification has been provided.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Change the content of this paragraph or change its header.	
192-193	14	Comment: "The IVRS/IWRS has to be validated and qualified and undergone (UAT). An audit trail should be implemented. The sponsor should confirm that this is the case" Again, this could take time, but agree that it is the right way to do this. Proposed change: None.	No comment required.
192-193	16	Updating expiry ….the system must be validated…. and undergone (UAT). As the expiry date in the IVRS/IWRS is a data base setting the changes of expiry date could be done by a programmed functionality by QA/QC (2.3.5.4) it might not be necessary to do a UAT. However this is applicable if this functionality is not covered in the IVRS/IWRS (2.3.5.1). Please make this clearer. Also, Requirement for validation is already mentioned in 2.3.1.1 and requirement for audit trail is already mentioned in 2.3.3.	Partly accepted. Clarification has been provided.
194	10	Comment: What is the significance of the "(QC)" in this line?	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Delete "(QC)".	
194-195	16	Comment: Expiry dates are data (table values) in the system database. These are not related to system coding. A requirement for change control of a validated system is already in 2.3.1.1 (Lines 142-143) Proposed change (if any): Please consider deleting "…and any changes to program coding".	Partly accepted. The difference between the manual update of expiry date and automatic update of expiry date has been clarified
194	5	*Key steps should be……and sign off by an independent department (QA/QC) As validation and development can be outsourced it needs to be specified if this QA/QC activity could be done by the vendor/provider of the IVRS/IWRS. Please clarify.	Accepted.
197-203	4	Comment: The process whereby a sponsor enters the update directly into a validated web interface should be addressed. The text implies that this case is not covered e.g. the phrases "well communicated", "Implemented" and "verified" are not applicable in this situation. Proposed change (if any):	Accepted.
197-203	16	Comment: The QP can have a role in the IVRS system and be responsible for expiry update in the live system. In that case, this section is not applicable.	Partly accepted. Section 2.3.5.4 has been moved to 2.3.5.2

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
197-199	14	Comment: If an email is not sufficient, what is recommended? An encrypted email? A Fax? Registered Mail? Proposed change: A robust process should exist between the sponsor and the provider to ensure that the new expiry date is well communicated and with sufficient time for the update to be implemented and verified. An encrypted email, fax or registered mail is not sufficient for this purpose	Partly accepted. Clarification has been provided.
199	9	States that “An email is not sufficient for this purpose”, but does not provide any further clarity regarding what would be considered suitable.	Partly accepted. Clarification has been provided.
199 & 202-203	8	Comment: Line 199 indicates that an email is not sufficient as a means of communicating a new expiry date between the sponsor and the provider. However, similar guidance is not provided for Lines 202 – 203: “The sponsor should have some confirmation that the update has been undertaken, in an appropriate timeframe.” We would argue that provided there is a robust process in place, including electronic signature, a mechanism for acknowledging email receipt and dictating the format and types of information that should be included and email should be sufficient for the purpose of lines 197-198 and 202-203. Proposed change: Delete line 199.	Not accepted. Clarification has been provided.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
199	10	Comment: It is strange to disallow the use of email as a form of correspondence. This is the most efficient and effective method of communication, which also provides an easy way to document the correspondence. Therefore, e-mails can be part of "a robust process" of communication. Also, in the business world, emails are legally recognized in case they bear certain information in the signature. In addition, there are less and less fax machines in offices. Not allowing emails in a process of demonstrating evidence would be a very severe restriction. Proposed change (if any): Perhaps rather than not permitting the use of emails, e-alerts should be allowed for this notification, including that the recipient must notify the receipt of the alert. If this is not acceptable the reflection paper should explain why email correspondence is not acceptable.	Partly accepted. Clarification has been provided.
200-201	10	Comment: It is not clear how the sponsor should and could do that. The sponsor is limited to reviewing the standard operation procedures (before the trial via system audit) and whether the processes are not only written on paper but also put to life (during a trial via a study audit). However, it is unrealistic for a sponsor to constantly perform tests and checks and/or to conduct interviews during the process of re-labelling.	Partly accepted. Clarification has been provided.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Add “by applying appropriate QA measures” after the end of line 201.	
200-201	16	Comment: Ensuring that the information is shared between the correct parties at the provider should be rather the responsibility of the provider.	Partly accepted. As above.
202-203	14	Comment: Documented in TMF Proposed change: The sponsor should have some confirmation documented in TMF that the update has been undertaken, in an appropriate timeframe.	Not accepted.
205	16	There is a mix of requirements to changes of data and changes to the IVRS/IWR system (“changes made to the data base” and “critical changes”) Please clarify as this can be very different (data change or IT system change)	Partly accepted. The difference between manual and system changes has been made apparent.
205	14	Comment: This may be difficult for some providers as their audit trails may cover data *in* the database as opposed to database structure itself. Will there be a grace period? Proposed change: It is important that any changes made to the database	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		have an audit trail behind them. For critical updates, such as expiry updating a second person should verify that the correct data has been entered and have been released to the live environment. These checks should be documented.	
205	5	There is a mix of requirements to changes of data and changes to the IVRS/IWR system ("changes made to the data base" and "critical changes"). Please clarify as this can be very different (data change or IT system change).	Partly accepted. Clarification on the difference has been provided.
205-209	4	Comment: Similar to above. It should be made clear these updates refer to manual changes and do not apply if an automated system is being used. This is certainly what we hope the message from the guidance is as other aspects of electronic transactions are currently not verified by a second signature. Proposed change (if any):	Partly accepted. Clarification on the difference has been provided.
205-207	1	Comment: This section requires that a second person verify expiry date changes. This may be a standard practice/process for facilities that manufacture/label product, but clinical trials are not typically set up to require verifying signatures by a second person for specific activities. (Investigators might provide an "approval signature" but this does not typically represent a second signature as required by this	Not accepted. Where changes are made in the data it is important that the changes are checked. This is particularly important with expiry updates.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		paper). Proposed change (if any): Remove the need for a second signature in the database.	
207	9	"These checks should be documented" – it would be beneficial to confirm that this documentation can be recorded electronically within the system and does not have to be on paper.	Accepted.
210	14	Comment: Is email acceptable here? Proposed change: "The provider should inform the sponsor that the update has been completed. Notification by email is acceptable in this instance".	Accepted.
211-213	14	Comment: In agreement. This may be new functionality for some systems....as they may have been tracking this manually. Again, the right thing to do. Proposed change: None.	No comment required.
211	10	Comment: The shipment could also be made from the manufacturer directly. Proposed change (if any): Change to "… from the	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		manufacturer or warehouse …"	
214	10	Comment: - Proposed change (if any): Add "The provider should" at the beginning of the line.	Accepted.
214	14	Comment: "Consider time taken for shipments to reach different countries" Proposed change: Consider "Provide an offset time taken for shipments to reach different countries"	Partly accepted.
215	10	Comment: This section has a similar title as section 2.3.5.1. Proposed change (if any): Add the content of section 2.3.5.4 to section 2.3.5.1.	Partly accepted. Clarification has been provided.
215-219	16	Add the following (see underline): ***Process at the sponsor for the update of the expiry <u>date in IRT</u>*** Where the system has been built to allow the sponsor to update the expiry themselves, conditions 216 surrounding the process in 2.3.4.1 apply and additionally <u>the following should apply to the IRT expiry dating change:</u>	Accepted.
217	9	Typo: 2.3.4.1 should be 2.3.5.1	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
219	5	There is a mix of requirements to changes of data and changes to the IVRS/IWR system. Section 2.3.5.4 – it is not clear if the requirements are for changes to data or to the IVRS/IWR system.	Partly accepted. Clarification has been given between data and system.
219-220	14	Comment: Could the agency be a little clearer of the form of verification that they are expecting? Does this include integration updates?	Partly accepted. Clarification has been provided.
219-220	1	Comment: Are there any specific recommendations as to how this information is to be verified and documented?	Accepted.
223-224	10	Comment: The content of this section belongs to section 2.3.5.3. Proposed change (if any): Move the content of this section to section 2.3.5.3.	Accepted.
223-224	14	Comment: “For other changes to the system as a result of protocol changes or bug fixes the same standards of computer system validation should be applied.” A good point to include in this reflection paper. Proposed change: None.	No comment required.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
226	10	Comment: The apostrophe is misplaced. Proposed change (if any): Replace “Inspector’s ” by “Inspectors’ ”	Accepted.
230	5	Reference 2, 3, 3, and 5 are without dates, version or other identifiers. German Ordinance on GCP is not very specific.	Accepted.
230	16	Add dates, version or other identifiers for reference 2, 3, 3, and 5.	Accepted.
231-237	10	Comment: Referencing is done not according to common medical writing standard. Proposed change (if any): Have all referencing reviewed in this document and apply common medical writing standard.	Partly accepted. References have been included consistent with EMA reflection papers.
231	10	Comment: This document has actually a proper title and a version number. Proposed change (if any): Add the proper title and a version number.	Accepted.
232	10	Comment: 1. It is often difficult to identify law texts if only the English translation of their original title is provided. 2. Law texts change over time, therefore the date of the referenced text should be indicated.	Accepted. Reference has been removed from text.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Indicate also the original title and add the date of the version you are referring to.	
233	10	Comment: The referencing is incomplete. Proposed change (if any): Add the exact title of the document, the editor and / or source and the version number and date.	Accepted. Document has been removed.
234 - 237	10	Comment: Although Annex 11 and Annex 13 are annexing the same document, the document which they are annexes to is referenced in two different ways. Proposed change (if any): Reference the document which Annex 11 and Annex 13 are annexing in a uniform way. Add version and dates of the annex texts.	Accepted.
240	10	Comment: As an IxRS is set up per clinical trial, the trial should be identified as well on the form. Proposed change (if any): Include trial identification on the form.	Accepted.
240 – 264 (Annex 1)	16	Comment: Annex 1 is disconnected from Annex 13, appropriate use of GMP QPs and quality management systems (ICH Q10). It is recommended this annex be deleted for the following reasons: Qualification including auditing of suppliers, in this case IRT suppliers is an integral part of the Quality Management System (ICH Q10) and	Not accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		thus, does not need separate compliance declaration of a QP. It is the sponsor senior management's responsibility to assure effectiveness of this Quality Management System. A QP belonging to the Key Personnel within the EU GMP quality system is not able to declare compliance with GCP requirements. There is no requirement for GMP QPs to have any specific expertise in GCPs. QP does not have sufficient knowledge of GCPs to know the standards at least equivalent to EU GMP and GCP are being followed at the site. Potentially imposes contractual obligations due to the following statement, "If substantial changes are made at the provide then it would be expected that some form of due diligence is undertaken." However, such changes and appropriate audit/due diligence is managed via the Quality Management system and is the responsibility of the sponsor senior management. Annex 1 is not considered necessary when a QP can release study medication, change the status of the study medication and extend expiry date in the live IRT. Proposed change: Delete Annex 1 (QP declaration) and include this principle outlined above e.g. in section "2.3.2 expected	

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Standards for Quality Systems"	
240 Annex 1	5	Please define "assembly site" and "distribution site" It does not seem to fit with a QP declaration on use of IVRS in the event of use for handling expiry dates. Line 258: This declaration is submitted by: From section 2.3.1 this "statement" (and not "declaration") is to be included in the Product Specification File and the TMF but nothing about being submitted. Please align with the appropriate action expected. However we see no point in making this declaration at all because if this functionality is in the IVRS/IWRS it will be stated in the IVRS/IWRS technical specification document.	Partly accepted. The paper has been revised to clarify.
240 Annex 1 continued	11	Comment: Should the declaration be retained, then (a) the focus should be on the IRS itself, not specific locations within the supply chain. (b) guidance notes on its completion will be required. For example, what is meant by the 'date of last audit (completion)'? Is this the last day of fieldwork; date of report issue; date of Corrective Action Plan acceptance; date of closure of all actions arising from the audit? Proposed change (if any):	Partly accepted. Clarification has been given. Document retention is throughout GCP and GMP.
240 - 264	3	Comment: Qualification including auditing of suppliers,	Not accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		in this case IRT suppliers is an integral part of the Quality Management System (ICH Q10) and thus, does not need separate compliance declaration of a QP. It is the senior management's responsibility to assure effectiveness of this Quality Management System. Furthermore a QP belonging to the Key Personnel within the EU GMP quality system is not able to declare compliance with GCP requirements. Proposed change: delete Annex 1 (QP declaration) and include this principle outlined above e.g. in section "2.3.2 expected Standards for Quality Systems".	This is a mechanism for NCAs to have an assurance of the system having been appropriately assessed where expiry dates are controlled in the IRT system.
242	10	Comment: The Annex is to be used for both IVRS and IWRS systems, but the title only refers to IVRS. Proposed change (if any): Add "IWRS" in the title or better: use "IxRS" throughout the document and its annex.	Accepted.
247	10	Comment: It is unclear whether "date of last audit" refers to the date of the last audit by the provider or the date of the last audit performed by or under supervision of the sponsor at this provider. Proposed change (if any): Specify this issue.	Not accepted. This is for the audit of the provider.
Line 247	16	Please define the following terms should annex 1 be kept in the reflection paper (please note the recommendation is to remove annex 1 as it is	Not accepted. Comment not clear.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		duplicative to the IRT, protocol and inappropriate for a GMP QP to declare compliance with GCPs). Assembly site Distribution site.	
247, 252	10	Comment: The rationale to request a listing of audit dates in relation to this declaration is unclear. Audits are not the only way to confirm "that compliance with GCP and GMP requirements has been assessed for the IxRS system as named below and found to be satisfactory". In addition one table would suffice (the one including the third party) asking whether a third party was involves (yes/no). Proposed change (if any): Re-consider the structure of this form.	Accepted.
254	10	If an audit of the site has not been performed. Which site is meant? Investigational site? Provider site? Proposed change (if any): Please clarify the text regarding audits.	Accepted.
254	9	"audit of the site" – the earlier parts of the form point to a number of sites. Suggest this should be "audit of a site".	Accepted.
Reference documents	12	Why only the GAMP and not the PIC/S, when the latter is the reference text for EMA GCP inspectors ?	Partly accepted. Annex 11 will be used as reference.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
NA	14	Proposed change: If IRS are controlling expiration dating without labels, alerts and notifications can also be a integral part of an effective expiry date monitory IRS. Safety alerts can be programmed to alert study staff in the event that a subject is: still on medication considered “active” in the study exceeded the next study visit interval has IMP expiring with in a study specific time threshold.	Accepted.