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4 **Reflection paper on the Use of Interactive Response**
5 **Technologies (Interactive Voice/Web Response Systems)**
6 **in Clinical Trials**
7 **Draft**

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8 Comments should be provided using this [template](#). The completed comments form should be sent to
9 gcp@ema.europa.eu

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Reflection paper on the Use of Interactive Response Technologies (Interactive Voice/Web Response Systems) in Clinical Trials

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1. Introduction

Over the last 15 years there has been an increasing utilisation of interactive voice response systems (IVRS) utilising telephones. Such systems have been developed further into interactive web based systems (IWRS) utilising the internet. These systems were developed initially to optimise drug availability at sites. However, this has expanded into other areas such as dose titration, unblinding and expiry date updating. This of course may, if not handled appropriately, pose an increased risk to the patient and so IVRS/IWRS is of increasing interest to National Competent Authorities (NCAs).

One specific example is the potential use of IVRS/IWRS to justify the removal of expiry dates from IMP labels. This paper seeks to provide guidance to Member States on what our expectations are of these systems and in particular their use in expiry updating. These positions will form guidance for sponsors and IVRS/IWRS providers.

Sponsors have previously contacted the regulatory agencies with requests to omit the use-by date on study medication in case of IVRS/IWRS use. An advantage of this approach would be avoiding issues related to relabelling of the use-by date on site, which can often cause issues in themselves with poor control of the expiry update labels. However, the request of the sponsors raises concerns for Regulatory Authorities; based on experience, for example GCP inspection findings around IVRS validation and the possibility of dispensing expired study medication to patients.

A White Paper by the ISPE/PDA Expiry Date Task Force produced in 2009, raises an important issue in that many sponsors, due to lack of knowledge, may not be able to use the IVRS/IWRS appropriately (p. 8, 3rd paragraph).

Currently, the information on the use of IVR/IWR systems is limited to the completion of a tick box in the clinical trial authorisation application filled in by the sponsor. Also, the protocol may only provide limited detail on the use of the IVR/IWR.

As IVR/IWR systems are developed to facilitate overall drug management and expanded to assist with dose titration, unblinding and expiry date update, the intent of the paper is to provide guidance to the sponsors and to the IVR/IWR providers in the use of the systems within clinical trials and detail the expectations of the NCA on such systems.

The potential for the revision of Annex 13, when it is next reviewed is also considered.

2. Discussion

2.1. Legal basis

Currently the worldwide regulations regarding expiry dating on labels of investigational medicinal products (IMP) are not uniform. In Japan the use-by date on the IMP label is not a mandatory requirement, nor does such a requirement exist in the US (21 CFR Part 211). In Europe, the labelling of the use-by date on the IMP is required except in certain circumstances. Annex 13 allows for omission of some information when the absence can be justified (e.g. use of IVRS/IWRS). "The following should be included on labels, unless its absence can be justified, e.g. use of a centralised electronic randomisation system." Annex 13 does not directly apply to clinical trials conducted in a number of Member States, where it is overruled by national law. However, some Member States have implemented the above mentioned provision of Annex 13 in their national regulations for example the German Ordinance on GCP allows in article 5 "Kennzeichnung von Prüfpräparaten" the omission of some labelling details under defined circumstances or under other justified conditions.

2.2. Circumstances where the removal of Expiry Dates could be justified

2.2.1. Conduct of Phase I clinical trials in Phase I Units

Even though IVRS/IWRS are often not used in Phase I clinical trials, exceptions may exist (e.g. biologics). 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 the following conditions:

- 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
- A copy of the certificate, e.g. the certificate of analysis (COA) or the certificate of compliance (COC), covering the batch(es) or kit numbers to be used, containing the use-by date and the dated signature of the QP is available to the Principal Investigators and Pharmacy at the phase I Unit. Provision should be made in documentation for the confirmation of the check of the expiry date prior to administration or dispensing
- IVRS/IWRS shall deliver a printout ('assignment report') for each allocated kit with information on trial subject, individual kit identifier and use-by date.

2.2.2. Conduct of Phase II to Phase IV clinical trials

Omission of the labelling of the use-by date could be justified if the following conditions have all been met:

- 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. Provision should be made in documentation for the confirmation of the check of the expiry date prior to administration or dispensing
- IVRS/IWRS shall assign individualised IMP-kits per visit with a suitable expiry to cover the period between visits
- IVRS/IWRS shall deliver a printout ('assignment report') for each allocated kit with information on trial subject, individual kit identifier and use-by date. It should be identifiable that the use-by date of the study medication is valid beyond the planned administration with adequate additional days prior to the expiry date in case of a delay in dosing. This buffer should be defined per clinical trial, under consideration of e.g. delays of administration due to unfavourable patient conditions, transport and distribution logistics, etc. This should be documented in the IVRS specification.
- 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

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:

- The pharmacist 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
- 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 planned administration with adequate additional buffer in case of delays as defined in the protocol and/or IMP handling procedures

- The labelling process should be described in a Standard Operating Procedure and adequate 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 within the scope of the effective regulations Directive 2005/28/EC.
- The final responsibility resides with the investigator.

2.2.3. Circumstances when this is not currently appropriate

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 the expiry date as provided by the manufacturer should be included on the original label. This is for reasons such as:

- Patients not returning kits and then utilising them past their expiry date.

2.3. Conditions surrounding the system and process

The following prerequisites for use-by updates in the IVRS/IWRS are required for the above processes to be acceptable.

2.3.1. Definition of standards for specification of IVRS/IWRS systems

Expectations for the validation of the system are detailed in Good Automated Manufacturing Practice (GAMP) and translate to the IVRS/IWRS setting. It is expected that GAMP principles would therefore be applied. Where a system is used it is expected that the National Competent Authority be notified by the inclusion of a statement in the protocol indicating that in IVRS/IWRS will be used. 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. It is expected that the sponsor should notify the QP of the validation status of the IVRS/IWRS and any auditing that the sponsor has undertaken.

Adaptation of Annex 11 for the validation requirements as well as the application of GAMP standards is required. As a minimum the following should be in place.

2.3.1.1. IVRS/IWRS validation

- Regardless of what clinical research activities are undertaken by the provider then the sponsor should assure themselves that they have adequately validated the system. This system should be subject to a robust change control procedure
- 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
- 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

- 150 • All incidents affecting functionality should be fixed prior to release and this documented
- 151 appropriately. A SOP should be established to record and analyse incidents and to enable
- 152 corrective actions to be taken
- 153 • There should be a formal sign off prior to use
- 154 • A readily accessible audit trail should be available for all data corrections and changes
- 155 • Key steps should be subject to review and sign off by an independent department (QA/QC).

156 **2.3.2. Expected Standards for Quality Systems**

157 The quality system at the provider should include:

- 158 • A system for recording, investigating and reviewing quality deviations
- 159 • Formal Standard Operating Procedures for GMP/GCP relevant processes and activities
- 160 • Training records
- 161 • A system for the control of change
- 162 • Formal corrective and preventive action system
- 163 • A programme of self inspection.

164 **2.3.3. Expectations of the System itself**

- 165 • Access permissions (personnel with these access rights at the site should be qualified for this
- 166 delegated activities)
 - 167 – Blinded and unblinded
 - 168 – Internal staff
 - 169 – Study staff
 - 170 – Site staff.
- 171 • Stock control
- 172 • Emergency unblinding, where applicable
- 173 • Disaster recovery
- 174 • Translations as required
- 175 • Audit trail
- 176 • Recall of product from warehouses and sites
- 177 • Real time updates to the system to ensure data is current
- 178 • Accessible 24 hours a day where studies are global or where there are other needs for example
- 179 blind breaking.

2.3.4. Expectations of the Sponsor

2.3.4.1. Sponsor responsibilities

- The sponsor will be expected to have undertaken some form of audit of the provider
- The sponsor should clearly define the study access permission requirements
- The sponsor should discuss any additional labelling or activities to be undertaken by the pharmacy at any pre-study visits
- The sponsor should assure themselves through UAT of the suitability of each system.

2.3.5. Updating of the System (including expiry updates)

2.3.5.1. Process at the Sponsor for expiry updating

- 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
- 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
- Change control procedures (QC) have to be implemented including QC check at critical steps and any changes to program coding. The sponsor should confirm that this is the case.

2.3.5.2. Process between sponsor and provider for expiry update

- 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 email is not sufficient for this purpose
- The sponsor should ensure that the information is shared between the correct parties at the provider
- The sponsor should have some confirmation that the update has been undertaken, in an appropriate timeframe.

2.3.5.3. Process at the provider for any changes

- It is important that any changes made to the database 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
- For changes made at an individual kit level, these checks should also be verified by a second person and the outcome documented
- The provider should inform the sponsor that the update has been completed
- The system should include dates after which shipments should not be made from the warehouse to investigator sites or after which the treatment should not be dispensed which would include provision of the length of treatment
- Consider time taken for shipments to reach different countries.

2.3.5.4. Process at the sponsor for the update of the expiry

- Where the system has been built to allow the sponsor to update the expiry themselves, conditions surrounding the process in 2.3.4.1 apply and additionally
 - There should be designated individuals in the sponsor who can perform this task
 - This update should be subject to some form of verification, both of the change and the “release” of the material
 - This module of the system should be validated to equivalent standards.

2.3.5.5. Other changes

- 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.

3. Conclusion

This reflection paper seeks to provide the current thinking of the Inspector’s working groups on the use of Interactive Voice/Web response systems, with particular mention of the removal of expiry dates from Investigational Medicinal Product. The paper seeks discussion on this topic from the wider pharmaceutical industry.

4. References

White Paper by the ISPE/PDA Expiry Date Task Force 2009

German Ordinance on GCP

Current version of GAMP

EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Annex 13, Investigational Medicinal Products

Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Annex 11: Computerised Systems http://ec.europa.eu/health/files/eudralex/vol-4/annex11_01-2011_en.pdf

Annex I

QP DECLARATION ON USE OF IVRS in the event of use for handling Expiry dates

I confirm that I am a QP and am authorised to make this declaration.

I declare that compliance with GCP and GMP requirements has been assessed for the IVRS system named below and found to be satisfactory.

Name of IVRS provider and assembly site and distribution site	Date of last audit (completion)

NB: If substantial changes are made at the provider then it would be expected that some form of due diligence is undertaken.

Audit conducted by third party

Name of IVRS provider and assembly site and distribution site	Third party	Date of audit (completion)

If an audit of the site has not been performed by or on behalf of the QP, please provide a brief justification and explanation on how the QP knows that standards at least equivalent to EU GMP and GCP are being followed at the site.

This declaration is submitted by:-

Signatory _____ Date _____

Print name _____