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DISCLAIMER

This reflection paper was initially published on 10 December 2013 under reference EMA/INS/GCP/600788/2011. It was updated on 02 February 2022 under reference EMA/61464/2022 in view of the entry into application of the Clinical Trials Regulation (CTR) No. 536/2014, only to clarify that the removal of expiry dates from the labels was not allowed for clinical trials conducted under the CTR. In line with the Commission Delegation Regulation (EU) C(2022)6240 amending Regulation (EU) No 536/2014 of the European Parliament and of the Council as regards labelling requirements for unauthorised investigational and unauthorised auxiliary medicinal products for human use, published on 06 September 2022 and eliminating the obligation to include an expiry date on the immediate packaging of unauthorised medicinal products used in clinical trials in specific circumstances, the wording in section 2.3 of this reflection paper is now reverted back to its original wording.
The list of references (Section 4) has been updated accordingly. The rest of the reflection paper was not reviewed and reflects the state of thinking at the time of initial publication. Additional information on the expected requirements for interactive response technologies may be found in the Guideline on computerised systems and electronic data in clinical trials, once finalised.

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Reflection paper on the use of interactive response technologies (interactive voice/web response systems) in clinical trials, with particular emphasis on the handling of expiry dates

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1. Introduction

Over the last 15 years there has been an increasing utilisation of interactive response technology (IRT), encompassing both interactive voice response systems (IVRS) utilising the telephone or tone diallers and interactive web response 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 emergency unblinding (code-breaking), dose titration and expiry date updating. This of course may, if not handled appropriately, pose an increased risk to the patient and so IRT is of increasing interest to national competent authorities (NCAs).

Sponsors have previously contacted the regulatory agencies with requests to omit the expiry date on study medication in the case of IRT use. The claimed advantage of this approach included avoiding issues related to relabelling of the expiry date on site, which can often cause issues in themselves with poor control of the expiry update labels. However, based on experience from, for example, GCP inspection findings around IRT validation and the dispensing of expired study medication to patients, the request of the sponsors raises concerns for regulatory authorities.

This paper seeks to provide guidance on what NCAs expect from such systems and in particular their use for handling of the expiry date of the Investigational Medicinal Product (IMP). These positions will form suggestions for sponsors and IRT providers on the validation requirements for systems. Specific computer system validation is not discussed in detail since this is the subject to a large number of other publications. This paper is aimed at sponsors and providers of such systems.

Currently, the information surrounding the use of IRT in the clinical trial authorisation (CTA) applications is only included with reference to IRT use in randomisation where this function is outsourced. As a consequence the national competent authority might have little knowledge of the extent of use of these systems, particularly where the system is an in-house one. For this reason it would be helpful if Appendix I be completed by the sponsor and submitted to the NCA along with the CTA.

2. Discussion

2.1. Legal basis

Currently the worldwide regulations regarding expiry date on labels of IMP are not uniform. In Japan the expiry date on the IMP label is not a mandatory requirement, nor does such a requirement exist in the USA Code of Federal Regulations. In Europe, under the Clinical Trial Directive (2001/20/EC), the labelling of the expiry date on the IMP is required except in certain circumstances. Annex 13 (refer to section 4 'References') allows for omission of some information when the absence can be justified; Annex 13 states: "the following should be included on labels, unless its absence can be justified, e.g. use of a centralised electronic randomisation system." Some Member States have implemented the above mentioned provision of Annex 13 in their national regulations, for example Germany. Under the Clinical Trial Regulation however, the expiry date shall not be omitted from the label regardless of the type of product and packaging (see Annex VI, D, point 9).

2.2. Conditions surrounding the system and process

The following sections discuss the general requirements for any IRT system, the expectations for the validation of the system and the responsibilities of the sponsor and the IRT provider, or the sponsor alone if the IRT system is an in-house one.

2.2.1. Definition of standards for specification and validation of IRT systems (responsibilities of the provider, this can include an in-house department)

The validation of the IRT system should be in line with the expectations of Annex 11, Volume 4 of Good Manufacturing Practice, and Medicinal Products for Human and Veterinary Use, hereafter called Annex 11. The principles of Good Automated Manufacturing Practice (GAMP) should be considered.

Where a system is used it is expected that the NCA be notified by the inclusion of a statement in the protocol, whenever possible, or at least some notification of the intent to use an IRT. The EudraCT form does not currently provide provision for this information, only where this is used for randomisation and outsourced. Where the system is used to control expiry dates a QP declaration is requested (Appendix I). To provide visibility of the expiry date process it is recommended that this declaration be included in the product specification file, the trial master file and the CTA application documentation. It is expected that the sponsor should notify the Qualified Person (QP) of the validation status of the IRT and any auditing that the sponsor has undertaken.

With regards to the validation, as a minimum, the following should be in place:

- Regardless of what clinical research activities are undertaken by the IRT, the sponsors should assure themselves that the IRT provider has adequately validated the system. This system should be subject to a robust change control procedure. The expectations would be the same for any in-house system.
- A user requirements specification (URS) or equivalent should be produced and approved by the sponsor. Any subsequent validation 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 tested.
- Client user acceptance testing (UAT) should always be offered to sponsors. This is an opportunity for the sponsor to test the system and this should be undertaken, preferably with test scripts written by the sponsor.
- All incidents affecting functionality should be fixed prior to release and this should be documented appropriately. It is acceptable for some bug fixes to be remedied at a later stage if they do not affect the initial calls into the system, for example an end of study visit (with the exception of early withdrawals); however, it is expected that a plan for fixing such incidents should be in place prior to the system going live. There should be clear traceability of the testing of these fixes right back to the URS.
- It is recommended that key steps should be subject to review and sign off by an independent department (QA), which could be at the IRT provider or outsourced.
- There should be a formal sign off of the system prior to use.
- When changes are made to the protocol, the sponsor should assess the impact on the IRT system and preferably contact the IRT provider to discuss. Changes to protocol do not always immediately appear to impact on the supplies; it is good practice to include the clinical supplies staff in these discussions and then ultimately the IRT provider as necessary. Where changes are subsequently made to the IRT system, the same standards of validation should apply.

2.2.2. Expected standards for quality systems (responsibilities of the provider, this can include an in-house department)

The quality system encompassing the IRT system should include:

- Standard operating procedures (SOPs) for GMP/GCP relevant processes and activities.
- A system for recording, investigating and reviewing quality deviations. This allows any bug fixes during development to be traced back to individual requirements of the system.
- Training records for all those involved in the development and day to day running of the system. This should include help desk personnel.
- A system for the control of change. Any changes required while the system is live should be subject to a change control process to ensure the impact on other functionality is assessed for any changes required.
- A corrective and preventive action system to facilitate the tracking of QA findings and their resolution.
- A programme of self inspection.

2.2.3. Expectations of the system itself

IRT systems can be designed to facilitate a number of clinical research activities which may include the following as detailed below. Where inclusion in a system design is essential this has been highlighted with an asterisk (*).

- Access permissions* - personnel with these access rights at the site should be qualified for these delegated activities. These permissions should be included in the project specification. It is important that the permissions be clear with respect to their ability to see what trial medication is being taken by a subject (blinded versus unblinded). Access permissions might include but not be limited to the following staff:
  - pharmacy staff;
  - principal investigator;
  - site research team, including any study coordinator, research nurse or sub-investigator;
  - contract research associate (CRA), where applicable;
  - sponsor staff, including project managers, clinical supplies staff.
- Control of investigational medicinal product – where this is controlled by the IRT system, it should be implemented in such a manner to ensure that sites have appropriate IMP and that subjects do not run out of medication.
- Emergency unblinding, where applicable - there should be provision to include the opportunity to unblind in an emergency with defined access permissions. These access permissions should not preclude the investigator from emergency unblinding without contacting the sponsor.
- Disaster recovery system* - there should be back-up systems in place such that if there is a server break-down the IRT is still able to keep running. There will be occasions when the system is down and the provider should have prepared for these such that manual interventions can be made, documented and the system updated when it is fully operational again.
- System access - the system should be accessible 24 hours a day where studies are global or where there are other needs, for example emergency unblinding.

- Translations as required - any translation should be verified to ensure that it is accurate and appropriate.
- A readily accessible audit trail* - audit trails should be available for all data including any alterations to the data either as a result of interacting with the system or manual interventions.
- Product recalls - the recall of product from warehouses and sites should be able to be facilitated.
- Currency of data - the system should be updated in real-time to ensure data is current.
- The system should include dates after which shipments should not be made from the manufacturer or warehouse to investigator sites or after which the treatment should not be dispensed which would include provision of the length of treatment.
- The time taken for shipments to reach different countries should be considered. This could be by the use of offset times in the system, i.e. including provision in the supplies for an extended shipment period for countries further afield.

2.2.4. Expectations of the sponsor

- The sponsor will be expected to have undertaken audits of the provider at appropriate intervals by adequately qualified auditors. This task could be outsourced to a third party.
- The sponsor should ensure that URS meets the needs of the protocol and the IMP.
- The sponsor should clearly define the study access permission requirements. This should include which staff are blinded to the study treatment.
- The sponsor should discuss any additional labelling or activities to be undertaken by the pharmacy at any investigator meetings, pre-study visits or initiation visits.
- The sponsor should assure themselves through UAT of the suitability of each system. It is expected that the sponsor write their own test scripts for testing the system. This should include not only sponsor activities undertaken in the IRT, but also investigator activities.

2.2.5. Updating of the system for expiry date changes

2.2.5.1. Process at the sponsor for expiry updating

- This updating process should only be undertaken after review of stability data and the extension of the expiry date of IMP by the QP. A process by which expiry dates are updated needs to be in place at the sponsor site.
- When stability data supports an extension to the expiry date this change should be communicated in the form of a revised certificate of analysis (CofA) or certificate of conformance (CofC), which includes the expiry date. This extension will have to have been approved in the CTA via an amendment, unless the expiry date extension plans have already been authorised as part of the investigational medicinal product dossier (IMPD).

2.2.5.2. Process between sponsor and IRT provider for expiry updates

- A robust process should exist between the sponsor and the IRT provider to ensure that the new expiry date is well communicated and with sufficient time for the update to be implemented and verified. A regular email is generally not sufficient for this purpose (inspectors have seen cases

where emails indicating an update to expiry have been sent by clinical project managers; it is expected that staff involved in the IMP manufacturing process, for example the QP, be involved in this expiry date update process). There should be some understanding at the provider as to who is able to update the expiry date and by what mechanism this will take place.

- The sponsor should ensure that the information is passed to the correct individual or department at the IRT provider.
- Where there is a web interface to provide an update of the expiry by the sponsor, access to this area should be controlled and reserved for those with the authority to make changes to the expiry date.
- Where another computer system (drug supply system) links to the IRT system to provide expiry information, this link should be thoroughly validated, such that any change in expiry date in the drug supply system is mirrored in the IRT system.
- The sponsor should have some confirmation documented in the trial master file (TMF) that the update has been undertaken in an appropriate timeframe.

2.2.5.3. Process at the provider for any changes

- It is important that any changes made to the data in the system 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; this may be by paper or electronically.
- For changes made at an individual kit level, these checks should also be verified by a second person and the outcome documented on paper or electronically.
- The IRT provider should inform the sponsor that the update has been completed.

2.3. Circumstances where the removal of expiry dates could be justified

The responsibility for the expiry date remains with the sponsor regardless of whether or not the expiry date appears on the labels.

2.3.1. Conduct of phase I to phase IV clinical trials

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

- a copy of the certificate, e.g. CofA, CofC or equivalent, covering the batch(es) or kit numbers to be used, containing the expiry date and the dated signature of the QP is available to the investigator and pharmacy staff as appropriate;
- IMP is administered by dedicated trial staff, which is qualified in that Member State to perform such duties, and no additional IMP is retained by the subject. Provision should be made in documentation for the confirmation of the check of the expiry date prior to administration or dispensing;
- IRT shall assign individualised IMP-kits per visit having a suitable expiry date to cover the period between visits. For open label studies these kits might not have a kit number as they are identified by the batch number in these circumstances;

- assignment confirmations should be made available to site personnel in an electronic or paper format for each allocated kit with information on trial subject, individual kit identifier (where appropriate) and expiry date. The expiry date of the study medication should be valid beyond the planned administration with adequate additional days prior to the expiry date in case of a delay in dosing and to account for visit windows. This buffer should be defined per clinical trial taking into consideration items such as delays of administration due to unfavourable patient conditions, transport and distribution logistics. This should be documented in the IRT specification;
- the assignment report should be checked by the investigator, or delegated person administering the IMP. This check should be documented and filed with the investigator site file.

2.3.2. Expiry date labelling at an investigator site or institution

A pharmacist or other person legally authorised in the Member State may manually add the expiry date on the label with a placeholder for this information when all the following conditions are met:

- the pharmacist or legally authorised individual has access to IRT;
- the system should provide the pharmacist or other legally authorised individual, for each allocated kit, information on trial subject, individual kit identifier and expiry date. This can be by way of a printout ('assignment report') or email or via access to the web;
- the kit labelling information is stored in the trial master file. This should include label reconciliations and confirmation of what was labelled;
- on administration or dispensing the pharmacist or authorised individual ensures that the expiry date of the study medication is beyond the planned administration having adequate additional buffer in case of delays as defined in the protocol and/or IMP handling procedures;
- the labelling process is described in a procedure at the site and adequate documentation is maintained and filed in the trial master file to evidence the process;
- the process is clearly defined in the protocol, or other documentation, for example a pharmacy manual. This alternative is currently already possible within the scope of Directive 2005/28/EC.

The final responsibility for the administration of the IMP resides with the investigator.

2.3.3. Circumstances when this is not currently appropriate

There is currently no justification for omission from the clinical trials label of expiry date if the IMP is handed out to trial subjects for use at home.

Where there is no possibility to add an additional label in accordance with the conditions described in section 2.3.2, the expiry date as provided by the manufacturer should be included on the original label.

3. Conclusion

This reflection paper seeks to provide the current thinking of the inspectors working groups on the use of interactive response technology systems, with particular mention of the removal of expiry dates from investigational medicinal product, for clinical trials conducted under the Clinical Trial Directive (2001/20/EC). It should be noted that this is a reflection paper and does not constitute guidance as outlined in European or national laws.

4. References

- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- EU Guidelines to Good Manufacturing Practice and Medicinal Products for Human and Veterinary Use Annex 11, Computerised Systems
- EU Guidelines to Good Manufacturing Practice and Medicinal Products for Human and Veterinary Use Annex 13, Investigational Medicinal Products
- GAMP® Good Practice Guide: A Risk-Based Approach to Operation of GxP Computerized Systems
- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
- Commission Delegation Regulation (EU) C(2022)6240 of 6 September 2022 amending Regulation (EU) No 536/2014 of the European Parliament and of the Council as regards labelling requirements for unauthorised investigational and unauthorised auxiliary medicinal products for human use.

Appendix I

QP DECLARATION ON USE OF IRT in the event of use for handling expiry dates

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

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

EudraCT #:

Protocol #/Title:

Name of IRT provider	**Date of last audit of IRT Provider (completion)**

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

Audit conducted by third party

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:

Signature _____ Date _____

Printed name _____