



Competent Authority (UK)
Medicines and Healthcare products Regulatory Agency

Guidance for notified bodies on the regulation of IVDs for self-testing

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1 Scope

Home testing is a growing area of health care that places new opportunities and responsibilities on those requiring healthcare. Users of in vitro diagnostics (IVD) for self-testing ('self-tests') will not have the benefit of a healthcare professional on hand to advise them how to perform the test or to analyse and interpret the results. It is therefore vital that self-tests are suitable for lay use.

The manufacturer of a self-test not covered in Annex II the IVD Directive [1], in addition to complying with the requirements for general IVDs must lodge an application with a notified body for the examination of the design of the device (section 6 of Annex III [1]). This will include aspects affecting its suitability for non-professional users.

More information on the regulation of IVDs for self-testing can be found in the MHRA guidance [note 19 'Guidance on the In Vitro Diagnostic Medical Devices Directive'](http://www.mhra.gov.uk) (www.mhra.gov.uk)

As part of a notified body's assessment of an application for a design examination certificate, it will review the studies that demonstrate the suitability of the device for a lay user alongside the labelling and instructions.

This guidance is intended to support the notified body assessment and although it is not aimed directly at manufacturers of self-tests, notified bodies may wish to share this guidance with prospective clients in order to demonstrate regulatory expectations.

This guidance is not aimed at people who use self-tests.

2 Lay studies for self-test devices

Notified bodies should assess the following:

- 1) Device.** Notified bodies should encourage manufacturers to provide an example of the actual device (where practicable). The device may be returned on completion of the review if required. The notified body will always need to see the current copy of all labelling.
- 2) Test reports.** Ensure test reports provide sufficient data to support all performance claims.

Consider also the following elements as appropriate to the device and intended use:

- Data to support sample type and storage as per intended use and labelling. The use of samples with results outside the expected range for the test may be appropriate.

- Environmental exposure limits / defined usage range, e.g. temperature and humidity. (See EN ISO 15197 [2] for more guidance as specifically applied to glucose monitoring systems)
- Mechanical resistance to shock, vibration, water damage, etc. (See EN ISO 15197[2] for more guidance as specifically applied to glucose monitoring systems)
- Safety and reliability testing, e.g. electrical and mechanical hazards. (See IEC 61010 [3] and IEC 61326 series[4])
- Software validation

3) Lay user studies. It is an expectation that lay user studies would be performed for all self-test devices unless similarity to previous devices renders this unnecessary. If not included, the notified body should critically assess the documented rationale for this decision.

Lay user studies are designed to test the ability of individuals without specialist training or knowledge to use and understand the results of the device itself in conjunction with the information provided on the labelling or accompanying instructions for use (IFU) to deliver effective results. Manufacturers should have identified the profile of the target end user as part of their technical documentation. Although aimed at blood glucose testing, EN ISO15197 [2] gives general guidance on running a lay user study. The MHRA document '[Guidance for manufacturers on clinical investigations to be carried out in the UK](#)' (available on our website www.mhra.gov.uk) may be of help in assessing the suitability of the lay user study.

Consider the following elements in assessing lay user studies:

- A lay-user trial protocol would be expected to include experimental design, data analysis and acceptance criteria
- The trial should replicate the conditions of use and the profile of the target end user.
- Device design and instructions for use (IFU) used in a successful trial should be the same as that submitted for assessment by a notified body. Improvements resulting from Lay study, e.g. text font/ layout, etc. may be incorporated subsequent to the study, but any substantive changes should be documented and risk assessed to determine whether further studies are required
- Studies should be designed proportionate to the complexity of the device and the clinical risk associated with the product.
- There are four main elements to a lay user study:
 - > sample collection (e.g. urine 'in-stream' and 'collect and dip') ease and correctness of obtaining sample.
 - > use of the device by following the labelling and instructions for use
 - > reading of results
 - > interpretation of results.
- The overall study should include all four elements. For some tests these elements may need to be performed in separate parts. For example, it may be appropriate in some studies to provide the subject with a sample of known value around the cut-off to determine whether the subject can obtain the

correct result; however, a different study may test whether the subject can obtain a sample using the IFU and conduct the test.

- Pre-determined samples may be useful in addition to the individual's own sample. Samples may be supplemented by random-coded/ contrived samples with values obtained by an accepted measurement method where appropriate. For example, samples of known value may be needed:
 - > for higher risk devices
 - > for low prevalence diseases
 - > to cover analytical range of device
 - > to assess the appropriateness of sample type for the study; or
 - > for ethical reasons.
- The study should be supervised by an identified professional person who will objectively verify the lay person's results. The supervisor should not tutor subjects in following the IFU. The manufacturer should audit the trial to ensure it has been conducted according to the protocol.
- The number of participants in the lay user trial should be sufficient to cover the profile of the end user for each of the four elements of the study. The trial is intended to determine the usability of the device, typically subjects of appropriate demographics representative of the appropriate end user population are used in trials. Consider factors such as:
 - > age
 - > socioeconomic background
 - > health (if samples are being provided by end user in trial, consider the impact of underlying health issues on the results – remember lay user studies are usually primarily concerned with the usability of the device, not necessarily for establishing clinical validity and interferences)
 - > lay user ability (e.g. consider impact of impaired eyesight, colour-blindness, motor skills, learning difficulties etc.)
- Study outputs could include:
 - > ability to take own sample correctly and deliver a valid result
 - > ability to obtain the correct result with pre-determined samples
 - > questionnaire on ease of use of device and instructions,
 - > interpretation of results, etc.
 - > supervisor's feedback on performance of test and IFU.
- Difficulties identified in a trial for use of devices and clarity of the instructions should be captured in the study documentation and addressed in the risk management and design process.
- Are the ergonomics of the device suitable for the target end user?

3 Labelling requirements for self-test IVD devices

Annex I of the IVD Directive [1] defines the requirements for the information to be supplied by the manufacturer under essential requirement 8 (ER 8), which must be appropriate for the training and knowledge of the potential user. Labelling includes the device labels and the instructions for use. Virtually all parts of ER 8 apply to self-test devices, but there are some specific labelling requirements for self-test devices only, under ER 8.7 (t).

These focus on the need for the labelling to be readily understood by a non-professional or lay user, including the concept of false negative/positive results, what actions to take based on the results and advice to consult a medical practitioner and not to change medication or treatment based on the result unless trained to do so. Potentially manufacturers can choose to omit some information which is not relevant to non-professional users.

To be able to adequately meet these requirements, manufacturers should consider the issues set out below, although this is not an exhaustive list and other issues may be relevant for particular devices.

When assessing the information to be supplied with the device, notified bodies should consider the following:

- **Copy of instructions for use (IFU):** For self-test devices, there must be an IFU with each test kit in paper or hard copy form. The use of e-labelling or the supply of IFU by other means can only be employed for professional user devices
- **Clear instructions:** The instructions or directions for using the test must clearly describe how to use the test properly to get the correct result in terms that a non-professional user can understand. It should address all the areas of risk for incorrect use identified in the manufacturer's risk assessment, to minimise the user error. e.g. timing of test, stability of results (user not to read after a certain period of time), biosafety (disposal of samples, used fingersticks, used test), use of internal control
- **Design of test:** critical elements of the actual design of the test should be addressed in the IFU to ensure the test is used correctly. Examples could be the sample type required, how the sample is collected ensuring no contamination, sample size required and steps to take if insufficient sample is obtained, and special conditions of use e.g. does the device have to be kept on a flat surface.
- **Intended use of device:** name of test/description of device and principles of test. Depending on the type of test a clear description of what the test result will mean to the patient e.g. test for analyte or biomarker compared to a test for a disease or condition. This should be made clear to the user in appropriate terms for a non-professional
- **Limitations:** the limitations of the test should be clear and understandable, to ensure that lay users don't attempt to use the device in circumstances that will affect the performance or outcome of the result, e.g. for a blood glucose test do not test immediately after eating because elevated blood glucose levels after a meal will not give an appropriate result. For pregnancy tests, hormone medication will affect the test. The concept of false negatives and false positives should be explained and put into context.
- **Interpretation of results:** The IFU should explain to lay users how to determine that the test has worked, including how to interpret an internal control (if included) as well as how to read the result e.g. positive or negative. Where there are potential variants or borderlines, they must be able to interpret these correctly e.g. only faint lines on a rapid pregnancy test; where appropriate further action should be indicated e.g. repeat test in X number of days.
- **Clarity of IFU:** How the IFU are written is extremely important for lay users to ensure that they understand what the test is for, what the results mean and how to use it correctly. Manufacturers could make use of the Flesch Reading Ease Score, which looks at average sentence length and syllables per word and rates

text for ease of reading (available as a tool in Microsoft Word and in other word processing packages). Guidance on clear writing is also available from the UK Plain English Campaign. Use of technical words e.g. desiccant, in vitro, should be avoided or explained.

- **Space limitations:** Space is often limited on IVD devices and immediate labelling. As a general guide the higher the risk the closer to the test it should be, so for example the lot number and expiry day should be on the immediate packaging.
- **Minimum amount of information required:** The performance of the kit should be described in a way that a lay user can understand. There may be key performance indicators or a minimum amount of information needed to be meaningful to a lay user.
- **Readability of IFU:** The physical presentation of the IFU can also have an impact - the size and type of font, colour, the line spacing and print and paper quality, all need to be sufficient for the lay user to be able to read. Text size, line spacing and colours should enable the IFU to be readable by the types of users intended for the test. IFU, warnings and results for devices specifically intended for users with visual impairment should be accessible to the intended audience. RNIB have produced guidance on accessible formats (http://www.rnib.org.uk/professionals/accessibleinformation/accessibleformats/Pages/accessible_formats.aspx)
- **Use of pictures:** Diagrams or pictures may be a simple and effective way of providing information, but they must also be clear and accurate, and match the actual device. Often these are used to show how to read results, so must be consistent with the instructions in text. Illustrated instructions may be helpful in addition to written instructions.
- **Language:** Self-test devices must have labelling information in the language(s) of the country where they are placed on the market, so where a manufacturer has several different language versions, there must be a correct translation to ensure clear instructions in that specific language. Mistranslation or poor grammar can cause issues with the comprehension of the text. The notified body will review the English text but will ensure that there is a suitable procedure for translation and verification of translation.
- **Accuracy and relevance of information:** Manufacturers can choose to limit the detailed analytical performance characteristic information in the IFU for self-test devices. However, the key performance for lay users should be identified, such as accuracy or sensitivity, in terms that are understandable. For example "Results may vary by up to 10%" could be more meaningful than "10% coefficient of variation" Where devices are intended for use by lay and professional users, any conflict of the needs of these different users must be resolved.
- **Medical practitioner:** The IFU must have a clear statement that directs lay users to seek a consultation with their medical practitioner before making medical decisions, and this is critical where the device is used for monitoring an existing disease. The IFU must advise the user not to change their treatment or medication without training or consultation.

Notified body assessment of self-test devices should include all the labelling and a sample of the actual device itself, to be able to verify that the labelling is clear and usable for non-professional users, and corresponds to the actual device.

3.1 Content of labelling for self-test devices

In July 2010, the new EN ISO 18113:2011 series of standards for labelling of IVD medical devices were harmonised by publication in the Official Journal (OJ) by the EU Commission. These have the same scope as the current standards that they will supersede. At present, manufacturers are able to claim compliance with either set of standards, but the current standards will expire on 31/12/2012, the date on which they will cease to provide a presumption of conformity.

For self-test devices, the key harmonised standards are therefore:

EN ISO 18113-4:2011- In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 4: In vitro diagnostic reagents for self-testing [5]. This replaces the current EN 376:2002

EN ISO 18113-5:2011 - In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 5: In vitro diagnostic instruments for self-testing [6]. This replaces the current EN 592:2002

Symbols may be used on the labels in accordance with the requirements of BS EN 980:2008 [7]. The requirements of ISO 15223-1 [8] also apply but this is not yet a harmonised standard.

3.2 Information to be provided on the outer container label

This is the information that would usually be provided on the outer carton or packaging of the product and should enable the user to identify the purpose of the test and what is being measured. It should contain the following information:

1. Manufacturer's name and address, including that of the authorised representative if applicable. The address should include the following information:
 - Street/road
 - Number/house/floor
 - Postal code
 - City
 - State/region
 - Country.
2. IVD reagent name i.e. brand name. This may also include a catalogue number. Where the name does not indicate the intended use, this should also be included on the label. It should also be clearly indicated that the assay is for self-testing e.g. blood cholesterol self-test.
3. A statement, or appropriate symbol, that the test is for in vitro diagnostic use.
4. Batch code, preceded by the word 'LOT'.
5. The contents should be identified e.g. number of tests/devices contained in the package.
6. Storage and handling conditions, in particular any factor that may affect the performance of the test e.g. storage temperature, exposure to light.
7. The label should state what type of sample is required to perform the test e.g. blood, urine or saliva.

8. Expiry date of the test.
9. Additional information:
 - Data on disease effects and prevalence should be accurate.
 - The outer label may also include the need for additional materials.
 - Further contact details (e.g. email addresses, helpline numbers and website details) should be accurate.

3.3 Information of the immediate container label

This is the information that should be provided on the label of each component where a test contains several components. The labels on the components should enable the user to identify each component and where practicable contain the same information as for the outer label. If the label is too small to contain all the information, then the most pertinent information should be included e.g. storage of reagents and shelf life once opened.

If the immediate label is the only label for the test, then it must contain the information as specified for the outer container label.

4 Information in the instructions for use (IFU)

1. Manufacturer's name and address in the same format as for the label. The authorised representative's address shall be included if applicable.
2. The information given in points for the outer container label except for points 4 and 8.
3. A brief summary of the principles of the examination method and the analyte being determined and how this is used to diagnose a condition or physiological state.
4. The kit contents, plus any additional items to perform the test
5. Any warnings or precautions to take including the handling of any hazardous materials, disposal of device or solutions. These should have been identified in the risk assessment for the device
6. A section on test limitations (from the risk analysis) should be included i.e. sample type, time of sample collection and the possibility of false negative or false positive results. It should also give any factors that can affect the test result e.g. age, gender, menstruation, infection, exercise, fasting, diet or medication. The user must be told to consult a physician to confirm the diagnosis or before changing medication on the basis of the result, unless the user has received training in adapting treatment where the test is used to monitor an existing condition.
7. Details of the test procedure should be given, including: any reagent preparation; sample collection and/or preparation; running the test and reading the result. This may be done with the use of pictograms. The results must be presented in terms that are understandable to the lay user, with a positive and negative result clearly defined with a clear description of visual results if applicable. A statement that the control (if included) must give a result for the test to be considered valid

8. Information on the interpretation and understanding of the result must be provided in an easily understandable form e.g. a positive result indicates possible pregnancy. Where a quantitative result is obtained, an explanation of normal, high and low results should be provided. It should be re-emphasised that a positive or abnormal result would need to be confirmed by a physician and for any results a physician should be consulted before changing any medication based on the result obtained. Some lay users will already have consulted with a physician on changing medication based on their results (e.g. people with diabetes testing for blood glucose).
9. Suitable performance characteristics of the device shall be given in terms that the lay user can understand e.g. accuracy, specificity. For quantitative assays this should also include the range over which measurements can be made and instructions if the result falls outside this range.
10. A 'questions and answers' (FAQ) section may be included that gives further information relating to the interpretation of the result, principle of the test and any factors that may affect the result obtained.
11. Relevant literature references may be provided if appropriate.
12. The version number of the IFU should be stated.

5 Conformity assessment routes for self-test devices

There are four potential conformity assessment routes available to manufacturers of self-test devices. The annexes listed below are from the IVD devices directive [1].

1. EC design examination – Annex III.6
2. Full quality assurance – Annex IV
3. EC type examination plus EC verification – Annex V + VI
4. EC type examination plus production quality assurance – Annex V + VII

Annex III.6 and IV are by far the most popular routes applied by manufacturers.

When modules that review the design of the product are applied (Annex III.6 or Annex V) the notified body assesses the design and instructions for use to determine whether they are suitable for non-professional users, as described in the earlier sections of this document.

When the quality assurance modules are applied (Annex IV and VII) the notified body assesses the quality system to determine that it is capable of creating products whose design and instructions for use plus labelling are suitable for non-professionals.

In both of these approaches the notified body will review the outputs of design such as the data from lay user trials and instructions for use and labelling to ensure they are suitable for a non-professional users; however, in the quality assurance modules the notified body will also ensure that the design inputs and design process itself are suitable to create an appropriate design, this will include, for example, a review of the risk assessment as well as meet the requirement in Annex III and also ISO 13485:2003 [9] if applied by the manufacturer.

When full quality assurance is applied, this enables the manufacturer to more easily add more products within the approved scope because the notified body has approved the system used to create these devices and the new products can be reviewed as part of the routine surveillance programme.

5.1 Typical documents which will be reviewed by notified body for self-test devices

Design inputs

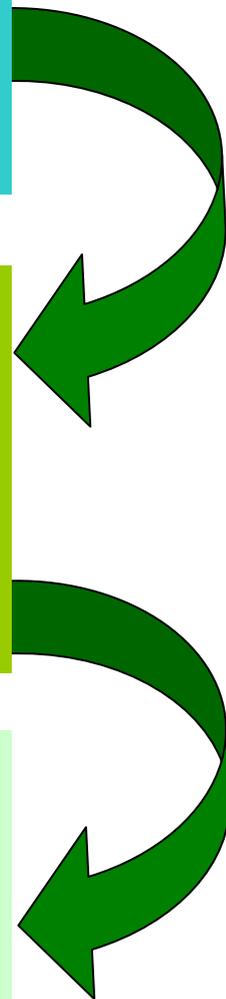
- Intended use / user profile
- Sample type
- Risk assessment
- Intended environment for use and storage
- Mechanical resistance
- Electrical safety
- Ergonomics
- Software.

Design verification / validation considerations

- Design of the lay user study protocol to address:
 - > user profile
 - > capability to obtain sample using IFU
 - > testing process
 - > reading the result
 - > result interpretation
- Content of performance evaluation
- Software validation.

Design output

- ER checklist
- Labelling / IFU
- Performance evaluation report
- Protocol and report of lay user study
- Annex VIII declaration (if performance evaluation study in EU)
- Risk management assessment.



5.2 Surveillance

Manufacturers who select Annex III.6 would not have a surveillance programme, and so would need to inform the notified body of changes to the design or IFU and labelling.

Manufacturers who select Annex IV or V + VII would have a surveillance visit at least annually to assess the quality system and review any changes.

For manufacturers who select Annex V + VI, the notified body would statistically sample and test product to ensure it still met the original type or design according to agreed modalities.

5.3 Transfer to another notified body

Notified bodies are required to accept the work of other notified bodies. For manufacturers who use Annex III.6, the notified body would review the existing certification including scope and expiry date and review the new labels and instructions for use bearing the new notified body number.

For manufacturers who select a conformity route including a quality assurance module, the transfer would include a review of the existing certification, including scope and expiry date and review the new labels and instructions for use bearing the new notified body number plus transfer of the IVD directive quality management system approval Annex IV or VII, which may or may not include ISO 13485 [8], plus the associated surveillance programme; this will require a review of recent audit reports and may also require a site visit. Provided the certificate is not close to expiry the new notified body will typically continue the surveillance programme as originally defined to ensure that the entire system is covered during the certification cycle. If the manufacturer uses Annex VI then the new notified body will need to establish new testing protocols and sampling criteria for the product.

The notified body taking on the device will always contact the original notified body to see if there are any reasons to prevent transfer.

6 References

1 Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. Official Journal L 331, 07/12/1998 P. 0001 – 0037.

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31998L0079:en:NOT>

2 EN ISO 15197:2003 In vitro diagnostic test systems -- Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus.

<http://www.iso.org/iso/home/standards.htm>

3 IEC 61010-1 ed3.0 Safety requirements for electrical equipment for measurement, control, and laboratory use - Part 1: General requirements. 2010

<http://webstore.iec.ch>

4 IEC 61326 Electrical equipment for measurement, control and laboratory use - EMC requirements. <http://webstore.iec.ch>

5 EN ISO 18113:2011 In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 4: In vitro diagnostic reagents for self-testing.

<http://www.iso.org/iso/home/standards.htm>

6 EN ISO 18113-5:2011 In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 5: In vitro diagnostic instruments for self-testing.

<http://www.iso.org/iso/home/standards.htm>

7 BS EN 980:2008 Symbols for use in the labelling of medical devices.

<http://shop.bsigroup.com>

8 ISO 15223-1:2011 Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements.

<http://www.iso.org/iso/home/standards.htm>

9 ISO 13485:2003 Medical devices - Quality management systems - Requirements for regulatory purposes. See also ISO 13485:2003/Cor 1:2009.

<http://www.iso.org/iso/home/standards.htm>

Website links correct at time of publication.