



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

**Assurance system regarding the
influence of medicinal products on
results of IVD tests**

RIVM Letter report 2018-0149
C. Moltó-Puigmartí et al.



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Colophon

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Synopsis

Influence of medicinal products on results of IVD tests

In order to make a diagnosis, a physician may decide to carry out a diagnostic test in a laboratory, for example based on blood samples. Some medicinal products can affect the outcome of a diagnostic test, making the result incorrect. It is therefore important that manufacturers, pharmaceutical companies and commercial laboratories exchange knowledge and information about the influence of medicinal products on the test result. Because this knowledge is not systematically shared with all interested parties, the information is not always known to them.

There is no central point where those stakeholders can find this information yet. In addition, laboratories are often unaware of the medication a patient is using. Therefore, it may not always be immediately clear that a medicinal product is the cause of a deviating test result. This is evident from research conducted by RIVM on behalf of the Health and Youth Care Inspectorate (IGJ).

Diagnostic tests in laboratories are called *in vitro* diagnostics (IVDs). The influence of medication, so-called interference, is not always known at the time an IVD is being developed. In some cases the interference becomes known after the IVD has been put on the market and used in laboratories.

If interference of a medicinal product with a diagnostic test is discovered, the manufacturer of the IVD will amend the instructions for use. Then laboratories know that they have to consider this interference when using the IVD.

It is unknown how often interferences between medication and IVDs occur. IGJ receives one or two reports of newly discovered interferences per year. It is possible that interferences are not always detected. The risk is therefore unknown. It should be noted that a physician often does not base his judgment exclusively on an IVD test. A doctor also often carries out other tests for diagnosis and considers the symptoms and complaints of the patient.

Keywords: medicinal product, *in vitro* diagnostic medical device, interference, risks, legislation

Publiekssamenvatting

Invloed van medicijnen op diagnostische tests

Om een diagnose te kunnen stellen, worden soms tests uitgevoerd in een laboratorium, bijvoorbeeld op basis van bloed. Sommige medicijnen kunnen invloed hebben op de diagnostische test, waardoor de uitslag niet goed is. Het is daarom belangrijk dat kennis en informatie over de invloed van medicijnen op de uitslag wordt uitgewisseld tussen bedrijven en laboratoria. Doordat deze kennis niet systematisch wordt gedeeld, is de informatie niet altijd bij hen bekend.

Er is nog geen centraal punt waar laboratoria, fabrikanten van tests en farmaceutische bedrijven deze informatie kunnen vinden. Daarnaast zijn laboratoria vaak niet op de hoogte van de medicijnen die een patiënt gebruikt. Daardoor is het niet altijd meteen duidelijk dat een medicijn de oorzaak is van een afwijkende testuitslag. Dat blijkt uit onderzoek van het RIVM in opdracht voor de Inspectie Gezondheidszorg en Jeugd (IGJ).

Diagnostische tests in laboratoria worden *in vitro* diagnostica (IVDs) genoemd. De invloed van medicijnen, zogenoemde interferenties, is niet altijd bekend op het moment dat het IVD wordt ontwikkeld. Ze komen vaak pas aan het licht nadat het in de handel is gebracht en wordt gebruikt in laboratoria.

Als wordt ontdekt dat een medicijn interfereert met een diagnostische test, past de fabrikant van het IVD de gebruiksinstructies aan. Dan weten laboratoria dat ze rekening moeten houden met deze interferentie.

Het is onbekend hoe vaak interferenties tussen medicijnen en IVD's voorkomen. Bij de IGJ komen per jaar één tot twee meldingen van nieuw ontdekte interferenties binnen. Het is mogelijk dat interferenties niet altijd worden ontdekt. Hierbij moet worden opgemerkt dat een arts zijn oordeel vaak niet alleen baseert op een IVD-test. Een arts voert vaak ook nog andere tests uit om een diagnose te stellen en weegt de symptomen en klachten van de patiënt mee.

Kernwoorden: geneesmiddel, *in vitro* diagnosticum, interferentie, laboratorium, wet- en regelgeving

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Summary

Introduction

In past years, the Dutch Health and Youth Care Inspectorate received several notifications from manufacturers regarding the influence of medicinal products (MPs) on the results of *in vitro* diagnostic medical devices (IVDs) marketed by these manufacturers. IVD manufacturers may study possible interactions between MPs and IVDs during the development of IVDs, or such an interaction may occur during use of the IVD in practice. If an interaction is found, they should take measures, like improvement of the IVD and/or a warning in the Instructions For Use (IFU) of the IVD. However, the role of and actions by all other stakeholders during development as well as marketing of the IVD is not fully clear.

Aim

The aim of this study was to gain insight into:

- a. how IVD manufacturers, medical laboratories and registration holders of MPs safeguard the process around interference of MPs with IVDs to minimize the risks for the patient (i.e. risk of incorrect results and potential incorrect diagnosis or treatment);
- b. how (new) knowledge about such interferences is shared amongst all stakeholders.

The study focuses on the commercially available IVDs. In-house developed IVDs are outside the scope.

Methods

As a first step, legislation, guidelines and standards were consulted to make an inventory of requirements regarding interferences between MPs and IVDs. Subsequently, an analysis was done on the case studies notified to the IGJ in the past few years. In addition, literature, documents, reports and announcements of Field Safety Corrective Actions were searched, using literature databases and internet. As a next step, interviews were held with umbrella organizations of field parties (IVD manufacturers, laboratories, MP agency, Notified Body) to learn from them whether and, if so, how interference of MPs with IVDs is dealt with in order to minimize the risks for the patient. Finally, a web-based survey was conducted amongst IVD manufacturers (in the EU) and medical laboratories (in the Netherlands).

Results and discussion

The results of this study show that both the *in vitro diagnostic medical devices Directive* (IVDD) and the *in vitro diagnostic medical devices Regulation* (IVDR) contain requirements for the IVD manufacturer considering the influence of interfering substances. However, these requirements are stated in a general manner and only the IVDR refers to 'medication'. In practice, interference of MPs with IVDs will frequently be detected by chance, for example during clinical trials (pre-market) or during use in practice (post-market).

In case laboratories/users of the IVD detect the interference, they will inform the IVD-manufacturer. The IVD manufacturer must report certain incidents with his product to a Competent Authority (CA). The manufacturer will withdraw or, if possible, redesign the IVD, or adapt the Instructions for Use. The majority of the manufacturers responding to the questionnaire indicated that the IVD users are informed. Most of the manufacturers will also inform the marketing authorization holder of the MP and the CA. However, few manufactures indicated to share the information with other IVD manufacturers.

New interferences, popping up post-market, may be discussed at the European Medicines Agency, e.g. when covering centrally authorised MPs. If applicable, the SmPC may be adapted. However, this occurs in a limited number of cases. If a laboratory knows that a patient is taking an MP known to interfere with an IVD test, an alternative analytical method is normally selected (if available) or a remark or warning is added to the results report. Only a minority of laboratories would proactively contact or inform the marketing authorization holder of the MP. Stakeholders do not systematically inform each other on (new) interferences.

Conclusion

The extent to which interferences between MPs and IVDs occur cannot be quantified. Although the issue of MP interference with IVDs is not addressed in detail in legislation and guidance documents, there are several safeguards to control the risks for the patient. It remains however unknown what the (magnitude of the) actual risks are. In theory, there may be risks related to incorrect diagnosis and/or treatment decision. However, because a physician often performs other diagnostic tests and also takes the patient's symptoms and complaints into account, an IVD test result is not always of decisive importance. Knowledge exchange between stakeholders about interferences between MPs and IVDs may be improved. In the near future, the Eudamed database might facilitate the dissemination of information.

List of abbreviations used

AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (Spanish agency)
ANSM	L'Agence nationale de sécurité du médicament et des produits de santé (French agency)
CA	Competent Authority
CAPA	Corrective and Preventive Action
CBG	College ter Beoordeling van Geneesmiddelen (Medicines Evaluation Board in the Netherlands)
CLSI	Clinical & Laboratory Standards Institute
Diagned	Umbrella organization of manufacturers and importers of IVDs in the Netherlands
EDMA	European Diagnostics Manufacturing Association
EMA	European Medicines Agency
EU	European Union
Eudamed	European Databank on Medical Devices
FSCA	Field Safety Corrective Action
FSN	Field Safety Notice
IFU	Instructions For Use (for medical devices)
IGJ	Inspectie Gezondheidszorg en Jeugd (Dutch Health and Youth Care Inspectorate)
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde (Portuguese agency)
IVD	In Vitro Diagnostic medical device
IVDD	In Vitro Diagnostic medical devices Directive
IVDR	In Vitro Diagnostic medical devices Regulation
MHRA	Medicines and Healthcare products Regulatory Agency (British agency)
MP	Medicinal Product
NVH	Nederlandse Vereniging voor Hematologie (Dutch Society for Haematology)
NVKC	Nederlandse Vereniging voor Klinische Chemie (Dutch Society for Clinical Chemistry)
NVMM	Nederlandse Vereniging voor Medische Microbiologie (Dutch Society for Medical Microbiology)
NWKV	Nederlandse Werkgroep Klinische Virologie (Dutch Working Group for Clinical Virology)
NVVI	Nederlandse Vereniging voor Immunologie (Dutch Society for Immunology)
PRAC	Pharmaceutical Risk Assessment Committee of the European Medicines Agency
SKML	Stichting Kwaliteitsbewaking Medische Laboratoriumdiagnostiek (Dutch Foundation for Quality Assessment in Medical Laboratories)
SmPCs	Summary of Product Characteristics (for medicinal products)

1 Introduction

1.1 Context

In past years, the Dutch Health and Youth Care Inspectorate (*Inspectie Gezondheidszorg en Jeugd, IGJ*) received several notifications regarding the influence of medicinal products (MPs) on the results of *in vitro* diagnostic medical devices (IVDs). These notifications sometimes concern MPs and tests that have been on the market already for a long time, whereas the interaction was noted only recently. An example, from April 2017, published by the PRAC¹ (Pharmaceutical Risk Assessment Committee) is the interaction between the MPs with Leflunomide (Arava) and Teriflunomide (Aubagio)² with a blood gas analyser (European Medicines Agency, 2017a). The measurement of ionized calcium levels might falsely show decreased values in patients under treatment with any of these two drugs, depending on the type of ionized calcium analyser used. Another example dates from 2003, when saccharides in peritoneal dialysis solutions used in kidney patients caused the test incorrectly to indicate elevated blood glucose levels (Schleis, 2007).

IVD manufacturers may study possible interactions between MPs and IVDs during the development of IVDs, or such an interaction may occur during use of the IVD in practice. The question is what actions are taken by IVD manufacturers, laboratories and registration holders of MPs in order to guarantee that the risks for the patient (i.e. the risk of incorrect results potentially leading to incorrect diagnosis or treatment) are minimized. This concerns actions during development as well as during marketing/use of the IVDs. It is also unknown how they share (new) knowledge about interferences with other stakeholders.

1.2 Aim and scope of the study

Aim

The aim of this study was to gain insight into:

- (1) how IVD manufacturers, laboratories and registration holders of MPs safeguard the process around interference of MPs with IVDs to minimize the risks for the patient (i.e. risk of incorrect results and potential incorrect diagnosis or treatment);
- (2) how (new) knowledge about such interferences is shared amongst all stakeholders.

Scope

This study focuses on the commercially available IVDs. In-house developed IVDs are outside the scope, since these fall under full responsibility of the laboratory.

¹ The Pharmacovigilance Risk Assessment Committee (PRAC) is the European Medicines Agency's (EMA) committee responsible for assessing and monitoring the safety of human medicines.

² Leflunomide is used in rheumatoid arthritis/psoriatic arthritis. Teriflunomide is used in multiple sclerosis.

2 Methods

In order to fulfil the aim of this study, the following four steps were taken:

2.1 Review of legislation, guidelines and standards

As a first step, legislation, guidelines and standards were consulted to make an inventory of requirements regarding interferences between MPs and IVDs. Search terms for internet were: IVD, in vitro, interference, interfere*, influence, drug, medicine, medicinal product, medication, cross-reactivity.

2.2 Searching for examples of cases

2.2.1 *Notifications to the IGJ*

A list of 18 notifications regarding interferences between MPs and IVDs received by the IGJ in the past 5 years (2014 and 2018) were analysed. The following information was extracted from each notification:

- 1) how the interference was found;
- 2) party submitting the notification;
- 3) actions taken, and
- 4) communication to the user regarding the interference.

2.2.2 *Literature search*

Articles, documents, notifications, and Field Safety Corrective Actions (FSCAs) published between 2014 and 2018 regarding interferences of MPs with IVDs were retrieved through a systematic literature search on the databases Embase, Scopus and Pubmed. The search strategy was designed in collaboration with the information specialist of the RIVM, see Annex I. In parallel to the systematic literature search, grey literature was compiled according to the search strategy in Annex II.

Only articles concerning the European Union (EU) were included for full review. As in step 2.1., the focus was on extracting the following information:

- 1) how the interference was found;
- 2) party submitting the notification;
- 3) actions taken, and
- 4) communication regarding the interference.

In addition, norms or guidelines mentioned in the retrieved documents were also duly noted.

2.3 Interviews with experts

Based on knowledge gained in the previous steps 1 and 2, an interview guide was prepared (see Annex III). This guide served as a basis to interview the following organisations: Diagned³, NVKC⁴, NVMM/NWKV⁵,

³ Umbrella organization of manufacturers and importers of IVDs in the Netherlands

⁴ Dutch Society for Clinical Chemistry

⁵ Dutch Society for Medical Microbiology/Dutch Working Group for Clinical Virology

the Medicines Evaluation Board in the Netherlands (CBG) and a Dutch Notified Body certifying IVDs (Dekra). The aim of this step was twofold: on one hand, to find out how different organisations handle and act upon interferences in practice, and on the other hand, to collect experiences regarding concrete cases of interference between MPs and IVDs. The outcome of the interviews was used to prepare the surveys.

2.4 Surveys among IVD manufacturers and laboratories

In this fourth step, a survey was distributed among manufacturers of IVDs (active or established in and outside the Netherlands) and among laboratories using IVDs (active or established in the Netherlands). The aim was to get insight into how manufacturers and laboratories deal with interferences between MPs and IVDs. The selection of manufacturers and laboratories was based on knowledge within the RIVM research team, the website of MedTech Europe⁶, the study of the cases (step 2), and the knowledge gathered by the different umbrella organisations interviewed (step 3). The survey questions are included in Annex IV.

⁶ <https://www.medtecheurope.org/about-us/members/> consulted on October 17, 2018

3 Results

3.1 Review of legislation, guidelines and standards

Two parts of IVD legislation were reviewed for relevant provisions on interference:

- Directive 98/79/EC on *in vitro* diagnostic medical devices (IVDD; European Commission, 1998); currently applicable;
- Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR; European Commission, 2017); applicable from May 26, 2022.

For MPs the following directive was consulted:

- Directive 2001/83 on the Community code relating to medicinal products for human use (consolidated version: 16/11/2012; European Commission, 2001).

In addition, guidelines and European harmonised standards related to this legislation were reviewed for any requirements related to interference. A distinction is made between the pre-market and post-market requirements. Annex V provides a complete overview of all documents reviewed.

3.1.1 IVDs

IVDs pre-market

Both the IVDD and the IVDR contain requirements for the IVD manufacturer to consider the influence of interfering substances or cross-reactivity on the performance of IVDs. The requirements are stated in a general manner, most likely due to the variety of IVDs that need to be covered by legislation. Comparing the requirements in the IVDD and IVDR, the IVDR puts more emphasis on interferences and includes requirements for studies on interference.

The essential requirements in Annex I of the IVDD (Annex I, requirement 3) state that "devices must achieve the performances stated by the manufacturer, including control of known relevant interference".

According to Annex I of the IVDR (general safety and performance requirements, chapter 2), the manufacturer shall consider known relevant endogenous and exogenous interference and cross-reaction during the design and manufacturing of the IVD. Annex I of the IVDR also requires the manufacturer to provide information in the IFU concerning interference(s) and cross-reactions. Regarding the information supplied with the device, this shall also include any factors that can affect the test result such as age, gender, menstruation, infection, exercise, fasting, diet or *medication*. According to Annex II of the IVDR (technical documentation, 6.1.2.3), the manufacturer shall describe in the technical documentation interference and cross-reactivity studies performed to determine the analytical specificity in the presence of other substances/agents in the specimen. Interfering and cross-

reacting substances or agents may include substances used for patient treatment such as *medicinal products*.

Apart from text in the Directive and the Regulation, also some specific *standards* for IVDs address the issue of interference.

In the case of blood glucose monitoring systems, the harmonized standard EN ISO 15197 for these devices contains specific requirements to test a number of interfering substances listed in that standard (CEN, 2015).

The harmonized standards EN ISO 18113 on labelling of *in vitro* diagnostic reagents and *in vitro* diagnostic instruments list the information that needs to be supplied by the manufacturer (CEN, 2011a, 2011b, 2011c and 2011d). According to these standards, information regarding any known clinically relevant interfering substances needs to be provided under the section of limitations of the examination procedure (part 2 and 4), and information regarding known interferences that present significant risk under the section warnings and precautions (part 3 and 5).

Lastly, two guidelines addressing the problem of interference at the pre-market stage were found: the WHO Guideline “instructions for compilation of a product dossier Prequalification of In Vitro Diagnostics Programme” (WHO, 2014) and the guideline of the Global Harmonization Task Force on clinical performance studies (Study group 5 GHTF, 2012). These guidelines recommend the study of possible interferences during the development phase of the IVD.

IVDs post-market

Both the IVDD and the IVDR contain requirements for manufacturers to obtain information about their products when placed on the market (according to IVDR: post-market surveillance, PMS; and according to IVDD: post-production surveillance). In the IVDD, the requirements are not elaborated upon, except for taking actions in case of incidents. In the IVDR, PMS is described in more detail, especially the goal of PMS and reporting the findings and actions of PMS. Although interfering substances are not specifically mentioned, information on interfering substances can be obtained as part of PMS; in this case, the manufacturer shall evaluate such information.

Annex III of the IVDD requires the manufacturer to “institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase and to implement appropriate means to apply any necessary corrective actions, taking account of the nature and risks in relation to the product. He shall notify the competent authorities of the following incidents immediately on learning of them...”.

Similarly, the IVDR states that “Manufacturers should play an active role during the post-market phase by systematically and actively gathering information from post-market experience Manufacturers should establish a comprehensive post-market surveillance system, set up under their quality management system..... Relevant data and information gathered through post-market surveillance, as well as lessons learned from any

implemented preventive and/or corrective actions, should be used to update any relevant part of technical documentation, such as those relating to risk assessment and performance evaluation,.....”.

According to the IVDR, “It is necessary to ensure that the clinical evidence of devices is updated throughout their lifecycle. Such updating entails the planned monitoring of scientific developments and changes in medical practice by the manufacturer. Relevant new information should then trigger a reassessment of the clinical evidence of the device thus ensuring safety and performance through a continuous process of performance evaluation”.

3.1.2 *MPs*

MPs pre-market

There is only one provision that covers the "specific interference with laboratory tests", included in the European Commission Guidelines on the Summary of Product Characteristics (SmPC; European Commission, 2009) within the section of Special warnings and precautions for use. It establishes that specific interference with laboratory tests should be mentioned, when appropriate, and clearly identified with a subheading in the SmPC.

MPs post-market

Abnormal laboratory findings are also considered unfavourable and unintended signs associated with the use of a MP. They are therefore included in the definition of ‘Adverse Events’, as described in the EMA Guideline on good pharmacovigilance practices, Annex I (EMA, 2017b). It should be noted, however, that the abnormal parameter is not specifically attributed to interference between the MP and the IVD and could be associated to other side effects of the MP.

3.2 **Examples of cases**

3.2.1 *Notifications to the IGJ*

The analysis of eighteen notifications from eight different manufacturers concerning interferences of MPs on the results of IVDs, received by the IGJ in the years 2014 to 2018 yielded the following information:

There are several ways how a manufacturer can become aware of interference. For the cases examined, possible interference was:

- notified to the manufacturer by the user of the IVD;
- discovered by the manufacturers themselves;
- read in the vigilance report from another manufacturer, or
- provided by a Competent Authority for medical devices (CA).

However, the majority of the vigilance reports do not mention how the problem of interference became known.

After receiving a notification on interference, the majority of manufacturers carry out research to confirm the problem that has been encountered. In some cases, this results in Corrective and Preventive Actions (CAPA). They also may improve internal procedures that are used to proactively find interferences, including the risk analyses. In some cases, the product is modified.

The finding of an interference led in all cases to a modification of the IFU to warn the IVD user about possible interference. About the half of the manufacturers indicated also to have issued a Field Safety Notice (FSN)⁷.

3.2.2 *Literature search*

A first systematic literature search yielded a cohort of 107 articles, of which only 12 were considered relevant. There was very little evidence published on interference of medicines with IVDs, and most of the articles dealt with testing of medicines on IVDs at preclinical stage. We opted to refine the search in consultation with the information specialist (search strategy available in Annex I). This second systematic search yielded 136 references; 106 articles were excluded after screening their title and abstract. From the remaining 30, 28 full text articles were screened; two were not retrievable from the RIVM library due to copyright issues. From the 28 articles screened, only one concerned the EU and included relevant information in line with our research question (See Annex V, Piketty et al., 2017).

Given the paucity of results obtained during the systematic search, we opted to perform a wide grey literature search, using the search engine Google. This grey literature search yielded 10 additional examples on interference of medicines on the results of IVD tests (See Annex V).

In summary, limited information was found regarding interference of MPs with IVDs published in the EU over the last four years. Examples of medicines found to interact with IVDs are Daratumumab, Heparine, Fulvestrant, Sulfasalazine and Sulfapyridine, Paracetamol, Metamizole, Ceftriaxone and certain vaccines. In addition, we found information on interferences caused by biotin, which is a nutritional supplement also used for therapeutic purposes. Only in very few cases, we were able to identify how the interference became known. A review mentions that in most of the cases the interferences are found in daily practice, when a discrepancy between the clinical findings and the laboratory results is noted. Once the manufacturer becomes aware of the interference, it is often notified to the CAs.

The following list includes actions mentioned in the literature to be taken to either avoid or confirm interference during the post-marketing phase:

- Clinicians should actively ask their patients about their medicines' intake;
- Clinicians should inform the laboratory about patients' medicines use;
- If interference is suspected, then test for linearity, retest, or confirm using an alternative method;
- If interference is known, then use an alternative method;
- If possible, run the IVD testing prior to medicines' intake;
- Modify the IFU; this should be done by the manufacturer;
- Manufacturers develop tests that mitigate known interferences, such as for instance the interference with Daratumumab.

⁷ FSNs are communications sent out by manufacturers in relation to actions taken for their product that is on the market.

3.3 Interviews with experts

Pre-market

According to the interviewees, the IVDD does not contain specific requirements on (the investigation of) interference of any kind. However, in the IVDR possible interference is mentioned as performance characteristic to be investigated, if applicable. This is in line with the literature search (see chapter 3.2).

In the MPs legislation, there is no standard requiring the investigation of interferences with IVDs during the development of a MP. However, interference may rise during clinical trials with the MP. If this interference is (possibly) clinically relevant, it should be mentioned in the SmPC.

Post-market

When the IVD is on the market, interference is not systematically monitored or investigated. It may however pop-up during use of the IVD in daily practice.

If an IVD test result does not seem to match the other clinical findings, one could consider the use of a MP as a cause for this deviating result. However, a causal connection is difficult to establish, because many other factors may be of influence. Possible other factors are, for example:

- Intake of food, food supplements or vitamins by the patient before the sampling;
- Substances naturally produced by the body of the patient;
- Issues related to the sampling procedure;
- Mistakes during analysis or malfunctioning equipment.

In case of a confirmed interference (i.e. a causal relationship with a MP has been established), the IVD manufacturer will inform his clients. Moreover, the test may either be withdrawn from the market or redesigned, and/or the IFU will be adapted. It is not known whether IVD-manufacturers inform MP registration holders.

Risks related to incorrect IVD test results

As indicated by interviewees, the risks may depend on various concomitant factors and are difficult to evaluate. Frequently, a physician takes into account a broad range of clinical symptoms and measures before a final diagnosis and treatment are established. Moreover, not every interference has clinical implications; the difference between the measured/incorrect value and real/correct value may be too small to have consequence for the treatment of the patient.

Sharing knowledge

Incidents, such as interferences formerly unknown, must be reported by the manufacturer to a CA. Several Notified Bodies also ask their clients to report these incidents to them (besides to a CA), but this is not always done.

New interferences may be discussed at the European Medicines Agency, e.g. when covering centrally authorised MPs. If applicable, the SmPC may be adapted. However, this occurs in a limited number of cases.

According to the interviewees, information is not always shared effectively between stakeholders. In addition, they state that there are differences in the way CAs of EU member states deal with communication regarding occurring interferences. If an IFU has been adapted, this is not actively communicated to other IVD manufacturers marketing comparable IVDs or to the MP manufacturer / marketing authorisation holder. Moreover, there is currently no central (European) database with information that can be consulted by stakeholders. In the near future, the Eudamed database might be helpful. This secure web-based portal acts as a central repository for information exchange between national competent Authorities and the Commission. It will comprise a database that includes data on incidents or near-incidents, which occur during the use of medical devices (including IVDs). But, as stressed by one interviewee, data is not the same as information; assessment of causal connections (e.g. MP causing incorrect IVD test results) is necessary, but may be difficult to confirm (see also above).

According to the interviewees, IFUs of IVDs rarely include information on interference of a MP with the IVD at issue. If included, no reference is made to the source of information (e.g. literature) and there is also no system in place to include comparable information in the SmPC of the MP.

Dealing with interferences in medical and laboratory practice

When using an IVD test for a specific patient, the laboratory has no access to the medical file of the patient (amongst others due to legislative hindrances related to privacy and professional confidentiality). Hence, the laboratory cannot check what kind of MPs the patient is using. For well-known interferences, however, it may be possible for the applicant of the IVD test to tick a box on the IVD application form to indicate whether the patient uses a particular MP.

At the laboratory level, the NVKC has prepared a guideline and database on interaction of clinical-chemical parameters with MPs⁸. A working group of clinical chemists and pharmacists evaluates interferences through systematic literature review and systematic validation of interactions. An important part of the validation report is advice for the applicant. There is neither a feedback loop to IVD manufacturers nor MP registration holders. The validity and usability of this system are under investigation.

⁸ https://www.nvkc.nl/sites/default/files/NTKC/N60_078992_NVKC_Januari2017_WO6.pdf.

3.4 Surveys among IVD manufacturers and medical laboratories

Out of the 71 laboratories that were invited to fill-out the survey, 22 responded. Out of the 45 manufacturers invited, only one initially responded. Subsequently, MedTech Europe kindly offered their help and forwarded the request to 42 IVD corporate members and to 25 IVD national association members. This yielded 20 extra completed questionnaires, bringing the total to 21.

Reactions from laboratories

Most of the laboratories completing the survey were active in the diagnostic area of infectious diseases (10/22). See also Figure 3.4.1. This was a multiple choice question; eleven labs selected more than one area, which explains why the total number of areas selected (55) is higher than the number of respondents (22).

1. In what kind of diagnostic areas is your laboratory active? (multiple options possible)

(Type vraag: Meerkeuze, meer antwoorden)

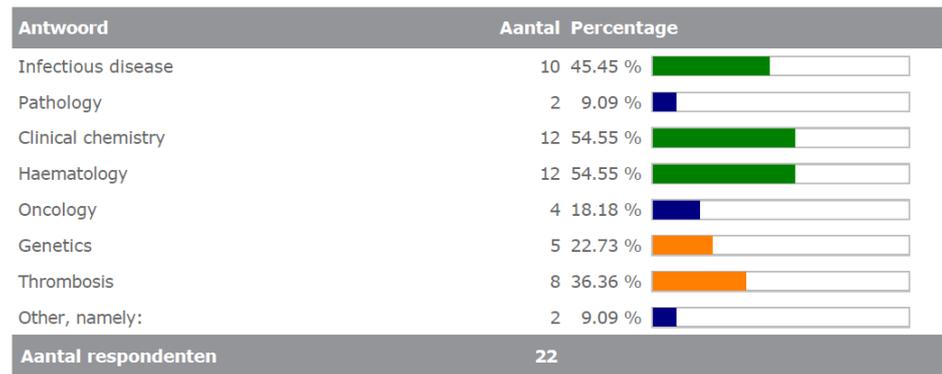


Figure 3.4.1. Diagnostic areas in which laboratories are active

About half of the laboratories (10) indicated that, in case of a known interference, they either select an alternative analytical method (if available) or request the physician to note down whether the patient takes that specific medication. See Figure 3.4.2. In three cases, the lab takes both of these actions at the same time (first ask the physician and then select an alternative method). In five cases, the respondent indicated that a remark or warning is added to the result report.

2. Suppose there is a known interference of a medicinal product with a commercial IVD test used at your department. How does your laboratory take that interference into account? (multiple options possible)

(Type vraag: Meerkeuze, meer antwoorden)

Antwoord	Aantal	Percentage
Interferences with medicinal products are not taken into account.	2	9.09 %
An alternative method of analysis or IVD is selected, if available.	10	45.45 %
The applicant/physician is informed and requested to note down on the application form whether the patient uses the medicinal product at issue.	10	45.45 %
Other options, namely:	9	40.91 %
Aantal respondenten	22	

Figure 3.4.2. Actions taken when an interference is known by the laboratory

All respondents (100%) (would) proactively contact the applicant/physician if an interference is (would be) found. Instead, only 18% of the respondents (would) proactively contact or inform the marketing authorization holder of the MP. See Figure 3.4.3a up to 3.4.32.

3a. Do you (or would you) proactively contact/inform the IVD manufacturer?

(Type vraag: Meerkeuze, één antwoord)

Antwoord	Aantal	Percentage
Yes	20	90.91 %
No	2	9.09 %
Aantal respondenten	22	

3b. Do you (or would you) proactively contact/inform the marketing authorization holder(s) of the medicinal product?

(Type vraag: Meerkeuze, één antwoord)

Antwoord	Aantal	Percentage
Yes	4	18.18 %
No	18	81.82 %
Aantal respondenten	22	

3c. Do you (or would you) proactively contact/inform the relevant professional associations in your field of diagnosis?

(Type vraag: Meerkeuze, één antwoord)

Antwoord	Aantal	Percentage
Yes	17	77.27 %
No	5	22.73 %
Aantal respondenten	22	

3d. Do you (or would you) proactively contact/inform the applicant/physician?

(Type vraag: Meerkeuze, één antwoord)

Antwoord	Aantal	Percentage
Yes	22	100 %
No	0	0 %
Aantal respondenten		22

Figure 1.4.3. Number and percentage of laboratories contacting relevant stakeholders when an interference is detected

Of the 22 laboratories completing the survey, 8 had received information on interferences between MPs and commercial IVDs from umbrella organizations of laboratories or by another laboratory in the past. See Figure 3.4.4.

4. Has your lab, in the last 5 years, been approached by umbrella organizations of laboratories or another laboratory about interferences between medicinal products and commercial IVDs?

(Type vraag: Meerkeuze, één antwoord)

Antwoord	Aantal	Percentage
Yes	8	36.36 %
No	14	63.64 %
Aantal respondenten		22

Figure 3.4.4 Number and percentage of laboratories that have been contacted regarding interferences

The opinions of the respondents were divided (50%) regarding whether the information on known interferences of MP with commercial IVDs is readily available or not. When asked what sources they obtain such information from, the IVD supplier/manufacturer/product insert (9 times mentioned), scientific literature (5), and the NVKC website (7) were the most frequently mentioned sources. Ideas for improving the flow of information included:

- newsletter, (targeted) communication from the IVD manufacturer to users or warning on the product (6);
- communication via professionals' organisations or via the NVKC database in progress (3);
- building a database with interferences or having an official website with all information on interactions with IVD tests (2), and
- automatically connecting the Laboratory Information System with the Pharmacy System (1).

Eighteen from the 22 respondents (82%) were not sure as to whether there are any bottlenecks in IVD regulation to assure that interferences between MP and commercial IVDs are adequately recognized and dealt with. See Figure 3.4.5. Half of the respondents (11/22) however believed that there were bottlenecks in laboratory practice. See Figure 3.4.6.

6. Are there any bottlenecks in IVD regulation to assure that interference between medicinal products and commercial IVDs is adequately recognized and dealt with?

(Type vraag: Meerkeuze, één antwoord)



Figure 3.4.5. Opinions regarding bottlenecks in IVD regulation

7. Are there any bottlenecks in laboratory practice to assure that interference between medicinal products and commercial IVDs is adequately recognized and dealt with?

(Type vraag: Meerkeuze, één antwoord)

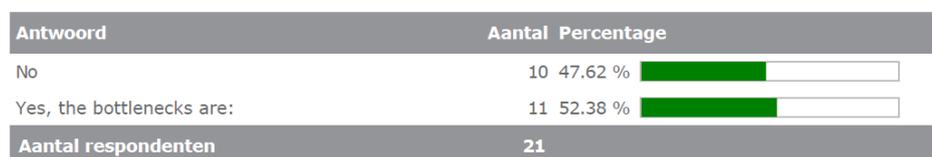


Figure 3.4.6. Opinions regarding bottlenecks in laboratory practice

Ten respondents mentioned the lack of patient information provided to the lab, including medication taken, as a bottleneck. Access to patient medication records or direct coupling of the laboratory information and management system to the pharmacy system was mentioned as a possible solution, but privacy regulation was identified as potential bottleneck. In three cases, increasing physician awareness and knowledge was considered important as well.

The opinions of the respondents were also divided when they were asked whether the issue of interference of MP with IVDs represented a significant problem requiring more attention and action and whether it posed a high risk for patients. See Figure 3.4.7 and 3.4.8. More than half of the respondents considered interference with MPs as a (potentially) high risk.

9. Do you consider the issue of interference of medicinal products with IVDs to be a significant problem that requires more attention and action?

(Type vraag: Meerkeuze, één antwoord)

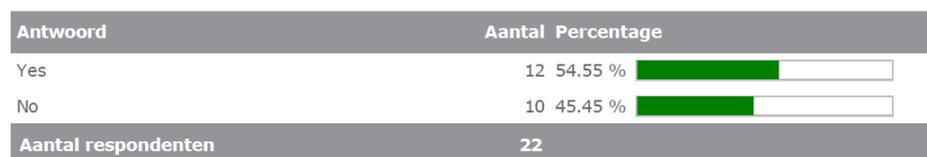


Figure 3.4.7 Opinions regarding necessity for attention and action

10. Do you consider the issue of interference of medicinal products with an IVD test to pose a high risk for patients?

(Type vraag: Meerkeuze, één antwoord)

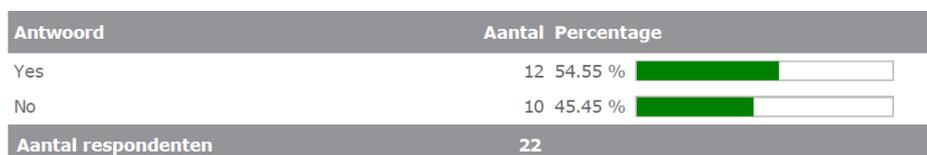


Figure 3.4.8 Opinions regarding risks for patients

The following issues were noted by the respondents in their comments field:

- There are too many interferences and it is therefore impossible to have all this knowledge available;
- It is not possible to keep up with all new MPs on the market;
- For specific MPs it could be an issue, although in general it is not;
- Risk depends on every individual case;
- Normally current state of disease is established using more parameters than the test result alone, therefore not a big issue;
- For the laboratory practice in pathology, this is not an issue;
- For nutritional supplements like biotin, interactions may be problematic;
- Even if it may not be a big issue in most of the cases, the potential risk should be avoided.

Reactions from IVD manufacturers

Most of the manufacturers completing the survey were active in the diagnostic area of clinical chemistry (10/21). See also Figure 3.4.9. This was a multiple choice question; 18 manufacturers selected more than one area, which explains why the total number of areas selected (52) is higher than the number of respondents (21).

Diagnostic areas mentioned under 'others' were: hemostasis, drug monitoring and special clinical chemistry, screening of rare disorders, autoimmune and rheumatoid diseases.

1. In what kind of diagnostic areas is your IVD company active? (multiple options possible)

(Type vraag: Meerkeuze, meer antwoorden)

Antwoord	Aantal	Percentage
Infectious disease	9	42.86 %
Pathology	6	28.57 %
Clinical chemistry	10	47.62 %
Haematology	7	33.33 %
Oncology	8	38.10 %
Genetics	4	19.05 %
Thrombosis	4	19.05 %
Other, namely:	4	19.05 %
Aantal respondenten	21	

Figure 3.4.9. Diagnostic areas in which manufacturers are active

The majority of the manufacturers (17) indicated that, during the development of a new IVD, the potential interference with MPs is considered. Half of these manufacturers indicated that the new IVD is tested against a set of MPs. See figure 3.4.10. Under 'otherwise' the following were mentioned: 'literature', 'we test only the food supplements known as interfering with our products', 'literature review, previous reports of interference with the method, experience with other reagents that may use similar indicator reactions'.

If yes: How is the potential interference of medicinal products with the new IVD investigated during its development?

(Type vraag: Meerkeuze, één antwoord)

Antwoord	Aantal	Percentage	
The extent of the investigation depends on the outcome of a risk analysis.	5	31.25 %	
The new IVD is tested against a set of medicinal products.	8	50 %	
Otherwise, namely:	3	18.75 %	
Aantal respondenten	16		

Figure 3.4. 10. Investigation of potential interference of MPs with the new IVD.

Five respondents mentioned factors that are considered in the risk analysis:

- The properties of the assay technology (2x);
- Previous information with similar assays;
- Presence of the potential interferent in the target patient population;
- Sample type;
- Clinical conditions, chemically related compounds and/or disease relevant substances;
- Literature search (2x);
- The risks of false results.

Eight respondents mentioned factors that determine the set of the MPs to which the new IVD is tested:

- Tested for any common over-the-counter drugs as acetaminophen, acetylsalicylic acid, and ibuprofen;
- Commonly prescribed drugs are tested (2x);
- The customer lab's input determines the choice of the drug panel. For example, a therapeutic drug monitoring analyte panel is tested against commonly prescribed analgetics, antimycotics or antibiotics;
- Based on scientific literature related to the condition associated with the IVD;
 - Clinical & Laboratory Standards Institute (CLSI) Standards and scientific literature;
- Competitors list;
- If it is a known test, we typically look at what has been tested previously for similar tests, this kind of data is publically available, for example, in FDA's decision summaries on the FDA website;
- If it is a new test (new markers), we often consult key opinion leader physicians to determine what might be relevant based on the patient and their disease as well as any common comorbidities;
- We review the literature related to the disease associated with the test and, if available, the literature related to the mechanism of the marker (when or where has it been elevated and might those conditions and associated medicines interfere).

The information on interference that is gathered during post-marketing surveillance is, to varied extents, shared with others, see figures 3.4.11 – 3.4.14

3a. Do you (or would you) proactively inform the marketing authorization holder(s) of this medicinal product?

(Type vraag: Meerkeuze, één antwoord)

Antwoord	Aantal	Percentage
Yes	12	57.14 %
No	9	42.86 %
Aantal respondenten		21

Figure 3.4.11. Sharing of information: marketing authorization holder of MP

Nine respondents indicated how the marketing authorization holders are informed:

- Directly to individual marketing authorisation holder(s) (5x);
- If the interference does not lead to a reportable event, it would likely lead to an investigation and a labeling change. We would then evaluate whether or not to involve the authorities.
- In product labeling and by written communication to the Notified Body
- In product labeling (2x)
- We would inform our Notified Body, the customers, and national authorities.

3b. Do you (or would you) share this information proactively with other IVD manufacturers?

(Type vraag: Meerkeuze, één antwoord)

Antwoord	Aantal	Percentage
Yes	4	19.05 %
No	17	80.95 %
Aantal respondenten		21

Figure 3.4.12. Sharing of information: other IVD manufacturers

Four respondents indicated that the information is shared with other manufacturers via:

- National MedTech Europe Organisation (Verband der Diagnostica-Industrie e.V);
- FSCA and FSN published on competent authorities websites;
- MedTech Europe;
- Umbrella organization.

3c. Do you (or would you) share this information proactively with users of these IVDs?

(Type vraag: Meerkeuze, één antwoord)

Antwoord	Aantal	Percentage
Yes	19	90.48 %
No	2	9.52 %
Aantal respondenten		21

Figure 3.4.13. Sharing of information: users of IVDs

The users that would be informed are mainly laboratories, see figure 3.4.14.

Under 'others' distributors and purchasers were mentioned.

If yes: Which users are (or would be) informed by you? (multiple options possible)

(Type vraag: Meerkeuze, meer antwoorden)

Antwoord	Aantal	Percentage	
Laboratories (e.g. medical, clinical, microbiology or pathology)	16	84.21 %	
Healthcare professionals (e.g. physicians, pharmacists, nurses)	5	26.32 %	
Others, namely:	5	26.32 %	
Aantal respondenten	19		

Figure 2.4.14. Users that would be informed about interference.

3d. Do you (or would you) share this information proactively with the health authorities or other formal stakeholders?

(Type vraag: Meerkeuze, één antwoord)

Antwoord	Aantal	Percentage	
Yes	14	66.67 %	
No	7	33.33 %	
Aantal respondenten	21		

Figure 3.4.15. Sharing of information: health authorities and other formal stakeholders

The 14 respondents that would inform the health authorities or other formal stakeholders named one or more of the organisations listed in figure 3.4.16.

If yes: Which authorities/formal stakeholders are (or would be) informed by you? (multiple options possible)

(Type vraag: Meerkeuze, meer antwoorden)

Antwoord	Aantal	Percentage	
European Medicines Agency	1	7.14 %	
National medicinal product agency	6	42.86 %	
Notified bodies	8	57.14 %	
Competent authorities	10	71.43 %	
Others, namely:	0	0 %	
Aantal respondenten	14		

Figure 3.4.16. The health authorities and other formal stakeholders that would be informed about interference

Only two respondents indicated to keep track of new MPs entering the market and evaluate the possible interference of these MPs. One respondent performs a risk analyses, the other investigates the possible interference.

Manufacturers ensure that information about the possible interference of MPs with IVDs reaches them, see figure 3.4.17. Under 'otherwise' the following were mentioned:

- We discuss with our Key Opinion Leader physicians;
- We look to FDA alerts for interferents;

- Listing of potential compounds in the CLSI guideline;
- We proactively check competitors' instructions for use.

5. How do you ensure that information on possible interference of medicinal products with IVDs reaches you? (multiple options possible)

(Type vraag: Meerkeuze, meer antwoorden)

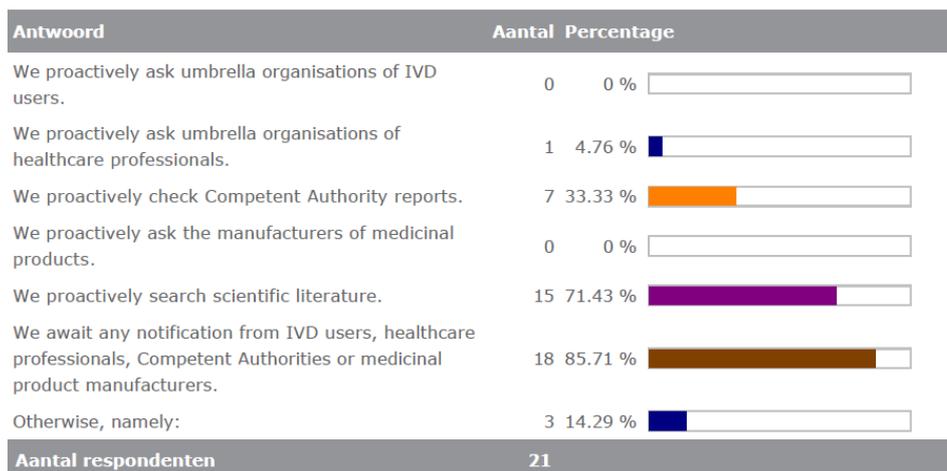


Figure 3.4.17. Ways to ensure that information about interference reaches the manufacturer of the IVD

Fifteen out of the 21 respondents (71%) were not sure as to whether there are any bottlenecks in IVD regulation to assure that interferences between MP and commercial IVDs are adequately recognized and dealt with, see figure 3.4.18. Three respondents mentioned the following bottlenecks:

- There is no mechanism in place to work with other IVD manufacturers or pharma companies.
- There does not seem to be a clear path for communication, unless we are filing a vigilance report.
- Lack of harmonized standards and guidances.

The last bottleneck seems to be recognized by more manufacturers, because 15 respondents indicated that the interference of MP with IVDs should be addressed through specific guidance for IVDs (e.g. ISO/NEN standards; Common Specification). The following reasons were mentioned:

- Common specifications would be a good source;
- Consistent level of safety in the industry (5x);
- To ensure that interference are correctly addressed
- It would be very useful to keep all informed properly (2x);
- No overlapping guidelines are needed. A single source of information ensures that all the manufacturers are aligned, and there is no unnecessary contradiction in the guidance. If gaps exist, the European authorities/ regulators should ensure that the widely recognized CLSI guideline for interference is updated.
- The range of available medicines is too wide. There is a need for a limited, but sufficient and relevant, list of substances to be tested according to the type of IVD MD considered

Eight of these respondents indicated additionally that interference of MPs with IVDs should be addressed through specific guidance for MPs (e.g. EMA guidelines). The following reasons were mentioned:

- Any official information which is trackable through e.g. RSS Feeds are a good tool to check the IVDs for a potential but generally unknown problem;
- Health practitioners should be aware of possible interferences with the diagnostic testing they prescribe so it is emphasized in the patient health records and the results of the diagnostic testing can be reviewed taking this risk into account;
- It is the best way to ensure the flow of information;
- IVD companies do not follow new MPs, MPs manufacturers can estimate possible interferences for some IVD products;
- To ensure consistency and monitoring for future updates and concerns.

6. Are there any bottlenecks in IVD regulation to assure that interference between medicinal products and commercial IVDs is adequately recognized and dealt with?

(Type vraag: Meerkeuze, één antwoord)

Antwoord	Aantal	Percentage
No	3	14.29 %
We don't know	15	71.43 %
Yes, the bottlenecks are:	3	14.29 %
Aantal respondenten	21	

Figure 3.4.18. Opinions regarding bottlenecks in IVD regulation

The opinions of the respondents were divided when they were asked whether the issue of interference of MP with IVDs represented a significant problem requiring more attention and action and whether it posed a high risk for patients. See Figure 3.4.19 and 3.4.20. Slightly more than half of the respondents considered interference with MPs as a (potentially) high risk.

9. Do you consider the issue of interference of medicinal products with IVDs to be a significant problem that requires more attention and action?

(Type vraag: Meerkeuze, één antwoord)

Antwoord	Aantal	Percentage
Yes	9	47.37 %
No	10	52.63 %
Aantal respondenten	19	

Figure 3.4.19 Opinions regarding necessity for attention and action

10. Do you consider the issue of interference of medicinal products with an IVD test to pose a high risk for patients?

(Type vraag: Meerkeuze, één antwoord)

Antwoord	Aantal	Percentage
Yes	10	52.63 %
No	9	47.37 %
Aantal respondenten	19	

Figure 3.4.20 Opinions regarding risks for patients

The following issues were noted by the respondents in their comments field:

- Consistency and monitoring for future updates and concerns must be assured;
- Depending on the IVD test and intended use;
- For our kind of products no significant problems are known;
- It can be, but does not often happen (2x);
- If not addressed in the assay design, and if not appropriately tested for, interference is a relevant source of false interpretations;
- In general it depends on the kind of product, means risk level;
- Interference is already recognized as a potential source of variability. CLSI guidance exists to guide appropriate testing; Manufacturers are aware, and can make risk analyses to concentrate their efforts on the most relevant compounds;
- Interferences by endogenous substances of prescribed drugs are very likely to be captured by our test systems;
- Most IVD companies routinely test for interference;
- Most IVDs are already tested;
- We have tested some of our high risk infectious disease assays regarding interferences when patients used illegal drugs. We did not find any interferences between those drugs and the assay result;
- Our products are well understood IVDs and in the past did not tend to be very sensitive for interferences with drugs / medication;
- Significant data base is available for the effects of drugs on clinical laboratory tests (2x);
- It is important that those prescribing IVD tests make note of any medication the patient is taking, so at least the laboratory professionals performing the test(s) are aware of the presence of a particular drug in the sample prior to analysis;
- This depends on the risk class of the test. However, also for higher risks classes, therapeutic decisions should not be performed on the basis of a single test result, but in the context of the patient's anamnesis, i.e. co-medications, metabolic conditions and test results of other related diagnostic parameters (e.g. metabolic parameters).

4 Discussion and conclusion

The aim of this study was to gain insight in:

- a. how IVD manufacturers, medical laboratories and registration holders of MPs safeguard the process around interference of MPs with IVDs to minimize the risks for the patient (i.e. risk of incorrect results and potential incorrect diagnosis or treatment);
- b. how (new) knowledge about such interferences is shared amongst all stakeholders.

Detecting interference

The results of this study show that both the IVDD and the IVDR contain requirements for the IVD manufacturer to investigate the influence of interfering substances or cross-reactivity on the performance of an IVD during its development. However, these provisions are stated in a general manner and only the IVDR specifically mentions interference with 'medication', whereas in the IVDD interference is mentioned generally.

Several IVD manufacturers indicated that interference of MPs with IVDs should be addressed through specific guidance for IVDs. The question is how specific this guidance could be. The number of authorised MPs is very large (more than 10.000 are currently available in the Netherlands) and each year new active substances enter the market (30 to 40 substances did so in the Netherlands during 2017⁹). It may not be feasible to test all these new substances for interference with existing or new IVDs. Assessing possible interference based on risk analysis could however be an option and be elaborated upon in guidance.

In reality, interference of MPs with IVDs is frequently detected by chance, during either clinical trials (pre-market) of the MP or use of the IVD in practice (post-market). The detection of MP interferences is however challenging due to several other factors that can affect the IVD test result (e.g. sampling procedure, interference of endogenous substances, analytical errors, human factors, etc.). In practice, interference with an MP will often not be the first factor considered in case of a deviating test result. Moreover, once interference is suspected, establishing a clear causal relationship with the MP it is not necessarily straightforward.

Assessing the risks for the patient

The IVD manufacturer should consider the outcome of interference testing in the risk analysis. In theory, the risk could be considerable when a deviation in test result has a significant impact on the diagnosis or treatment of a patient. A majority of the laboratories and little more than half of the IVD manufacturers regarded the risk substantial.

In this study, it remained unknown how often interference of a MP with an IVD has led to an incorrect diagnosis or treatment decision.

⁹ CBG Jaarverslag 2017

Frequently, a physician takes into account a range of clinical symptoms and measurements before establishing a final diagnosis and treatment and the risk of any interference will partly be mitigated by the professional experience of the physicians responsible.

Controlling interference

During the development 81% of the manufacturers responding to the questionnaire considers the potential interference of MP with the IVD, either through risk analyses or testing on a set of MPs. If interference with an MP is confirmed during use of the IVD in daily practice, the IVD manufacturer should inform their clients and possibly withdraw or redesign the IVD, and/or adapt the IFU (in line with the IVDD/IVDR). The majority of the manufacturers that responded to the questionnaire indicated that users will be informed (90%). Most of the manufacturers will also inform the marketing authorization holder (57%) and the authorities (67%). However, few manufacturers will share the information with other IVD manufacturers (9%).

Only 9% of the IVD manufacturers that responded to the questionnaire keeps track of new MP entering the market and evaluates these for potential interference. All manufacturers indicated that they actively search for information on possible interference of MPs with IVDs. However, it is unclear whether the PMS system of the IVD manufacturer will capture any interference from new MPs.

The survey results show that when a laboratory is aware that a patient is taking an MP known to interfere with an IVD test, an alternative analytical method is normally selected (if available) or a remark or warning is added to the results' report. Both the interviews and the results of the survey show, nevertheless, that the laboratories very often miss information on the MPs taken by a patient. Only in the case of well-known interferences, the applicant of the IVD test may have the possibility to tick a box on the IVD application form to indicate the use of specific MPs by the patient. The initiative of the NVKC (see section 3.3.) to connect the hospital pharmacy system with the clinical-chemical laboratory database might be helpful to detect and handle possible interference of MPs with IVDs.

Communication

Once interference has been confirmed, the IVDD as well as the IVDR require action to be taken by the manufacturer, which could be a notification of the interference in the IFU of the IVD at issue. According to the interviewees, there are a limited number of interferences included in IFUs. This may indicate that either little information on interferences is available or that interferences are not always communicated. Moreover, respondents also mentioned that any changes to the IFU were not actively communicated to other IVD or MP manufacturers or in order to adapt the IFU respectively SmPC. Furthermore, it remains unknown whether marketing authorisation holders of MPs notify interferences to IVD manufacturers.

All responding laboratories state that they (would) proactively contact the applicant of the IVD test. As mentioned above, the NVKC is working

on a database on interferences. Also, the Eudamed database may be used to provide information.

The manufacturers' survey indicates that the communication between the different stakeholders could be improved so that all have the same information available.

Conclusion

It remains unknown what the (magnitude of the) actual risks are. In theory, there may be risks due to incorrect diagnosis and/or treatment decision. According to experts, a physician often conducts several diagnostic tests and takes the patient's symptoms and complaints into account. This means that in most cases, the result of one IVD test will not be of decisive importance for the diagnosis.

Although legislation and guidance documents do not address in detail the issue of MP interference with IVDs, several safeguards to control the risks for the patient are included. In order to minimize any risk, knowledge exchange between stakeholders about interferences between MPs and IVDs may be improved. In the near future, the Eudamed database might facilitate the dissemination of information.

Acknowledgement

With special thanks to the interviewees for the kind and open conversation in preparation for the surveys and to all respondents of the surveys. We also wish to express our gratitude to MedTech Europe and their members for their assistance in sending the survey to IVD companies.

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Annex I Systematic literature search strategy

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#47 #41 OR #42 OR #46 136
#46 #44 AND #45 10
#45 vitro:ti,ab 1333814
#44 #27 AND #43 212
#43 'interfere*':ti OR 'interact*':ti OR 'cross reacti*':ti 327745
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#23 #11 OR #22 4244662
#22 diagno*:ti 679313
#21 #6 AND (#8 OR #18) 10978
#20 #4 AND #19 AND [2014-2018]/py 497
#19 #6 AND #18 9615
#18 vitro:ti 332564
#17 (#6 OR #11) AND #4 AND #16 AND [2014-2018]/py 209
#16 interferen*:ti OR 'cross reacti*':ti 30840
#15 #12 AND #14 AND [2014-2018]/py 36
#14 #4 AND #13 161732
#13 #7 AND #11 505459
#12 vitro:ti AND diagno*:ti 1521
#11 'diagnostic procedure'/exp/mj 3842542
#10 #4 AND #9 AND [2014-2018]/py 168
#9 #6 AND #8 2451
#8 'in vitro study'/exp/mj 145095
#7 'in vitro study'/exp 5232019
#6 'medical device'/exp/mj 884759
#5 'medical device'/exp 2265248
#4 #1 OR #2 OR #3 6244017
#3 'drug'/exp 2730663
#2 drug:ti OR drugs:ti OR medicine*:ti 693040
#1 'medicine'/exp 3185619

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Annex II Grey literature search strategy

1. We scoped the first 50 results, within the time window between 2014 and 2018, obtained when searching the following key terms:
 - “interference IVD with medicine”
 - “interference IVD with medicinal drug”
 - “interference IVD with pharmaceutical product”
 - “interference IVD with drug”
 - Interference AND (IVD OR "in vitro diag*" OR test) AND (medicine OR "medicinal product" OR drug) AND Europe -"drug abuse"
 - “advisory note IVD” AND interference
 - “field safety corrective action” AND interference
 - “Manufacturer incident report” AND interference

2. We also searched for “Dear doctor letters” using the following terms:
 - Interference AND (IVD OR "in vitro diag*" OR test) AND "dear doctor letter"
 - Interference AND (IVD OR "in vitro diag*" OR test) AND (medicine OR "medicinal product" OR drug) AND "dear doctor letter"
 - Interference AND (IVD OR "in vitro diag*" OR "in vitro test") AND (medicine OR "medicinal product" OR drug) AND "dear doctor letter"
 - Interference AND (IVD OR "in vitro diag*" OR "in vitro test") AND (medicine OR "medicinal product" OR drug) AND "dear doctor letter" AND Europe
 - Interference AND (IVD OR "in vitro diag*" OR "in vitro test") AND (medicine OR "medicinal product" OR drug) AND "dear doctor letter" AND Europe -"drug abuse" -"electromagnetic"

3. We searched the keywords “field safety notice” and interference on the websites of designated agencies or bodies responsible for Medical Devices (drug regulatory agencies; health Technology Assessment bodies; health Inspectorates) of the following countries:
 - Netherlands: CBG (we did not search on the website of the IGJ since in step 1 of the project we had already evaluated the information coming from notifications received by the IGJ)
 - United Kingdom: MHRA
 - France: ANSM
 - Spain: AEMPS
 - Portugal: INFARMED

4. We searched the websites of the European Medicines Agency, the European Commission and the World Health Organization.

Annex III Interview guidelines

A. For manufacturers of IVDs

- How is the possible influence of medicinal products on the test results of IVDs addressed before the IVD comes on the market?
 - Based on which criteria do you make choices for testing interference with existing medicinal products?
 - Is possible interference part of the risk analysis during the development of the test method?
- Do you receive (unsolicited) notifications about (possible interference)? If so, from whom do you receive these notifications?
- Are you actively performing PMS in order to detect interferences with medicinal products?
- How do you ensure that you are kept informed on new medicinal products entering the market or on changes to existing medicinal products that may influence the outcome of the IVD test?
 - What do you do with this information?
- Do you actively communicate (new) knowledge about interference of medicinal products with IVDs to the marketing authorisation holders of medicinal products? If so, how? If not, what are your motives for not doing this?
- How do you bring the knowledge of interference gained by you to the attention of the users of the IVD?
 - (How) do you share this knowledge with other manufacturers of IVD? If not, what are your motives for not doing this?

B. For laboratories using IVDs

- How do laboratories ensure that the (known) influence of medicinal products on results of IVDs is taken into account:
 - in the choice for the IVD and
 - the interpretation of the results?
- How does a presumption of interference arise? Do you also have examples of this?
- Is the suspicion of interference detected by you also reported to the manufacturer IVD? If not, what are your motives for not doing this?
- How is possible interference communicated to the applicants for the tests and are these applicants alerted to consult the patient's medication status?
- Are you approaching the umbrella organizations of laboratories (e.g. NVKC, NVMM, Diagned, SKML) about your suspicion of interference and vice versa?

C. For manufacturers, registration holders of medicines, and Medicines Evaluation Board

- Is the interference of medicinal products with IVDs considered during the market authorisation procedure for medicinal products?
 - If yes, when, where and how?
- Is (new) knowledge about the interference of medicinal products with IVDs:
 - communicated to the IVD manufacturers or
 - made available in other ways?
- Is knowledge about interferences of medicinal products with IVDs included in the Summary of Product Characteristics and package leaflet) of the medicinal products at issue?
- Do you ever get reports of interferences?
 - And if so, from whom?
- Do you actively study the occurrence of interferences with IVD?

Annex IV Survey among manufacturers of IVDs and laboratories

A. For laboratories using IVDs

1. In what kind of diagnostic areas is your laboratory active? (multiple options possible)

- Infectious disease
- Pathology
- Clinical chemistry
- Haematology
- Oncology
- Genetics
- Thrombosis
- Other, namely:

2. Suppose there is a known interference of a medicinal product with a commercial IVD test used at your department. How does your laboratory take that interference into account? (multiple options possible)

- Interferences with medicinal products are not taken into account.
- An alternative method of analysis or IVD is selected, if available.
- The applicant/physician is informed and requested to note down on the application form whether the patient uses the medicinal product at issue.
- Other options, namely:

3. Suppose you identify a new interference of a medicinal product with one of the commercial IVDs in use at your laboratory.

3a. Do you (or would you) proactively contact/inform the IVD manufacturer?

- Yes
- No

3b. Do you (or would you) proactively contact/inform the marketing authorization holder(s) of the medicinal product?

- Yes
How (e.g. via umbrella organisation EFPIA or EGA, or directly to individual marketing authorisation holders)?
- No

3c. Do you (or would you) proactively contact/inform the relevant professional associations in your field of diagnosis?

- Yes
- No

3d. Do you (or would you) proactively contact/inform the applicant/physician?

- Yes
- No

4. Has your lab, in the last 5 years, been approached by umbrella organizations of laboratories or another laboratory about interferences between medicinal products and commercial IVDs?

- Yes
- No

5. Is information on known interferences of medicinal products with commercial IVDs readily available?

- Yes
- No

5a. From which sources do you obtain this information?

5b. How could the flow of information be improved?

6. Are there any bottlenecks in IVD regulation to assure that interference between medicinal products and commercial IVDs is adequately recognized and dealt with?

- No
- We don't know
- Yes, the bottlenecks are:

7. Are there any bottlenecks in laboratory practice to assure that interference between medicinal products and commercial IVDs is adequately recognized and dealt with?

- No
- Yes, the bottlenecks are:

8. What could be improved in laboratory practice to assure that interference between medicinal products and IVDs does not affect the decisions taken based on the results of the test?

9. Do you consider the issue of interference of medicinal products with IVDs to be a significant problem that requires more attention and action?

- Yes, additional comments:
- No, additional comments:

10. Do you consider the issue of interference of medicinal products with an IVD test to pose a high risk for patients?

- Yes, additional comments:
- No, additional comments:

For manufacturers of IVDs

*1. In what kind of diagnostic areas is your IVD company active?
(multiple options possible)*

- Infectious disease
- Pathology
- Clinical chemistry
- Haematology
- Oncology
- Genetics
- Thrombosis
- Other, namely:

2. During the development of a new IVD, does your company consider the potential interference of medicinal products with this IVD?

- Yes
- No

If yes: How is the potential interference of medicinal products with the new IVD investigated during its development?

- The extent of the investigation depends on the outcome of a risk analysis.
Which factors are considered in the risk analysis?
- The new IVD is tested against a set of medicinal products.
Which factors determine the choice of this set?
- Otherwise, namely:

3. In the case that interference of a medicinal product with one of your marketed IVDs is (or would be) identified during post-market surveillance:

3a. Do you (or would you) proactively inform the marketing authorization holder(s) of this medicinal product?

- Yes
How (e.g. via umbrella organisations EFPIA or EGA, or directly to individual marketing authorisation holder(s))?
- No

3b. Do you (or would you) share this information proactively with other IVD manufacturers?

- Yes
How (e.g. via MedTech Europe, or directly to individual manufacturers)?
- No

3c. Do you (or would you) share this information proactively with users of these IVDs?

- Yes
- No

If yes: *Which users are (or would be) informed by you? (multiple options possible)*

- Laboratories (e.g. medical, clinical, microbiology or pathology)
- Healthcare professionals (e.g. physicians, pharmacists, nurses)
- Others, namely:

3d. *Do you (or would you) share this information proactively with the health authorities or other formal stakeholders?*

- Yes
- No

If yes: *Which authorities/formal stakeholders are (or would be) informed by you? (multiple options possible)*

- European Medicines Agency
- National medicinal product agency
- Notified Bodies
- Competent authorities
- Others, namely:

4. *Does your company keep track of new medicinal products entering the market?*

- Yes
- No

4a. *If yes: Does your company consider interference of this new medicinal products with your marketed IVDs?*

- Yes
- No

If yes: *How is the interference of this new medicinal product with your IVD investigated?*

- The type and extent of the investigation depends on the outcome of a risk analysis.
- We investigate possible interference of the new medicinal product with the IVD device/test.
- We contact the manufacturer of the new medicinal product to ask for information on possible interference.
- Otherwise, namely:

5. *How do you ensure that information on possible interference of medicinal products with IVDs reaches you? (multiple options possible)*

- We proactively ask umbrella organisations of IVD users.
- We proactively ask umbrella organisations of healthcare professionals.
- We proactively check Competent Authority reports.
- We proactively ask the manufacturers of medicinal products.
- We proactively search scientific literature.

- We await any notification from IVD users, healthcare professionals, Competent Authorities or medicinal product manufacturers.
- Otherwise, namely:

6. Are there any bottlenecks in IVD regulation to assure that interference between medicinal products and commercial IVDs is adequately recognized and dealt with?

- No
- We don't know
- Yes, the bottlenecks are:

7. Should interference of medicinal products with IVDs be addressed through specific guidance for IVDs (e.g. ISO/NEN standards; Common Specification)?

- Yes, because:
- No

8. Should interference of medicinal products with IVDs be addressed through specific guidance for medicinal products (e.g. EMA guidelines)?

- Yes, because:
- No

9. Do you consider the issue of interference of medicinal products with IVDs to be a significant problem that requires more attention and action?

- Yes, additional comments:
- No, additional comments:

10. Do you consider the issue of interference of medicinal products with an IVD test to pose a high risk for patients?

- Yes, additional comments:
- No, additional comments:

Annex V Overview of legislation, guidelines and standards reviewed

Source	Version/date	Subject	Provision/guidance/text of relevance
IVDD	1998		<p>Article 11, Vigilance procedure.</p> <p>1. Member States shall take the necessary steps to ensure that any information brought to their knowledge, in accordance with the provisions of this Directive, regarding the incidents mentioned below involving devices bearing the CE marking is recorded and evaluated centrally:</p> <p>(a) any malfunction, failure or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health;</p> <p>(b) any technical or medical reason in relation to the characteristics or performance of a device for the reasons referred to in subparagraph (a), leading to systematic recall of devices of the same type by the manufacturer.</p> <p>2. Where a Member State requires medical practitioners, the medical institutions or the organisers of external quality assessment schemes to inform the competent authorities of any incidents referred to in paragraph 1, it shall take the necessary steps to ensure that the manufacturer of the device concerned, or his authorized representative, is also informed of the incident.</p> <p>3. After carrying out an assessment, if possible together with the manufacturer, Member States shall, without prejudice to Article 8, immediately inform the Commission and the other Member States of the incidents referred to in paragraph 1 for which appropriate measures, including possible withdrawal, have been taken or are contemplated.</p>

Source	Version/date	Subject	Provision/guidance/text of relevance
			Annex I: The devices must be designed and manufactured in such a way that they are suitable for the purposes referred to in Article 1(2)(b), as specified by the manufacturer, taking account of the generally acknowledged state of the art. They must achieve the performances, in particular, where appropriate, in terms of analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of known relevant interference, and limits of detection, stated by the manufacturer.
Besluit in-vitro diagnostica	2016		-

Source	Version/date	Subject	Provision/guidance/text of relevance
IVDR	2017		<p data-bbox="1104 395 2112 592">Page 4, 32: The risk management system should be carefully aligned with and reflected in the performance evaluation process for the device, including the clinical risks to be addressed as part of performance studies, performance evaluation and post-market performance follow-up. The risk management and performance evaluation processes should be inter-dependent and should be regularly updated.</p> <p data-bbox="1104 624 2112 820">Page 7, 63: It is necessary to ensure that the clinical evidence of devices is updated throughout their lifecycle. Such updating entails the planned monitoring of scientific developments and changes in medical practice by the manufacturer. Relevant new information should then trigger a reassessment of the clinical evidence of the device thus ensuring safety and performance through a continuous process of performance evaluation.</p> <p data-bbox="1104 852 2112 1273">Page 9, 75: Manufacturers should play an active role during the post-market phase by systematically and actively gathering information from post-market experience with their devices in order to update their technical documentation and cooperate with the national competent authorities in charge of vigilance and market surveillance activities. To that end, manufacturers should establish a comprehensive post-market surveillance system, set up under their quality management system and based on a post-market surveillance plan. Relevant data and information gathered through post-market surveillance, as well as lessons learned from any implemented preventive and/or corrective actions, should be used to update any relevant part of technical documentation, such as those relating to risk assessment and performance evaluation, and should also serve the purposes of transparency.</p> <p data-bbox="1104 1305 2112 1433">Page 9, 76: In order to better protect health and safety regarding devices on the market, the electronic system on vigilance for devices should be made more effective by creating a central portal at Union level for reporting serious incidents and field safety corrective actions.</p>

Source	Version/date	Subject	Provision/guidance/text of relevance
			<p>Page 16, 60: 'adverse event' means any untoward medical occurrence, inappropriate patient management decision, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a performance study, whether or not related to the device for performance study;</p> <p>Page 17, 62: 'device deficiency' means any inadequacy in the identity, quality, durability, reliability, safety or performance of a device for performance study, including malfunction, use errors or inadequacy in information supplied by the manufacturer;</p> <p>Page 17, 67: 'incident' means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any harm as a consequence of a medical decision, action taken or not taken on the basis of information or result(s) provided by the device;</p> <p>Page 23, 12: Manufacturers shall have a system for recording and reporting of incidents and field safety corrective actions as described in Articles 82 and 83.</p> <p>Page 33, Article 29 Summary of safety and performance 2. The summary of safety and performance shall include at least the following aspects: (a) the identification of the device and the manufacturer, including the Basic UDI-DI and, if already issued, the SRN; (b) the intended purpose of the device and any indications, contra-indications and target populations; (c) a description of the device, including a reference to previous generation(s) or variants if such exist, and a description of the differences, as well as, where relevant, a description of any accessories, other devices and products, which are intended to be used in combination with the device; (d) reference to any</p>

Source	Version/date	Subject	Provision/guidance/text of relevance
			<p>harmonised standards and CS applied; (e) the summary of the performance evaluation as referred to in Annex XIII, and relevant information on the PMPF; (f) the metrological traceability of assigned values; (g) suggested profile and training for users; (h) information on any residual risks and any undesirable effects, warnings and precautions.</p> <p>Page 49, Article 56 Performance evaluation and clinical evidence. Confirmation of conformity with relevant general safety and performance requirements set out in Annex I, in particular those concerning the performance characteristics referred to in Chapter I and Section 9 of Annex I, under the normal conditions of the intended use of the device, and the evaluation of the interference(s) and cross-reaction(s) and of the acceptability of the benefit-risk ratio referred to in Sections 1 and 8 of Annex I, shall be based on scientific validity, analytical and clinical performance data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III.</p> <p>Page 50. Article 57 General requirements regarding performance studies 2. Where appropriate, performance studies shall be performed in circumstances similar to the normal conditions of use of the device.</p> <p>Page 65. Article 78 Post-market surveillance system of the manufacturer 1. For each device manufacturers shall plan, establish, document, implement, maintain and update a post-market surveillance system in a manner that is proportionate to the risk class and appropriate for the type of device. That system shall be an integral part of the manufacturer's quality management system referred to in Article 10(8). 2. The post-market surveillance system shall be suited to actively and systematically gathering, recording and analysing relevant data on the quality, performance and safety of a device throughout its entire lifetime,</p>

Source	Version/date	Subject	Provision/guidance/text of relevance
			<p>and to drawing the necessary conclusions and to determining, implementing and monitoring any preventive and corrective actions.</p> <p>Annex I. GENERAL SAFETY AND PERFORMANCE REQUIREMENTS Page 86, REQUIREMENTS REGARDING PERFORMANCE, DESIGN AND MANUFACTURE</p> <p>9. Performance characteristics</p> <p>9.1. Devices shall be designed and manufactured in such a way that they are suitable for the purposes referred to in point (2) of Article 2, as specified by the manufacturer, and suitable with regard to the performance they are intended to achieve, taking account of the generally acknowledged state of the art. They shall achieve the performances, as stated by the manufacturer and in particular, where applicable: (a) the analytical performance, such as, analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and quantitation, measuring range, linearity, cut-off, including determination of appropriate criteria for specimen collection and handling and control of known relevant endogenous and exogenous interference, cross- reactions; and...</p> <p>Page 95, The instructions for use shall contain all of the following particulars:</p> <p>(w) Confirmation of conformity with relevant general safety and performance requirements set out in Annex I, in particular those concerning the performance characteristics referred to in Chapter I and Section 9 of Annex I, under the normal conditions of the intended use of the device, and the evaluation of the interference(s) and cross-reaction(s) and of the acceptability of the benefit-risk ratio referred to in Sections 1 and 8 of Annex I, shall be based on scientific validity, analytical and clinical performance data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III.</p>

Source	Version/date	Subject	Provision/guidance/text of relevance
			<p>Page 96, REQUIREMENTS REGARDING INFORMATION SUPPLIED WITH THE DEVICE</p> <p>20. Label and instructions for use. 20.4.2 In addition, the instructions for use for devices intended for self-testing shall comply with all of the following principles:</p> <p>(e) information shall be provided with advice to the user on action to be taken (in case of positive, negative or indeterminate result), on the test limitations and on the possibility of false positive or false negative result. Information shall also be provided as to any factors that can affect the test result such as age, gender, menstruation, infection, exercise, fasting, diet or medication.</p> <p>Annex II. TECHNICAL DOCUMENTATION</p> <p>Page 99, 6. PRODUCT VERIFICATION AND VALIDATION The documentation shall contain the results and critical analyses of all verifications and validation tests and/or studies undertaken to demonstrate conformity of the device with the requirements of this Regulation and in particular the applicable general safety and performance requirements. This includes:</p> <p>6.1.2.3. Analytical specificity This Section shall describe interference and cross reactivity studies performed to determine the analytical specificity in the presence of other substances/agents in the specimen. Information shall be provided on the evaluation of potentially interfering and cross-reacting substances or agents on the assay, on the tested substance or agent type and its concentration, specimen type, analyte test concentration, and results. Interferents and cross-reacting substances or agents, which vary greatly depending on the assay type and design, could derive from exogenous or endogenous sources such as: (a) substances used for patient treatment such as medicinal products; (b) substances ingested by the patient such as alcohol, foods; (c) substances added during specimen preparation such as preservatives, stabilisers; (d)</p>

Source	Version/date	Subject	Provision/guidance/text of relevance
			<p>substances encountered in specific specimen types such as haemoglobin, lipids, bilirubin, proteins; (e) analytes of similar structure such as precursors, metabolites or medical conditions unrelated to the test condition including specimens negative for the assay but positive for a condition that can mimic the test condition.</p>
<p>NEN EN ISO 18113-1 IFU IVD general requirements</p>	<p>2011</p>	<p><i>In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 1: Terms, definitions and general requirements</i></p>	<p>Page 5, 3.21 hazardous situation circumstance in which people, property or the environment are exposed to one or more hazards NOTE Incorrect IVD examination results can contribute to a hazardous situation for a patient. See ISO 14971:2007, Annex H.</p> <p>Page 8, 3.35 limitation of the procedure specific situation in which an IVD examination procedure might not perform as intended</p>

Source	Version/date	Subject	Provision/guidance/text of relevance
			<p>NOTE 1 Factors that affect the performance of an IVD examination procedure can be physiological as well as analytical.</p> <p>Page 12, 3.53 precaution statement that alerts users to special care or activities necessary for safe and effective use of an IVD medical device or to avoid damage to the IVD medical device that could occur as a result of use, including misuse NOTE 1 The distinction between warnings and precautions is a matter of degree, considering the likelihood and seriousness of the hazard. See the definition of warning (3.74).</p> <p>Page 27, A.3.2 analytical interference interference: systematic effect on a measurement caused by an influence quantity, which does not by itself produce a signal in the measuring system, but which causes an enhancement or depression of the value indicated NOTE Interference with measurement results is related to the concept of analytical specificity (A.3.4).</p> <p>Page 30, A.3.12 cross-reactivity degree to which a substance other than the analyte binds to a reagent in a competitive binding immunochemical measurement procedure EXAMPLES Antibody binding to metabolites of the analyte, structurally similar drugs, etc. NOTE 1 Analytical specificity (A.3.4) is a related concept.</p> <p>Page 32, A.3.19 interfering quantity interferent: quantity that is not the measurand but that affects the result of the measurement</p>

Source	Version/date	Subject	Provision/guidance/text of relevance
			<p>EXAMPLES</p> <ul style="list-style-type: none"> -Effect of bilirubin, haemoglobin, lipids or coloured drugs on certain colorimetric measurement procedures; -cross-reacting metabolites in an immunochemical measurement procedure (see cross-reactivity, A.3.12).
NEN EN ISO 18113-2 labelling IVD reagents professional use	2011	<i>In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 2: In vitro diagnostic reagents for professional use</i>	<p>Page 5, Benefits and limitations of the IVD medical device with respect to the intended use shall be described, where appropriate.</p> <p>Page 8, 7.18 Limitations of the examination procedure Any limitations of the examination procedure shall be described, including information regarding</p> <ul style="list-style-type: none"> a) known clinically relevant interfering substances, b) the examination of inappropriate primary samples and potential consequences, if known, c) factors and circumstances that can affect the result, together with precautions to avoid incorrect results, d) potential for carryover.
NEN EN ISO 18113-3 labelling IVD equipment professional use	2011	<i>In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 3: In vitro diagnostic instruments for professional use</i>	<p>Page 3, 7.3 Intended use The intended use of the IVD instrument shall be described. EXAMPLE Measurement of analytes in biological primary samples, using reagents and calibrators intended for use with this instrument. Benefits and limitations of the IVD medical device with respect to the intended use shall be described. Medical use may be described, where appropriate.</p> <p>Page 4, 7.5 Warnings and precautions Information relevant to the following shall be given:</p> <ul style="list-style-type: none"> a) residual risks related to installation, operation, maintenance, transportation, storage or disposal of the IVD instrument and/or its accessories; <p>EXAMPLE Risks related to handling and disposal of infectious or potentially infectious materials.</p>

Source	Version/date	Subject	Provision/guidance/text of relevance
			<p>b) known interferences that present significant risk; c) electromagnetic compatibility, emission and immunity, and the requirements of IEC 61326-2-6 apply;</p> <p>Page 8, 7.20 Troubleshooting Information shall be provided on the following: a) interpretation of malfunction messages; b) determining causes of common malfunctions; c) malfunctions that can be corrected by the user; d) malfunctions necessitating service calls; e) measures to be taken in the event of a change in the performance characteristics of the IVD instrument.</p>
NEN EN ISO 18113-4 labelling IVD reagent self-testing	2011	<i>In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 4: In vitro diagnostic reagents for self-testing</i>	<p>Page 5, 7.3 Intended use The intended use shall be described in appropriate detail, including, where appropriate, the measure and, primary sample type and patient population, in terminology suitable for a lay person. Benefits and limitations of the IVD medical device with respect to the intended use shall be described, where appropriate.</p> <p>Page 8, 7.17 Limitations of examination procedure Any limitations of the examination procedure shall be described, including information regarding a) known, clinically relevant interfering substances, b) the examination of inappropriate primary samples and potential consequences, if known, c) factors and circumstances that can affect the result, together with precautions to avoid incorrect results. EXAMPLES Fasting, medication.</p>
NEN EN ISO 18113-5 labelling IVD instruments self-testing	2009	<i>In vitro diagnostic medical devices - Information supplied by the</i>	<p>Page 4, 7.5. Warnings and precautions Information relevant to the following shall be given: a) residual risks related to installation, operation, maintenance, transportation, storage or disposal of the IVD instrument and/or its</p>

Source	Version/date	Subject	Provision/guidance/text of relevance
		<i>manufacturer (labelling) - Part 5: In vitro diagnostic instruments for self-testing</i>	<p>accessories; EXAMPLE Risks related to handling and disposal of infectious or potentially infectious materials. b) known interferences that present significant risk; c) electromagnetic compatibility, emission, and immunity, and the requirements of IEC 61326-2-6 apply;</p> <p>Page 5, 7.9 Limitations of use Information shall be provided on the limitations of use of the IVD instrument. EXAMPLES Sample viscosity, accessory compatibility, computer connectivity.</p> <p>Page 5, 7.12 Control procedure Adequate information about a means to verify that the IVD instrument is performing within specifications shall be provided. EXAMPLES For glucose meters, identification of acceptable control materials, frequency of examination of control materials, actions to be taken when control data are out of established control limits.</p> <p>Page 5, 7.13 Reading of examination results Instructions on how to read the result of the IVD examination shall be provided. Results shall be expressed and presented in a way that can be readily understood by a lay person. Results shall be expressed and presented in such a way as to avoid misinterpretation by a lay person. Information shall be provided on factors that may lead to incorrect results, together with appropriate precautions.</p>
Nederlandse praktijkrichtlijn NPR ISO/TR 24971 Guidance on the application	2013	<i>Application of risk management to medical devices</i>	Page 2 , For hazards or hazardous situations that are identified for the particular medical device but are not specifically addressed in any standard, the manufacturer needs to address those hazards or hazardous situations in the risk management process. The manufacturer is required

Source	Version/date	Subject	Provision/guidance/text of relevance
of ISO 14971			<p>to estimate and evaluate the risks and, if necessary, control these risks (see 4.4 and Clauses 5 and 6 of ISO 14971:2007).</p> <p>Page 6, Production and post-production feedback loop Typically, the initial risk assessment is based on experience with similar medical devices or applications on the market, or on assumptions when new medical devices are released to the market. Information received after market entry is valuable for confirming or correcting assumptions and estimates (both overestimates and underestimates), or identifying omissions made during the risk analysis and risk control phases. Clause 9 of ISO 14971:2007 requires that a feedback loop is established in the manufacturer's organization to collect and evaluate such information for potential relevance to medical device safety (see Figure 2). The feedback loop should consist of the following steps:</p> <ul style="list-style-type: none"> — Observation and transmission — Assessment — Action <p>For the feedback loop to be effective, it is necessary that the responsibility for maintaining the risk management file is defined.</p> <p>...For information to be relevant to a manufacturer's medical device it need not be directly related to their own or a competitor's product. Information relating to similar medical devices with similar intended use or similar principles of operation can yield useful post-market information on the relevance of the risks of the manufacturer's medical device.</p> <p>Page 8, The means of transmission of this information will depend on the source of the information. Some information will be pulled (initiated by the manufacturer) and some information will be pushed (initiated by sources like the customer, authorities, or patient). In either case, the organization should ensure that efficient communication channels are</p>

Source	Version/date	Subject	Provision/guidance/text of relevance
			<p>planned and established to allow for timely and accurate receipt of information. The rate at which the manufacturer pulls information from the various sources (including users) depends on the maturity of the medical device, its technology and the specific market.</p> <p>Page 10, Information for safety can be given in the form of a warning label attached to medical devices or as a warning statement in the instructions for use. Some examples are given below.</p> <ul style="list-style-type: none"> — Warning: Do not step on surface. — Warning: Do not remove cover, risk of electric shock. — Warning: Use with caution. Serum samples containing more than 60 mg/dl haemoglobin will interfere with the test principle, thereby limiting the diagnostic result.
Common technical specifications for in vitro - diagnostic medical devices	2009	<p><i>COMMISSION DECISION of 3 February 2009 amending Decision 2002/364/EC on common technical specifications for in vitro-diagnostic medical devices</i></p>	<p>Page 4, 3. COMMON TECHNICAL SPECIFICATIONS (CTS) FOR PRODUCTS REFERRED TO IN ANNEX II, LIST A OF DIRECTIVE 98/79/EC</p> <p>3.1.13. Devices shall be evaluated to establish the effect of potential interfering substances, as part of the performance evaluation. The potential interfering substances to be evaluated will depend to some extent on the composition of the reagent and configuration of the assay. Potential interfering substances shall be identified as part of the risk analysis required by the essential requirements for each new device but may include, for example:</p> <ul style="list-style-type: none"> — specimens representing “related” infections, — specimens from multipara, i.e. women who have had more than one pregnancy, or rheumatoid factor positive patients, — for recombinant antigens, human antibodies to components of the expression system, for example anti-E. coli, or anti-yeast,
NEN EN ISO 13485 OMS for medical device manufacturers	2016	Medical devices - Quality management	-

Source	Version/date	Subject	Provision/guidance/text of relevance
		systems - Requirements for regulatory purposes	
NEN EN ISO 14971 Risk management for medical devices	2007	<i>Nederlandse norm NEN-EN-ISO 14971 (en) Medical devices - Application of risk management to medical devices (corrected and reprinted 2012-07) (ISO14971:2007-03, IDT)</i>	<p>Page 51, Questions C.2.13 Is the medical device intended for use in conjunction with other medical devices, medicines or other medical technologies? Factors that should be considered include identifying any other medical devices, medicines or other medical technologies that can be involved and the potential problems associated with such interactions, as well as patient compliance with the therapy.</p> <p>Page 89, H.2.4 Identification of known and foreseeable hazards H.2.4.4 Identifying hazards in normal use unexpected influence of other constituents (interfering factors) in the sample matrix: new drugs, biochemical metabolites, heterophilic antibodies and sample preparation materials can affect the performance characteristics of an IVD examination procedure;</p> <p>Page 94, H4 Risk Control H.4.2.3 Information for safety H.4.2.3.1 Performance characteristics Laboratory directors and healthcare providers need to know the relevant performance characteristics in order to determine if the IVD medical device is suitable for their use. This information is supplied by the manufacturer. Reliable estimates of performance characteristics at recognised medical decision points disclose residual risks and enable the proper interpretation of examination results; e.g., – analytical specificity (e.g., effects of interfering or cross-reacting substances);</p>

Source	Version/date	Subject	Provision/guidance/text of relevance
			<p>Page 98, The following limitations should be considered when estimating the reduction in risk resulting from specific information supplied by the manufacturer.</p> <ul style="list-style-type: none"> – Instructions for use provided with professional use IVD medical devices are intended for medical laboratories; information about contra-indicated uses, interfering drugs, and other information pertaining to the use of IVD examination results might not reach the physicians who order the examinations.
NEN EN ISO 15197 Blood-glucose monitoring systems	2015	<i>In vitro diagnostic test systems - Requirements for blood-glucose monitoring systems for selftesting in managing diabetes mellitus (ISO 15197:2013, IDT)</i>	<p>Page 35, Annex A (informative) Possible interfering substances</p> <p>A.1 Purpose The purpose of this annex is to identify substances that could be present in the blood of intended users and that have been found to interfere with one or more glucose measurement procedures. This list is not intended to include all possible interfering substances and is not intended to require testing if there is no reason to suspect possible interference. Manufacturers should consider whether these substances can potentially interfere with their system, as described in 4.3.2. Interference testing requirements are described in 6.4.4. Decisions not to evaluate substances listed in this annex shall be justified in the risk analysis.</p> <p>A2 Possible interfering substances</p> <ul style="list-style-type: none"> a) Acetaminophen (paracetamol) b) Ascorbate (ascorbic acid) c) Bilirubin d) Cholesterol e) Creatinine

Source	Version/date	Subject	Provision/guidance/text of relevance
			<ul style="list-style-type: none"> f) Dopamine g) EDTA h) Galactose i) Gentisic acid j) Glutathione k) Haemoglobin l) Heparin a) Ibuprofen b) Icodextrin c) L-DOPA (L-3,4-dihydroxyphe- nylalanine) d) Maltose e) Methyl-DOPA f) Pralidoxime Iodide (PAM) g) Salicylate h) Tolbutamide i) Tolazamide j) Triglycerides k) Urate (uric acid)

Source	Version/date	Subject	Provision/guidance/text of relevance
			<p data-bbox="1115 424 1317 451">l) Xylose</p> <p data-bbox="1104 520 1738 547">Page 9, 4.3.2 Risk assessment and control</p> <p data-bbox="1104 555 2085 611">Risks shall be assessed at a minimum from the following possible causes of hazardous situations:</p> <ul style="list-style-type: none"> <li data-bbox="1104 619 2078 675">a) interference by endogenous and exogenous blood components, other than the measured, including where appropriate those listed in Annex A; <li data-bbox="1104 683 1906 710">b) influence of packed cell volume on the measured values; <li data-bbox="1104 718 1787 745">c) failure to adjust the meter properly, e.g. coding; <li data-bbox="1104 753 1469 780">d) use of expired reagents; <li data-bbox="1104 788 1525 815">e) improper test strip insertion; <li data-bbox="1104 823 1503 850">f) insufficient sample volume; <li data-bbox="1104 858 2067 885">g) result beyond the measuring interval displayed, e.g. higher or lower; <li data-bbox="1104 893 1899 920">h) font style and size of display for visually impaired users; <li data-bbox="1104 928 2056 956">i) misread of the measured value if the display has a missing segment; <li data-bbox="1104 963 1832 991">j) impact of battery removal on stored data or values; <li data-bbox="1104 999 2078 1026">k) effect of moving the device or touching buttons during measurement; <li data-bbox="1104 1034 2022 1061">l) hazards associated with transmitting data, e.g. by cable, wireless; <li data-bbox="1104 1069 2107 1102">m) risk control measures shall be implemented where necessary to reduce or control the risks to an acceptable level. <p data-bbox="1104 1142 1603 1169">Page 25, 6.4 Influence quantities</p> <p data-bbox="1104 1177 1473 1204">6.4.1 General requirements</p> <p data-bbox="1104 1212 2074 1329">The effect of influence quantities, such as packed cell volume and interfering substances in blood, shall be evaluated and addressed in the risk management process. Effects that exceed the acceptability criteria shall be disclosed in the instructions for use.</p> <p data-bbox="1104 1369 1630 1396">Page 28, 6.4.4 Interference testing</p> <p data-bbox="1104 1404 1384 1431">6.4.4.1 Study design</p>

Source	Version/date	Subject	Provision/guidance/text of relevance
			<p>The evaluation shall be conducted at a minimum of 2 glucose concentrations, one within the interval of 2,8 mmol/l to 5,5 mmol/l (50 mg/dl to 100 mg/dl) and the other within the interval of 13,9 mmol/l to 19,4 mmol/l (250 mg/dl to 350 mg/dl). Substances to evaluate for possible interference shall be identified by risk analysis. The requirements of ISO 14971 pertaining to hazard identification apply. Annex A contains a list of substances that could be present in blood and have been found to interfere with a glucose measurement procedure. These substances shall be considered in the risk analysis. If a substance listed in Annex A is not evaluated experimentally, the decision shall be justified. A paired-sample experimental design that compares measured glucose values from samples with an added substance to a control sample without the added substance is recommended. Other experimental designs (e.g. multifactorial) are acceptable with statistical justification.</p> <p>NOTE Reference[13] provides guidelines for evaluating potentially interfering substances, including recommended test concentrations. A reference measurement procedure with suitable precision and trueness shall be used to assign glucose reference values to the samples.</p> <p>6.4.4.2 Acceptance criteria</p> <p>6.4.4.3 Sample preparation</p> <p>6.4.4.4 Evaluation procedure</p> <p>6.4.4.5 Data analysis and presentation of results</p>

Annex VI Results of the literature/internet study

Reference	IVDs	Medicine	How did the interference become known	Who notified the interference	What actions were taken when the interference was found
www.Sebia.com , accessed May 2018	Immunofixation test	Daratumumab	Not mentioned	Not mentioned	Interaction of daratumumab with IVD tests is well known. This company has designed a new IVD to mitigate the interference.
patient.info, accessed May 2018	Thyroid Function Tests	Heparin, non-steroidal anti-inflammatory drugs or high-dose aspirin (>2 g/day) may cause analytical interference (increased FT4 by displacement).	Not mentioned	Not mentioned	The requesting doctor should provide adequate clinical information to guide the laboratory in the selection of the most appropriate thyroid function test.
https://www.hpra.ie/docs/default-source/field-safety-notice/may-2018/v36031_fsn.pdf?sfvrsn=2	Tests based on NAD(H) and/or NADP(H) reaction principle: ALAT (GPT) FS (IFCC mod.); ATP Hexokinase FS; CK-MB FS; GLDH FS DGKC	Sulfasalazine- and sulfapyridine	Not mentioned	Manufacturer (Diasys) FSN	Actions by manufacturer: updated package inserts by inserting note into "Warnings and Precautions" sections for the products mentioned, namely: <i>"Sulfasalazine and sulfapyridine medication may lead to false results in patient samples. Blood collection must be done before drug administration. Please inform all users of the affected products immediately."</i>

Reference	IVDs	Medicine	How did the interference become known	Who notified the interference	What actions were taken when the interference was found
Poels, 2017 (www.afmps.be)	Estradiol immunoassays	Fulvestrant	Not mentioned	Competent Authority	By the competent authority: List, confirmation and feedback on the verification actions
Poels, 2017 (www.afmps.be)	Trinder Glucose activity test	"certain drugs"- not further specified	Not mentioned	Competent Authority	By the competent authority: List, confirmation and feedback on the verification actions
Piketty et al., 2017	Streptavidin-biotin-based immunoassays	Biotin (supplement) B-complex vitamin	Discrepancy between the clinical picture and the laboratory results, namely by: <ul style="list-style-type: none"> --- Showing a lack of coherence with the clinical presentation; --- Comparing physiologically dependent variables; --- Extremely unusual analyte concentration; --- Markedly different results given by different analytical methods. 	N.A.	Informing research teams properly. <ul style="list-style-type: none"> a) Introduce sampling time protocols b) Comparing the results with an alternative method c) Reagent companies reformulated assays aiming at minimizing risk of misleading results e) clinicians actively ask their patient about biotin intake f) Laboratories give systematic warning on biotin interference together with any result of a method involving the streptavidin-biotin interaction. g) Test for linearity, retesting off biotin h) Critical analysis of results, open communication between laboratory and clinical staff

Reference	IVDs	Medicine	How did the interference become known	Who notified the interference	What actions were taken when the interference was found
MHRA, 2016	Estradiol immunoassays	Fulvestrant. This drug has a similar chemical structure to estradiol and may cross-react with the antibodies used in immunoassays.	Not mentioned	Manufacturers. Both Siemens and Roche have issued FSNs communicating that the drug fulvestrant (Faslodex®) may cause falsely elevated estradiol results in assays.	<p>Action by Laboratory staff:</p> <ul style="list-style-type: none"> • Determine if estradiol immunoassays are used in the laboratory. • Continue to use affected estradiol immunoassays for patients not on fulvestrant. • If measuring estradiol levels in patients on fulvestrant consider alternative methods, such as LC-MS. • Consider the need to carry out a review of previously reported test results. • Monitor regulator website or subscribe to email alerts for any possible further FSNs on this issue. <p>Action by Healthcare personnel managing patients on this drug:</p> <ul style="list-style-type: none"> • When test requests include estradiol, state if the patient is on fulvestrant. • Consider reassessing the menopausal status of patients on fulvestrant by other means where necessary.
MHRA, 2016	Different assays utilized by Siemens ADVIA instruments	N-acetylcysteine (NAC)	Not mentioned	Not mentioned	<p>Action by all healthcare personnel managing patients on these drugs:</p> <ul style="list-style-type: none"> • Ensure all relevant members of staff receive the manufacturer's FSN and that they understand the problem and the advice given by the manufacturer. • Continue to only use affected assays on patients that are not being treated with NAC.

Reference	IVDs	Medicine	How did the interference become known	Who notified the interference	What actions were taken when the interference was found
					<ul style="list-style-type: none"> • Ensure bloods are taken prior to NAC treatment. • When requesting any of the affected assays, record on the request if the patient is being treated with NAC. • Monitor the MHRA website or subscribe to email alerts for any further FSNs on this issue.
Roche, 2014	IVDs using tests based on Trinder Reaction	1. Acetaminophen (Paracetamol) and the metabolite N-acetyl-p-benzoquinone imine (NAPQI) 2. N-Acetylcysteine (NAC) 3. Metamizole (Novaminsulfone, Dipyron) and the metabolites 4- Aminoantipyrine (4-AAP) and 4-Methylaminoantipyrine (4-MAP)	Not mentioned	Manufacturer (Roche) notice	Actions taken by Roche Diagnostics: a) Added info into "Limitations - interference" section of the Trinder test method sheets. b) Adjusted package inserts, including the information that venipuncture should be performed prior to the administration of Metamizole. Actions to be taken by the customer/user: a) Being aware that the recovery of Trinder tests may be falsely low when the blood sample is taken while levels of NAC, NAPQI, and Metamizole are still present. b) Venipuncture should be performed prior to the administration of Metamizole. c) Venipuncture immediately after or during the administration of Metamizole may lead to falsely low results.

Reference	IVDs	Medicine	How did the interference become known	Who notified the interference	What actions were taken when the interference was found
AEMPS, 2014	Accu-check compact	Ceftriaxone	Not mentioned	Notified by manufacturer	Healthcare professional can advise their diabetic patients to temporarily use an alternative method.
AEMPS, 2014	Some ELISA tests to detect antibodies against HIV1, Hepatitis C virus, or HTLV virus.	Vaccine against flu	Not mentioned	Manufacturer, via Summary of Product Characteristics	Mentioned in the SmPC: <ul style="list-style-type: none"> Use the technique of Western Blot to confirm a false positive result. A temporary false positive result may be due to the production of IgM due to the vaccination.

