Sensitivity & Specificity Summary with Example

Sensitivity

Sensitivity measures how often a test/device correctly generates a positive result for people who have the condition that's being tested for (also called positive control). A test/device that's highly sensitive will flag almost everyone who has the disease and not generate many false-negative results.

Sensitivity is a method to detect how accurately a device or test or drug is performing its role. Take for example a protein which is specifically express in one tissue; An antibody was developed to determine the expression of that protein by using IHC method is called the IVD device in this example; To detect the Sensitivity of that antibody, IHC study should perform on both known positive control, negative control. A Positive control should show positive and negative control should show negative expression by using this antibody.

Intra and inter runs: Intra run is test results of the same lot# of manufactured device/drug/test kit on different days. Intra run explains about the reliability of the product performance. Inter run is the test results of different Lot# (minimum 3 lots) manufactured on different dates on different samples. Inter run explains the reproducibility of products performance.

Summary to detect Sensitivity for the claimed test/IVD/drug:

- The Literature search for the same or similar kind of device performed in different patients or tissues to find out the device's purpose and exact role
- Literature search to detect cases and controls
- There should be inclusion and exclusion criteria for the literature search
- Also, it is very important that there should be Inter and Intra runs to be run with good results

Table: **Overview of the literature included**

Year	Authors	Journal	Title of Article	Study Subjects	Method/ Procedure	Results/ Findings	Potential Claims	Sensitivity	Specificity

To determine the comparable performance of the test/device, a literature search should perform to find out the gold standard procedure (A procedure which is already approved or already used in literature) for positive and negative controls for that specific test/device.

Table: **Gold Standard procedure**

Gold standard procedure available	Similar kind of test/device/drug	Outcome of the Gold standard	Outcome of the claimed test/device/drug	Equivalence

To determine the claims of the proposed device, the device should perform the test more specifically by the same procedure which was found on literature search.

Table: **Data appraisal**

Criteria	Description	Performance
Appropriate device	Was the claimed device is the same as available in literature?	Same Similar kind Another device
Appropriate performance	Does the device is performing exactly the same as shown in the intended use?	Same Minor deviation Major deviation
Sensitivity	What is device's is a high true positive rate	99 – 100% 90 – 98% < 90%
Acceptable quality	Do the device is having an acceptable range of Sensitivity and Specificity	Yes No

Table: **Inter run and intra run**

Test/Device/Drug Manufactured date	Inter run data	Outcome of Inter run	Intra run data	Outcome of Intra run

Specificity

Specificity measures a test's/device's ability to correctly generate a negative result for people who don't have the condition that is being tested for (also called negative control). A high-specificity test will correctly rule out almost everyone who doesn't have the disease and won't generate any false-positive results.

Sensitivity and Specificity are the methods to detect how specifically a device or test or drug is performing its role. Specificity is the most important in IVD validation.

Intra and inter runs: Intra run is test results of the same lot# of manufactured device/drug/test kit on different days. Intra run explains about the reliability of the product performance. Inter run is the test results of different Lot# (minimum 3 lots) manufactured on different dates on different samples. Inter run explains the reproducibility of product performance.

Summary to detect Specificity for claimed test/IVD/drug:

- Specificity can be detected by the same method/procedure followed in sensitivity
- Literature search for same or similar kind of device performed in different patients or tissues to find out the device purpose and exact role
- Literature search to detect case and controls
- There should be inclusion and exclusion criteria for literature search
- Also it is very important that there should be Inter and Intra runs to be run with good results

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Table: **Data appraisal**

Criteria	Description	Performance
Appropriate device	Was the claimed device is the same as available in literature?	Same Similar kind Other device
Appropriate performance	Does the device is performing exactly the same as shown in the intended use?	Same Minor deviation Major deviation
Specificity	What is device's is a high true positive rate	99 – 100% 90 – 98% < 90%
Acceptable quality	Do the device is having an acceptable range of Sensitivity and Specificity	Yes No

Table: **Inter run and intra run**

Test/Device/Drug Manufactured date	Inter run data	Outcome of Inter run	Intra run data	Outcome of Intra run

Example: Estrogen Receptor (ER) monoclonal antibody to detect ER antigen on human FFPE tissues

Sensitivity and Specificity were interconnected thus summarized both simultaneously.

Sensitivity and Specificity

Introduction

Estrogen Receptor (ER) is a group of proteins found inside of human cells. This protein is a receptor for the estrogen hormone present in the nucleus of the cell. Once activated by estrogen, the ER can translocate into the nucleus and bind to DNA to regulate the activity of different genes (i.e. it is a DNA-binding transcription factor). However, it also has additional functions independent of DNA binding.

ER is playing the most important role in cancer. Its expression was increased by about 70% of breast cancer cases. Binding of estrogen to ER stimulates the proliferation of mammary cells, cell replication and eventually forms tumors. Thus, using this principle using the estrogen receptor modulator drugs can help cancer patients to treat further spreading of tumors.

'ER antibody' is used to detect the levels of ER protein in cells by Immunohistochemistry (IHC). *Company A* is manufacturing the ER monoclonal antibody to detect the ER protein by IHC method. This review is to determine the Sensitivity and Specificity of ER antibody manufactured by *Company A*.

Revision

Initial release

Objectives

The objective of this review is to understand the state of art, Specificity, Sensitivity of ER antibody in determining the ER protein expression accurately on human FFPE tissues.
If this explorative review finds scientific evidence, this may be used for substantiating performance claims of equivalent products by using IHC method.

Literature search strategy

The Literature search was made on PubMed, Google Scholar. The terms used for the literature search are ER, IHC, Antibody, Human FFPE, and gold standard protocol. Two articles were found with a comparison with different types of ER antibodies. One article was eliminated due to a different population.

Methodology

IHC staining should perform on different organs, known positive and negative controls, results should be evaluated by a certified pathologist before filling this review format.

Table 1. **Overview of literature included**

Year	Authors	Journal	Title of Article	Study Subjects	Method/ Procedure	Results/Findings	Potential Claims	Sensitivity	Specificity
1986	Kenneth S. McCarty Jr., Eva Szabo, Julie L. Flowers, Edwin B. Cox, George S. Leight, Larry Miller, John Konrath, John T. Soper, Debra A. Budwit, William T. Creasman, Hilliard F. Seigler, and Kenneth S. McCarty Sr.	Cancer Research	Use of a Monoclonal Anti-Estrogen Receptor Antibody in the Immunohistochemical Evaluation of Human Tumors	3 cohorts with a total number of samples 396.	IHC on human FFPE tissue	A linear correlation was demonstrated between the logarithm of the quantitative biochemical estrogen receptor assay of tissue homogenate extracts (fmol radio labeled estradici bound per mg protein) and the total HSCORE of tissue sections. The correlation coefficient ranged from 0.64 for the 262 cases of primary breast cancer in the 5-year series to 0.79 for the 62 primary breast cancer cases in the single-year series.	ER antibody specifically binds to ER protein present in the nucleus. No cytoplasmic and membrane staining was observed	The Uterine cervix is found to be an appropriate positive tissue control for ER staining: In optimal protocols, virtually all epithelial cells throughout the layers of the squamous epithelium and in the glands show a moderate to strong and distinct nuclear staining reaction.	To validate the specificity of the IHC protocol further, an ER negative breast carcinoma must be included as primary negative tissue control, in which only remnants of normal epithelial and stromal cells must be ER-positive, serving as internal positive tissue control.

Positive controls: Uterine Cervix, well differentiated breast carcinoma, endometrial adenocarcinoma.

Negative controls: Endocervical adenocarcinoma, ovarian clear cell carcinoma, normal breast

Table 2. **Detection of Gold Standard Procedure for ER**

Ref.	Gold standard procedure available	Similar kind of test/device/drug	Outcome of the Gold standard	Outcome of the claimed test/device/drug	Equivalence
Harvey et al., 1999	Adequate testing of ER expression via immunohistochemistry is considered the gold standard for selecting patients for neoadjuvant and adjuvant hormonal therapies by the IHC method.	The Previously approved antibody was considered as the best reference device	IHC method should run by using an already approved antibody on known positive and negative control tissues (see table 1 for controls). For example Company XXX1 ER antibody was already approved for the detection of ER protein. This antibody was used to detect the ER antibody on the same tissues used to detect Sensitivity and Specificity for claimed ER antibody.	The claimed ER antibody manufactured by Company A should show similar results as the Gold standard method. IHC should run on the same samples run in the gold standard method.	The claimed ER antibody was showed exactly the same results as the Gold Standard protocol. Thus the device is equivocally performing as already approved antibody.

Table 3. **Inter run and intra run**

Test/Device/Drug Manufactured date	Intra run data	Outcome of Inter run	Inter run data	Outcome of Intra run
ER antibody clone EP1	IHC staining was performed on Breast cancer tissues by using one manufactured lot of ER antibody. Same test was repeated on 10 consecutive days on same tissues. All the results were evaluated by certified pathologist.	No changes were observed between runs. All the runs showed significant results.	IHC staining was performed on Breast cancer tissues by using ER antibodies manufactured on three different days (3 lots).	IHC staining results were similar for all the different runs. No change was observed between different lots.

Table 4. **Data appraisal**

Criteria	Description	Performance
Appropriate device	Was the claimed device is the same as available in literature?	Same **Similar kind** Other device
Appropriate performance	Does the device is performing exactly the same as showed in intended use?	**Same** Minor deviation Major deviation
Sensitivity	What is device's is high true positive rate	**99 – 100%** 90 – 98% < 90%
Specificity	What is device's is high true negative rate	**99 – 100%** 90 – 98% < 90%
Acceptable quality	Do the device is having an acceptable range of Sensitivity and Specificity	**Yes** No

Determination of Claims

Gold standard procedure: According to Harvey et al., 1999, it is determined that IHC by using already approved ER antibody was considered as gold standard procedure for detecting ER protein.

Positive control: Uterine cervix and well-differentiated breast carcinoma tissues are good positive controls to validate the ER antibody.

Negative control: Endocervical adenocarcinoma and ovarian clear cell carcinoma are good negative controls to determine the sensitivity of ER antibody.

Equivalence: The IVD device (ER antibody) was showing same results as the already approved similar kind of device. Thus the claimed device is working as per intended use.

Sensitivity: The device is showing positive for 70 cases out of 100 random cases. The gold standard also showed 70 cases positive out of 100 cases. The results were evaluated by a certified pathologist. Thus, the ratio of true positives is 100%.

Specificity: The device is showing negative for 30 cases out of 100 random cases. The gold standard also showed 30 cases negative out of 100 cases. The results were evaluated by a certified pathologist. Thus, the ratio of true negative is 100%.

Conclusion

Based on this review, it is concluded that the ER antibody manufactured by Company A may have high sensitivity and specificity. The device is working as per the intended use.

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