

FDA Executive Summary

Over-the-Counter Diagnostic Tests for the Detection of Pathogens Causing Infectious Diseases

Prepared for the
August 16, 2016 meeting of the
Microbiology Devices Panel of the
Medical Devices Advisory Committee

Contents

1. Introduction and Purpose of the Panel Meeting	3
2. Background.....	4
a. Regulation of <i>In Vitro</i> Diagnostic Devices	4
i. Class I Devices	4
ii. Class II Devices.....	5
iii. Class III Devices	6
b. Class II OTC Devices.....	7
3. Is there a need for or public benefit from OTC Testing?	7
4. Benefits and Risks Associated with OTC Diagnostic Tests	8
a. OTC Diagnostics for the Detection of Influenza.....	8
i. Risks and Potential Mitigations.....	10
ii. Benefits.....	11
b. OTC Diagnostics for the Detection of GAS.....	12
i. Risks and Potential Mitigations.....	13
ii. Benefits.....	15
c. OTC Diagnostics for the Detection of CT/NG.....	15
i. Risks and Potential Mitigations.....	17
ii. Benefits.....	18
5. Sample Collection.....	19
a. Respiratory specimens.....	19
b. STIs.....	19
6. Questions for the Panel.....	19

FDA Executive Summary

1. Introduction and Purpose of the Panel Meeting

The Division of Microbiology Devices (DMD) in the Office of In Vitro Diagnostics and Radiological Health (OIR), Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA), has regulatory oversight of diagnostic tests for the detection of pathogens causing infectious diseases. FDA is convening this Advisory Panel meeting to discuss the risks and benefits of over-the-counter (OTC) diagnostic tests for the detection of selected common infectious pathogens.¹ The focus of this meeting is on OTC diagnostic tests for the detection of pathogens causing viral respiratory infections (e.g., influenza), pharyngitis due to group A streptococcus (GAS), and sexually transmitted infections (STIs), focusing on *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (CT/NG).

There are precedents for FDA approval of OTC diagnostic devices for infectious diseases. A well-known example is the OraQuick[®] In-Home HIV Test (OraSure Technologies, Inc.) a rapid OTC HIV test kit, was approved by FDA following a May 15, 2012 Blood Products Advisory Committee (BPAC) meeting. Based on the data presented to the advisory committee, the panel recommended approval of OraQuick[®] In-Home HIV Test because there was a strong benefit to risk case for its approval and commercialization as an additional tool to combat the HIV epidemic.²

Since this pioneering action there has been increased interest from test developers and others in expanding the availability of OTC diagnostic tests for other infectious diseases. DMD has received multiple inquiries through FDA's pre-submission program³ on the appropriate regulatory pathway for OTC diagnostic tests intended for the detection of infectious diseases, most prominently for the detection of influenza and GAS pharyngitis. Home specimen collection, where actual testing is done elsewhere (as opposed to collecting *and* performing the test at home), has been of particular interest for the detection of STIs such as CT/NG. An example of an approved OTC test where the specimen is collected at home and sent to a clinical laboratory is the Home Access[®] Hepatitis C CheckSM (Home Access Health Corporation). With the exception of the aforementioned OTC HIV test and Hepatitis C specimen collection kit, there are no other OTC diagnostic tests for infectious diseases in commercial distribution in the United States (U.S.).

¹ OTC diagnostic tests for non-infectious uses are not uncommon, but are outside the scope of this meeting. Examples include cholesterol assays, menopause assays that measure follicle-stimulating hormone (FSH), ovulation assays, vaginal pH assays, pregnancy tests, glucose meters to manage diabetes, and drugs of abuse tests.

² May 15, 2012 meeting of the Blood Products Advisory Committee, transcript and materials available at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm298652.htm>.

³ For information on the pre-submission process, see FDA's guidance document entitled "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff," <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf>.

The purpose of the August 16, 2016 panel meeting is to discuss benefits and risks of OTC diagnostic tests for the detection of influenza, GAS, and CT/NG, for the Advisory Panel to make recommendations for appropriate clinical studies and acceptable performance criteria for these tests, and to discuss possible special controls that can aid in ensuring device safety and effectiveness.

2. Background

a. Regulation of *In Vitro* Diagnostic Devices

FDA regulations applicable to *in vitro* diagnostic devices are based on the FDA classification of the device. The current approach to classification is the result of several laws, most prominently the 1976 Medical Device Amendments to the Food, Drug and Cosmetic Act (the FD&C Act) (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/>). Generally speaking, medical devices, including *in vitro* diagnostic devices, are classified by evaluating the amount of regulation that provides reasonable assurance of the safety and effectiveness of a device. For *in vitro* diagnostic devices, risks may include unfavorable or harmful health outcomes from inaccurate test results and other safety considerations such as risk to users.

The three regulatory classes for device categorization are:

- Class I: Devices for which general controls are sufficient to provide a reasonable assurance of safety and effectiveness of the device.
- Class II: Devices which require both general and special controls to provide a reasonable assurance of safety and effectiveness of the device.
- Class III: Devices for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness.

i. Class I Devices

Class I devices are primarily those devices for which general controls are determined to be sufficient to provide reasonable assurance of device safety and effectiveness. Class I devices may also be devices that do not present a potential unreasonable risk of illness or injury. General controls are controls not unique to any specific device but are controls that can be applicable to devices in general. Examples of general controls include:

- Registration of manufacturing facilities and listing of products;
- 510(k) premarket notification requirement (see below under Class II devices);
- Good manufacturing practices (GMPs);
- Provisions for notification of risks and of repair, replacement, or refund;
- Restrictions on sale and distribution or use; and
- Other regulatory controls, e.g., labeling, adverse event reporting, misbranding, adulteration of the device.

Due to their low risk, FDA has exempted almost all class I devices (with the exception of reserved devices⁴) from the 510(k) requirement, including those devices that were exempted by final regulation published in the Federal Registers of December 7, 1994, and January 16, 1996. If a manufacturer's device falls into a generic category of exempted class I devices, then a 510(k) submission and FDA clearance are generally not required before marketing the device in the U.S. However, these devices have not been exempted from other general controls (e.g., registration and listing, GMP regulations, etc.). In addition, all devices exempt from the premarket notification requirement are only exempt as long as they do not exceed the limitations to their exemption. Limitations to exemptions for microbiology devices are found in 21 CFR 866.9. Of these limitations on exemptions, an exemption especially relevant to many of microbiology diagnostic devices is 21CFR 866.9(c)(6) "For identifying or inferring the identity of a microorganism directly from clinical material," as many of these tests under this exemption are intended for use to detect microorganisms directly from clinical specimens.

Further, although all manufacturers of medical devices are subject to the Quality System Regulation (21 CFR Part 820), FDA has exempted almost all class I devices from the design controls requirement. The intent of the design controls regulation is to implement processes and procedures to allow for identifying deficiencies in the design input requirements in early stages of the development of a device and it also applies to all changes to the device or manufacturing process design, including those occurring long after a device has been introduced to the market. These changes are part of a continuous, ongoing effort to design, develop, and make available a device that meets the needs of the user and/or patient.

ii. Class II Devices

Class II devices are those that cannot be classified as class I because general controls alone are insufficient to provide reasonable assurance of device safety and effectiveness, but where there is sufficient information to establish special controls that can provide such assurance. Examples of special controls may include:

- performance standards;
- post-market surveillance;
- patient registries;
- special labeling requirements;
- user education and training;
- design controls; and
- other appropriate actions deemed necessary for mitigating the risks of the device.

Class I reserved (non-exempt) and class II submissions are reviewed by FDA under what is referred to as the 510(k) process. Under the 510(k) paradigm, a device can be cleared for marketing if it is determined to be as safe and effective as a preexisting 'predicate' device (the

⁴ Information regarding reserved devices is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpd/3151.cfm>.

device is ‘substantially equivalent’ to the predicate device).⁵ Substantial equivalence broadly encompasses the following:

- The new device has the same intended use as the predicate and the new device has the same technological characteristics as the predicate,
- or**
- The new device has the same intended use as the predicate, the new device has different technological characteristics that do not raise new questions of safety and effectiveness, and the sponsor demonstrates that the device is at least as safe and effective as the legally marketed device.

As described on the FDA web site, “a claim of substantial equivalence does not necessarily imply that the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable.” The determination of ‘substantial equivalence,’ is therefore a multifaceted examination of the new device focused heavily on the intended use and not independent of the underlying technology.⁶

iii. Class III Devices

Class III devices are those for which insufficient information exists to determine that general and special controls can provide reasonable assurance of the safety and effectiveness, or where these devices are life sustaining or life supporting, of substantial importance in preventing impairment of human health, or present unreasonable risk of illness or injury. Class III devices require ‘pre-market approval’ (PMA) applications⁷ which include data to demonstrate a reasonable assurance of safety and effectiveness of the device as well as documentation of a quality manufacturing process for the device. For IVD tests, a reasonable assurance of safety and effectiveness is generally demonstrated through a reasonable assurance of analytical validity, clinical validity, and safety under its conditions of use.⁸

A *de novo* request for classification of a new device type may be appropriate when that device is class III by operation of section 513(f)(1) of the FD&C Act (21 U.S.C. 360c(f)(1)), there is not a legally marketed predicate device (e.g., this is a new device type intended for a new analyte) on

⁵ Devices which are submitted under a 510(k) are ‘cleared’ for marketing by FDA; under the PMA process (described below) devices are ‘approved’ by FDA.

⁶ More detailed information regarding pre market applications under the 510(k) process is available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm>, reproduced as an attachment to this document.

⁷ Certain types of devices classified into Class III that were in commercial distribution in the United States before May 28, 1976, and those determined to be substantially equivalent to such devices, may be marketed based on a premarket notification (rather than premarket approval) until FDA issues an administrative order requiring them to go through the premarket approval process. *See* Section 515(b)(1) of the FD&C Act, 21 U.S.C. § 360e(b)(1).

⁸ More detailed information regarding pre market PMA applications is available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm>.

which to base substantial equivalence in a 510(k), and the device is appropriate for classification in class I or class II.

b. Class II OTC Devices

There are generally two types of diagnostic tests regulated by FDA that are intended for home use: OTC tests (e.g., pregnancy tests) and tests for ‘home use by prescription’ (e.g., PT/INR test which is used to test coagulation for patients on Warfarin). OTC tests do not necessarily involve a health care professional whereas tests that are intended for home use by prescription must be prescribed by practitioner, such a physician, licensed by law to direct the use of the test. For the purposes of this meeting, we will focus only on OTC diagnostics and not on prescription home use assays. The premarket review of IVD performance generally centers upon assessment of analytical and clinical validity of the device. When FDA reviews a premarket submission for an IVD test, performance data from analytical and clinical studies (as appropriate), may be necessary to assess the analytical validity and clinical validity of the IVD. Analytical studies for OTC diagnostics would likely be similar to those for non-OTC diagnostics, though adapted to specific circumstances as necessary for OTC use (e.g., storage conditions, etc.). Flex studies, which would be unique to OTC-marketed tests, are discussed below in section 4.b.i.

In general, OTC diagnostic devices are divided into two categories: 1) OTC collection kits where the patient collects the sample at home and mails it to a laboratory for testing and professional result interpretation and, 2) OTC diagnostic tests where the patient collects the sample, performs the test, and interprets the result at home. For the purposes of this Advisory Panel Meeting, the devices to be discussed during this meeting are limited to the latter and include certain class II microbiology devices regulated under 21 CFR 866, Subparts C and D.⁹

3. Is there a need for or public benefit from OTC Testing?

Several trends suggest that there is a need or public benefit for OTC diagnostics for common infectious diseases. For instance:

- There is a readiness and interest by manufacturers to develop these tests. This is well reflected by the number of pre-submissions to FDA requesting feedback on analytical and clinical study designs for possible OTC submissions. Many of the submissions FDA reviewed are at a stage where there is at least a prototype device, and developers have often conducted market research or queried expert clinicians regarding a demand for such devices.
- There is evidence that lay persons are purchasing diagnostic tests that are not legally marketed for OTC use via popular internet shopping websites. For example, a popular online retailer’s site shows 28 customer reviews of a rapid GAS test. Influenza tests that are not cleared or approved for OTC use are similarly available online. Several websites

⁹ For a list of all 21 CFR 866 analytes (not limited to those be discussed at the meeting today), see <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=866>.

offer mail-in sample testing for STIs, and in some states OTC sample collection may be permitted by state law under limited circumstances. Several studies have concluded that there is both patient acceptability and cost effectiveness for home testing or collection, although several reviews have noted the need for additional study of OTC use.

- There has been public embracement of FDA approved HIV OTC collection devices as evidenced by over 170,000 specimens for the Home Access[®] HIV Test (BP950002) alone being submitted for testing during the first year of sale. Other studies have shown acceptance and accuracy for home collection or home-based testing.^{10,11,12} A focus group-based study in a large urban population reported that women wanted a range of testing options that included the option of self-administered swabs, and that this choice was preferred because it allowed patients to maintain confidentiality and privacy when compared to an in-clinic testing.¹³

4. Benefits and Risks Associated with OTC Diagnostic Tests

The primary risks of an inaccurate OTC diagnostic test result, whether performed in a laboratory or collected and (potentially) performed at home, are a consequence of either false positive or false negative results.

The performance of OTC tests may suffer due to the relative inexperience of the untrained users, particularly when interpreting visually-read lateral flow assays. At this panel meeting FDA is seeking recommendations from clinicians, health care professionals, and others regarding the benefits and risks of IVD OTC diagnostic tests for the detection of pathogens causing infectious diseases, specifically OTC diagnostics for the detection of influenza, GAS, and CT/NG. Each of these is discussed below for the panel to consider, with examples of the unique risks and benefits associated with OTC testing for each infection.

a. OTC Diagnostics for the Detection of Influenza

Influenza is a common, primarily seasonal infection that can range from asymptomatic illness to severe, life-threatening respiratory infection. Based on data from 1979 to 2001, the Centers for Disease Control and Prevention (CDC) estimates there were 19 million cases of influenza annually in the U.S. population. During the 2014-2015 season, there were 19,151,941 medically attended cases and 974,000 hospitalizations, although the 2014-2015 influenza season was

¹⁰ Smith KS et al. The acceptability and cost of a home-based chlamydia retesting strategy: findings from the REACT randomised controlled trial. *BMC Public Health*. 2016 Jan 28;16(1):83. <http://www.ncbi.nlm.nih.gov/pubmed/26822715>.

¹¹ Graseck AS et al. Home compared with clinic-based screening for sexually transmitted infections: a randomized controlled trial. *Obstet Gynecol*. 2010 Dec;116(6):1311-8. <http://www.ncbi.nlm.nih.gov/pubmed/21099596>.

¹² Fajardo-Bernal L. et al. Home-based versus clinic-based specimen collection in the management of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections. *Cochrane Database Syst Rev*. 2015 Sep 29;(9):CD011317. <http://www.ncbi.nlm.nih.gov/pubmed/26418128>.

¹³ Rompalo AM. Point-of-Care Tests for Sexually Transmissible Infections: What Do ‘end Users’ Want?’ *Sexual Health* 2013 Dec; 10(6): 541–545. <http://www.ncbi.nlm.nih.gov/pubmed/24160838>.

marked by a relatively ineffective vaccine.¹⁴ Primary influenza commonly leads to secondary bacterial pneumonia, estimated as a contributor in approximately 25% of influenza-related deaths. Current CDC recommendations for treatment are specific to high-risk groups, but that “Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset.”¹⁵ Treatment with neuraminidase inhibitors is recommended, although CDC recommendations may not wholly correspond to the currently labeled drug Indications for Use. Regardless, treatment initiation as soon as possible after illness onset is strongly recommended whenever antiviral therapy is being considered.

Table 1 is a summary of selected risks and benefits associated with use of OTC diagnostics for the detection of influenza. These are further discussed below:

¹⁴ <http://www.cdc.gov/flu/about/disease/2014-15.htm>.

¹⁵ Centers for Disease Control and Prevention. Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60(RR-1:9). <http://www.cdc.gov/mmwr/pdf/rr/rr6001.pdf>.

Table 1. Benefits and Risks Associated with OTC Influenza Tests

Benefits of an OTC Influenza Test:	Risks of an OTC Influenza Test:
Greater access to testing and earlier testing <ul style="list-style-type: none"> Potential for patients seeking earlier treatment Possibly reduced community spread 	False Negative Result: <ul style="list-style-type: none"> Potential loss of treatment benefit Untreated influenza Increased community spread of infection
Home testing may decrease healthcare visits for: <ul style="list-style-type: none"> Worried well (negative results) Lower risk patients with positive results 	False Positive Result: <ul style="list-style-type: none"> Unnecessary anti-viral medications Patient may not seek treatment for true cause of illness
Labeling/packaging gives an opportunity for user education: <ul style="list-style-type: none"> The lack of need for antibiotics for positive viral results The importance of avoiding spread of infection The importance for high-risk populations to seek medical care and potential, treatment (i.e., persons with asthma, diabetes, or cardiovascular disease), regardless of result 	Less testing in health care facilities could negatively impact surveillance activities: <ul style="list-style-type: none"> Fewer specimens tested at public health labs for tracking resistance and/or detection of novel influenza viruses Missing data on prevalence of influenza-like illness visits
	Poor Positive Predictive Value when influenza has low prevalence: <ul style="list-style-type: none"> Patients who test when influenza is not active in their area have a higher risk of a false positive result
	Potential for inaccurate results may increase if circulating flu strains change, most significantly if new strains emerge.

i. Risks and Potential Mitigations

The primary risks associated with an OTC influenza test come from the potential for false positive and false negative results, and accordingly, misunderstanding of test positive and negative predictive values (PPV and NPV). Similar to other diagnostic tests, positive and negative predictive values are not constant but may change dramatically depending on disease prevalence: high prevalence increases the positive predictive value, i.e., a positive test result is more likely to be a true positive with high prevalence, and with low prevalence the converse is true, i.e., a positive result is relatively more likely to be a false positive. False positive and false negative rates are directly related to the sensitivity and specificity of these devices in the hands of intended users (for OTC devices, primarily untrained users) and the prevalence of influenza in the community at the time of testing. Risks of user error and inappropriate testing can be potentially mitigated by use of samples that are easy to obtain, assays that are easy to perform and interpret, and device labeling that clearly indicate when testing is appropriate. It is essential that device sensitivity and specificity is demonstrated by studies with untrained users.

False negative results can lead to failure to treat when antiviral treatment is indicated and thereby potentially increase risk of hospitalization or other complications. Other risks include potential absence of precautions that spread infection. Conversely, false positive results could lead to unnecessary restrictions, e.g., missing work or school. Additional risks from false positive results include the possibility of inappropriate treatment, though this may be mitigated by health care assessment prior to prescribing antiviral therapy.

There is also the risk associated with true negative or true positive results; even with accurate results, e.g., the presence or absence of influenza, a user may delay assessment by a health care professional when an alternative illness is present that needs treatment (e.g., bacterial pneumonia as either the etiology of symptoms or as a superinfection). These risks may be partially mitigated by warnings and associated educational material integrated into device labeling and packaging, e.g., labeling and assay directions for use can warn against inappropriate testing during non-influenza seasons or refer to resources where up-to-date information regarding prevalence is available. Regardless, the absence of test interpretation in the context of clinical assessment by a health care professional always remains a risk with OTC testing.

PPV and NPV may be important considerations for the panel when addressing the appropriate performance estimates that should be observed in clinical studies for device clearance.

Loss of the potential for active surveillance is also a significant concern with use of OTC tests for the detection of influenza in that there may be a significant loss of information on overall prevalence, the distribution of circulating viruses (including potentially novel strains), and drug susceptibility; in addition, future influenza and influenza-like illness (ILI) surveillance data may not be comparable to past data before the advent of OTC testing.

ii. Benefits

Assuming highly sensitive and specific assays (although even very high performing tests may not assure adequate PPV with low prevalence), potential benefits from OTC influenza testing include easier access to testing that could enable earlier testing of patients and possibly earlier treatment if medical care is sought. Access to testing may result in greater identification of infected patients and accordingly, potentially reduced community spread of influenza if interpretation of results and assay labeling includes an educational component. OTC testing could potentially rule out certain pathogens, and accordingly assist groups, such as employers or school administrators, in encouraging and supporting individuals to remain at home while they are most contagious. In addition, as most influenza cases are self-resolving, the absence of medical intervention may reduce unnecessary burdens on the health care system, and is unlikely to pose patient risk.

FDA welcomes additional discussion during the panel meeting for means to mitigate risks and other concerns. For example, other mitigating measures could include results that are digitally linked to prevalence information via a voluntary mobile app which could also aid in estimating the users PPV and NPV based on local conditions; to address concerns on tracking prevalence properly, a strategy for patients to record results anonymously via a web site or other means

could partially address loss of prevalence information. Web-based information could also serve an important educational role, i.e., links to local health departments for appropriate follow-up in patients with positive test results. Interventions for connecting patients to clinical information could be included as part of clinical studies with untrained users and assessed for utility.

b. OTC Diagnostics for the Detection of GAS

Group A beta-hemolytic streptococcus (GAS; *Streptococcus pyogenes*) is likely the most common bacterial cause of pharyngitis. In clinical studies submitted to FDA for device clearance conducted during peak seasons from 2002 to 2016, average prevalence of GAS in patients with signs and symptoms of pharyngitis was consistently between ~25-30% (based on results from bacterial culture), although these studies may be biased towards higher GAS prevalence. CDC estimates that there are several million cases of GAS infection in the U.S. each year, 9,000 to 11,500 of which are invasive, with 1,000 to 1,800 attributable deaths.¹⁶ Globally, the World Health Organization (WHO) estimates there are approximately 616 million new cases of GAS pharyngitis each year, 1.78 million of which are severe and with approximately 517,000 GAS-associated deaths.^{17,18}

GAS primarily affects children from 5 to 15 years of age.¹⁹ Complications of untreated tonsillopharyngeal streptococcal infection include local complications such as peritonsillar abscess, cervical lymphadenitis, and mastoiditis. GAS tonsillopharyngitis has also been associated with cellulitis, abscesses, otitis media, sinusitis, necrotizing fasciitis, and meningitis/brain abscess, as well as systemic immune-associated non-suppurative illness such as acute rheumatic fever, Scarlet fever, streptococcal toxic shock syndrome, and acute glomerulonephritis.

Antibiotic therapy is associated with a reduction in the rate of GAS transmission, faster symptom resolution, and the prevention of complications such as suppurative tonsillitis and abscess formation; more significant but infrequent complications such as rheumatic fever are prevented by treatment within 7 – 10 days of disease onset, although with some exceptions (e.g., glomerulonephritis).

Differentiating GAS pharyngitis from viral pharyngitis can be challenging based solely on clinical presentation as the clinical presentations of both illnesses overlap.¹⁵

¹⁶ <http://www.cdc.gov/groupAstrep/about/faqs.html>

¹⁷ WHO. The Current Evidence for the Burden of Group A Streptococcal Diseases. http://www.who.int/maternal_child_adolescent/documents/fch_cah_05_07/en/.

¹⁸ Sims S et al. Global Disease Burden of Group A Streptococcus. In *Streptococcus Pyogenes: Basic Biology to Clinical Manifestations*, edited by JJ Ferretti, DL Stevens, and VA Fischetti. Oklahoma City (OK): University of Oklahoma Health Sciences Center, 2016. <http://www.ncbi.nlm.nih.gov/books/NBK333415/>.

¹⁹ Shulman ST, et. al. Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, 2012 55(10):e86-102. http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/2012%20Strep%20Guideline.pdf.

Table 2 is a partial summary of risks and benefits from OTC diagnostics for GAS. These are further discussed below.

Table 2. Benefits and Risks Associated with an OTC Test for GAS

Benefits of an OTC GAS Test	Risks of an OTC GAS Test
Greater access to testing and earlier testing <ul style="list-style-type: none"> • Early diagnosis can reduce morbidity of disease 	False Negative Result <ul style="list-style-type: none"> • Untreated infection can prolong symptomatic disease, and/or lead to complications such as peritonsillar abscess, acute rheumatic fever, scarlet fever, streptococcal toxic shock syndrome
Labeling and packaging gives an opportunity to educate users <ul style="list-style-type: none"> • Discourage inappropriate antibiotic use absent health care intervention 	False Positive Result <ul style="list-style-type: none"> • Unnecessary treatment with antibiotics can result in adverse effects, such as rash, allergic/hypersensitivity reaction, candidiasis, diarrhea, <i>C. difficile</i> colitis, etc.) • Inappropriate use of antibiotics contributes to increased antibiotic resistance
Home testing may decrease healthcare visits for users with negative results	True Positive Result <ul style="list-style-type: none"> • Patient may not seek treatment for true cause of illness • Test could detect colonized individuals who do not necessarily need treatment
.	Specimen collection may be difficult for untrained users because of the need to sample the posterior pharyngeal area and may lead to unsuspected false negative results or adverse events

i. Risks and Potential Mitigations

The risks for a GAS OTC assay are primarily associated with inaccurate results (i.e., false negative and false positive results) and potential adverse events from obtaining the specimen for testing. Incorrect results can be due to suboptimal test performance (i.e., poor device sensitivity and specificity), or may occur through user error at any step of the process. User error can occur at different steps from sample collection through testing (e.g., poor or improper specimen collection, failure to adequately follow assay instructions, failure to properly interpret test results, use of expired tests, etc.). During the meeting, FDA will discuss with the panel the types of flex studies developers generally perform to ensure that tests are sufficiently robust to address possible human errors.

For most GAS tests used in clinical laboratories, false negative results are mitigated by recommendations for reflex culture to confirm negative results unless the device is sufficiently sensitive such that reflex culture is not recommended or testing is from certain populations where

reflex culture is not recommended due to laboratory or clinical practice. The risk from a false positive GAS result is unnecessary treatment. Risks of unnecessary treatment with antibiotics are well recognized and include rash, allergic/hypersensitivity reactions, gastrointestinal reactions, candidiasis, diarrhea, *C. difficile* associated colitis, and other less common adverse effects. Serious adverse reactions are uncommon. Inappropriate use of antibiotics is also accepted as a major contributing factor to increased antibiotic resistance.

FDA previously held a Microbiology Devices Panel Meeting for evaluation of an OTC assay, the First Response Strep Throat Screening Test²⁰ on July 31, 1989. Although the panel recommended against clearance of the test, during the meeting panel members outlined many of the risks and benefits associated with an OTC test for GAS that should be assessed and mitigated. One of the most significant risks discussed during this meeting was the risk from inappropriate sample collection. Proper sample collection is critical to attaining a valid diagnostic result. As noted in the 2012 IDSA “Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis”²¹, “throat swab specimens should be obtained from the surface of either tonsils (or tonsillar fossae) and the posterior pharyngeal wall.” Samples from other areas may be more likely to result in false negative results, and untrained users may have difficulty obtaining proper specimens from such a specific, potentially difficult to reach anatomical site. Pharyngeal sampling also has the risk of inducing laryngeal spasm, although this may not be common.²² Risk of inadequate collection of pharyngeal specimens is likely far higher for self-collection than if at least one additional person aids in the procedure.

Similar to OTC influenza assays, true negative results may also pose potential risks if negative results delay pursuing health care assessment for other potentially serious causes of pharyngitis (or other upper respiratory pathology misinterpreted as pharyngitis).

It should be noted that false negative results may be somewhat mitigated by a relatively low probability of serious complications such as rheumatic fever, and educational materials advocating health care follow-up if symptoms persist.

For OTC diagnostics for GAS, risk of overtreatment for colonization is mitigated in most cases by the need for contact with a health care professional for obtaining antibiotics. This same principle mitigates inaccurate test results for all of the diseases to be discussed, i.e., health care contact (and possible repeat testing) can significantly aid in identifying results that may be inaccurate or in identifying when testing was inappropriate, regardless of results.

²⁰ Buchta, RM. Use of a Rapid Strep Test (First Response) by Parents for Detection of Streptococcal Pharyngitis. *The Pediatric Infectious Disease Journal* 8, no. 11 (November 1989): 829–33.

<http://www.ncbi.nlm.nih.gov/pubmed/2687793>

²¹ Shulman, ST, et al. Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, 2012 55(10):e86-102. http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/2012%20Strep%20Guideline.pdf.

²² Murray, MA et. al., 2015, "Equal Performance of Self-Collected and Health Care Worker-Collected Pharyngeal Swabs for Group A Streptococcus Testing by PCR" *JCM* v53, issue 2, 573-578.

<http://www.ncbi.nlm.nih.gov/pubmed/25502528>.

ii. Benefits

Benefits from use of rapid OTC tests for GAS include the potential for immediate diagnosis, thereby reducing morbidity by earlier treatment and (in the setting of a negative result), potentially avoiding unnecessary non-physician prescribed antibiotic exposure (e.g., “left-over antibiotics”).

OTC GAS tests may reduce unnecessary health care visits as well as (similar to other OTC diagnostics) empowering patients for their own health care. Availability of testing for GAS as OTC may also provide a valuable tool for physicians who believe that patients can collect specimens properly.

It is believed that for an OTC test for GAS sponsors should demonstrate adequate performance in the intended use population and demonstrate that the specimens can be collected safely. FDA intends to ask the panel members to address these issues, as well as other risks and benefits from this proposed use.

c. OTC Diagnostics for the Detection of CT/NG

Approximately 1.79 million STIs are due to CT/NG as reported to CDC in 2014, ~1.44 million for CT and ~350,000 for NG.²³ Data suggested that a large number of STIs go unreported (e.g., the 2007-2012 National Health and Nutrition Examination Survey study estimated that approximately 400,000 CT infections went undiagnosed annually.²⁴). Asymptomatic infection represents a major reason for under-reporting and asymptomatic infection (the majority of all CT/NG infections) can remain undetected unless identified by routine screening or contact tracing.²⁵ Furthermore, even when symptomatic, the high prevalence of CT among high risk sexually active young people suggests poor access to testing that may be due to cost, lack of health coverage, or associated stigma.^{26,27,28,29,30}

²³ <http://www.cdc.gov/std/stats14/std-trends-508.pdf>

²⁴ <http://www.cdc.gov/nchstp/newsroom/2014/stds-among-youth-studies-of-interest.html>

²⁵ <http://www.cdc.gov/std/chlamydia/stdfact-chlamydia-detailed.htm>

²⁶ Cunningham SD et al. Relationships between perceived STD-related stigma, STD-related shame and STD screening among a household sample of adolescents. *Perspectives on Sexual and Reproductive Health* 2009;41:225-30. <http://www.ncbi.nlm.nih.gov/pubmed/?term=20444177>

²⁷ Gaydos CA et al. Can e-technology through the Internet be used as a new tool to address the Chlamydia trachomatis epidemic by home sampling and vaginal swabs? *Sex Transm Dis*. 2009 Sep;36(9):577-80. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3187612/>

²⁸ Elliott BA, Larson JT. Adolescents in mid-sized and rural communities: foregone care, perceived barriers, and risk factors. *Journal of Adolescent Health*. 2004;35:303-9. <http://www.ncbi.nlm.nih.gov/pubmed/15450544>

²⁹ Tilson EC et al. Barriers to asymptomatic screening and other STD services for adolescents and young adults: focus group discussions. *BMC Public Health* 2004;4:21. <http://www.ncbi.nlm.nih.gov/pubmed/15189565>

³⁰ Kraut-Becher JR, Aral SO. Gap length: an important factor in sexually transmitted disease transmission. *Sexually Transmitted Diseases* 2003;30:221-5. <http://www.ncbi.nlm.nih.gov/pubmed/12616140>

Studies from the U.S. and other developed countries have addressed the acceptability and feasibility of a home specimen collection for CT/NG clinical testing.^{31,32,33,34,35} While these studies report an improvement in the rate or acceptance of CT/NG testing, it is still lower than recommended by public health officials. Reasons that have been listed include lack of understanding of sexually transmitted infections, lack of trust in testing, and patient held stigma associated with sexually transmitted infections.^{36,37} Whether OTC tests (or home collection devices) can address concerns such as a lack of screening in high risk populations (i.e., whether self-initiated ‘screening’ for asymptomatic high-risk individuals is achievable) is also uncertain.

Table 3 is a partial summary of risks and benefits from OTC CT/NG diagnostics. These are further discussed below:

³¹ Spielberg F et al. Fully integrated e-services for prevention, diagnosis, and treatment of sexually transmitted infections: results of a 4-county study in California. *Am J Public Health*. 2014 Dec;104(12):2313-20.

³² Rotblatt H et al. There's no place like home: first-year use of the "I Know" home testing program for chlamydia and gonorrhea. *Am J Public Health*. 2013 Aug;103(8):1376-80. <http://www.ncbi.nlm.nih.gov/pubmed/23327247>

³³ Chai SJ et al. Internet-based screening for sexually transmitted infections to reach nonclinic populations in the community: risk factors for infection in men. *Sexually Transmitted Diseases* 2010 Dec; 37(12):756-63. <http://www.ncbi.nlm.nih.gov/pubmed/20644498>

³⁴ Blake DR et al. Could home sexually transmitted infection specimen collection with e-prescription be a cost-effective strategy for clinical trials and clinical care? *Sexually Transmitted Diseases* 2015 Jan; 42(1):13-9. <http://www.ncbi.nlm.nih.gov/pubmed/25504295>

³⁵ Shih SL et al. Screening for sexually transmitted infections at home or in the clinic? *Current Opinions in Infectious Diseases*. 2011 Feb;24(1):78-84. <http://www.ncbi.nlm.nih.gov/pubmed/21124216>

³⁶ Graseck AS et al. Home versus clinic-based specimen collection for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *Expert Review of Anti Infective Therapy*. 2011 Feb;9(2):183-94. <http://www.ncbi.nlm.nih.gov/pubmed/21342066>

³⁷ Hsieh YH et al. Perceptions on Point-of-Care Tests for Sexually Transmitted Infections - Comparison between Frontline Clinicians and Professionals in Industry. *Point of Care*. 2012 Jun 1;11(2):126-129. <http://www.ncbi.nlm.nih.gov/pubmed/22844231>

Table 3. Benefits and Risks Associated with OTC CT/NG Tests

Benefits of OTC CT/NG Tests:	Risks of OTC CT/NG Tests:
<p>Greater access to testing and earlier testing</p> <ul style="list-style-type: none"> • Earlier treatment • Reduced community spread 	<p>False Negative Result</p> <ul style="list-style-type: none"> • Untreated infection in women can lead to complications, e.g., infertility • Patient may spread infection to partners
<p>OTC testing has the potential to reach patients:</p> <ul style="list-style-type: none"> • who are concerned about confidentiality • who cannot readily access health care • who may want to test their sexual partners before sexual encounters 	<p>False Positive Result</p> <ul style="list-style-type: none"> • Unnecessary treatment with antibiotics (i.e., rash, allergic/hypersensitivity reaction, candidiasis, etc.) • Inappropriate use of antibiotics contributes to increased antibiotic resistance • Potentially significant emotional burden, may seriously impact and/or disrupt personal relationships of patient
<p>OTC testing would permit self-collection of genital samples, which has been shown to be a preferred sample collection method for women.</p>	<p>True Positive Result</p> <ul style="list-style-type: none"> • Patient may not seek treatment
<p>Labeling gives an opportunity to educate the user about safe sexual practices and the importance of testing for sexually transmitted infections</p> <ul style="list-style-type: none"> • Labeling could allow patients to access outreach organizations that promote sexual health and other education and/or informational activities 	<p>True Negative Result</p> <ul style="list-style-type: none"> • Patient may interpret the result as reinforcing high risk sexual behavior • Patients may mistake this as evidence that they are free of all sexually transmitted infections • Other causes of symptoms may not be detected
	<p>Less testing in healthcare centers could negatively impact surveillance activities</p> <ul style="list-style-type: none"> • Both CT and NG are reportable infections and there is currently no validated method for accurately capturing results from OTC tests • Contact tracing is not possible for unreported infections • Obtaining isolates for tracking resistance may be impaired

i. Risks and Potential Mitigations

As with tests for influenza and GAS, risks associated with use of the device include false positive and false negative results. For CT/NG, false negative test results could lead to untreated

infections and the potential sequelae thereof (e.g., pelvic inflammatory disease or possible infertility). False negative results may be a particular concern in special populations such as pregnant women. In addition, there is the concern of potentially increased spread of infection by untreated patients due to the false security from inaccurate test results falsely suggesting that they are not infectious. Potential mitigations for the risk from false negative results include mandating high test sensitivity in the hands of intended users, meticulous attention to human factors engineering during development³⁸, and the inclusion of educational material in device labeling, with access to additional information as needed.

OTC testing, even when results are accurate, omits the possibility of health care professional education associated with testing, testing for other possible STIs, and testing for extra-genital CT/NG. Cost of an OTC test for CT/NG may also remain a significant barrier in certain high risk populations, even if available.

Risks associated with false positive results include inappropriate antibiotic treatment and a potentially significant emotional toll from being inappropriately diagnosed with a sexually transmitted disease. Such results could also potentially have negative implications to relationships. OTC testing (or home sample collection) for CT/NG may also significantly affect both surveillance and contact tracing. It is critical that sponsors consider alternative means to capture this information. This may be less of a concern for home collection devices, though such testing may not offer anonymity if testing results mandate public health follow-up.

ii. Benefits

OTC testing for CT/NG could lead to increased testing and earlier diagnosis through expanded access to testing, particularly for underserved populations and individuals that may lack ready access to health care. The stigma and embarrassment of having to seek testing and discuss intimate relationships with a health care provider may present a significant barrier for certain groups, particularly teenagers or for members of certain traditional cultures. Preference for self-collection of samples has been studied and described in the literature.^{39,40} In addition, OTC testing could allow greater outreach and opportunities for testing or test distribution in non-traditional settings where screening or testing may be valuable, e.g., at health fairs or on college campuses.

³⁸ Applying Human Factors and Usability Engineering to Medical Devices Guidance
<http://www.fda.gov/downloads/MedicalDevices/.../UCM259760.pdf>

³⁹ Gaydos CA et al. The use of focus groups to design an internet-based program for chlamydia screening with self-administered vaginal swabs: what women want. *Sex Health*. 2006 Dec;3(4):209-15.
<http://www.ncbi.nlm.nih.gov/pubmed/17112429>

⁴⁰ Mahilum-Tapay L. New point of care Chlamydia Rapid Test--bridging the gap between diagnosis and treatment: performance evaluation study. *BMJ*. 2007 Dec 8;335(7631):1190-4.
<http://www.ncbi.nlm.nih.gov/pubmed/18055487>

5. Sample Collection

a. Respiratory specimens

Although sample collection for influenza, respiratory syncytial virus (RSV), and GAS testing is generally considered minimally invasive when performed by health care professionals, this may not be true when performed by untrained users. Nasopharyngeal swabs are invasive and unpleasant, and analyte detection may be reduced without vigorous swabbing. Nasal swabs are less invasive and better tolerated by patients, but would need to be evaluated separately from nasopharyngeal swabs. Throat swabs sampling for GAS testing also has risks, and although uncommon, inappropriate swabbing of the back of the throat can lead to laryngeal spasm with potentially adverse consequences. There has been little innovation in currently marketed devices away from the specimen types for laboratory based tests. FDA believes that the potential for FDA clearance of OTC tests may spur development of alternative sample types and collection methods.

b. STIs

Similar challenges are relevant to OTC STI sample collection. STI testing is complex because of performance differences across sample types and a limited number of sample collection devices cleared or approved for genital swab self-collection. For example, it is well documented by clinical studies that for currently cleared STI assays, CT/NG testing of female urine samples is less accurate than testing of vaginal swab samples. In contrast, male urine testing is equal in performance to either urethral swabs or meatal swabs, with better tolerance for urine self-collection. It may be challenging to develop adequate labeling that would sufficiently warn women against using urine samples in lieu of vaginal swab sampling. However, despite this challenge, it may be determined that the benefits outweigh the risks of the device even if performance is lower.

6. Questions for the Panel

1. Do you agree with the benefits and risks described above for OTC testing of each of the following pathogens, and are there any other benefits or risks that should be considered:
 - a. Influenza
 - b. Group A Streptococcus
 - c. CT/NG
2. What measures would be appropriate to mitigate the risks associated with OTC diagnostic tests for the detection of each of the following pathogens?
 - a. Influenza
 - b. Group A Streptococcus
 - c. CT/NG

3. What would be recommended minimum performance criteria for testing of each pathogen?
4. Please discuss recommendations for ensuring that individuals representing the appropriate intended use population are enrolled in the clinical studies to demonstrate the device performance and support OTC claims for each of the pathogens discussed here.
5. Please discuss appropriate ways to connect patients to healthcare services should OTC tests for the pathogens being discussed here become available.
 - a. Are there any recommendations regarding potential patient access to additional resources that diagnostic test manufacturers should be responsible for, e.g., a hotline, etc.? Does this differ across the diseases described above?