FDA Infectious Disease Next Generation Sequencing Based Diagnostic Devices: Microbial Identification & Detection of Antimicrobial Resistance & Virulence Markers (Draft Guidance)

Explains the clinical and analytical information that FDA will likely use to evaluate an Infectious Disease Next Generation Sequencing Diagnostic device for premarket approval.

Updated last October 12, 2016 for the 05/13/16 Draft Guidance

WHAT IT DOES

Infectious Disease Next Generation Sequencing Diagnostic devices (NGS Dx devices) aid the diagnosis of microbial infection and in selecting appropriate therapies. These devices create the opportunity to improve efficiency in detection of the presence or absence of pathogens and antimicrobial resistance and virulence markers.

The draft guidance (noticed via 81 Federal Register 29869) explains the Food and Drug Administration (FDA)’s current thinking on how its Center for Devices and Radiological Health (CDRH) will evaluate NGS Dx devices for Class II premarket notification. It describes a “one-system” based approach to evaluate all components necessary to generate a result: the device, instruments, reagents, and software associated with collecting the specimen; the instruments, reagents, software, and data collection elements associated with preparing and sequencing the specimen; and the data assembly, analysis, annotation, variant calling, etc. associated with the data analysis pipeline.

To lower the regulatory burden on industry, the FDA proposes using a public reference database of validated regulatory-grade microbial genomic sequences from diverse infectious microorganisms, known as the FDA dAtabase of Regulatory-Grade micrObial Sequences (FDA-ARGOS). NGS Dx devices may use this database to compare sequences for clinical evaluation. In some cases, the pipeline will involve contributing novel findings to the database.

The draft guidance sets forth specific clinical and analytical information from studies that FDA expects to review as part of an Infectious Disease NGS Dx device’s premarket submission application. Devices may use two different sequencing approaches—targeted and agnostic—to identify microbial pathogens and antimicrobial resistance and virulent markers. Targeted sequencing involves prior knowledge of the pathogen being tested for, whereas agnostic sequencing does not. Application information should include:

- Benefit-Risk Analysis – the risks of generating inaccurate results when the nature of the infectious disease does not allow time for retesting, such as:
  - False positives and the attendant risk of inappropriate treatment;
  - False negatives and the attendant risk of delayed treatment.

- Detailed Device Description – including the following characteristics:
  - Intended Use – the specific infectious agent or antimicrobial and viral markers the device is meant to detect, whether targeted or agnostic in approach;
  - Test Methodology – a comprehensive and detailed explanation of the scientific approach (targeted/agnostic), including strategies, methods, protocols, instrumentation, enzymes, compounds, and many other specifics of the device’s scientific methodology;
  - Ancillary Reagents – items that are “required but not provided” with the device kit to carry out the diagnostic test, either general (e.g. ethanol) or specific (e.g. Enzyme Brand X), that the user will need to supply (as well as risk-assessment and qualifying data for an ancillary reagent);
  - Controls – daily controls run during the studies, including negative, positive, internal, and (if possible) external controls, as well as information regarding the nature, function, protocol, and criteria for each control; and
Result Interpretation and Report – a description of the “computational pipeline,” that is, the software, relevant data values, and calculations used to translate the data into an identification of diagnostic markers.

Device Validation – detailed information about how the studies were designed to evaluate each of the following characteristics:

- **Pre-Analytical Factors** – including specimen collection & handling; specimen preparation for sequencing; sequencing, chemistry, & data collection; data storage; and clinical call determination.
- **Performance Metrics** – including data sets; sequencing strategy; selected targets & reference sequences used for target identification; clinical call informatics pipeline; subtraction rationale; quality controls; sequencing and read mapping; contaminant analysis; sample to result turn-around time; and data storage.
- **Analytical Performance** – including limit of detection; inclusivity & reactivity; interfering substances; precision (reproducibility & repeatability); carryover and cross-contamination; and stability.
- **Clinical Evaluation** – including negative percent agreement; positive percent agreement; data presentation; and study specimens & specimen types.

Device Modification – how the device platform can be modified or updated to identify new or additional targets.

**RELEVANT SCIENCE**

**Infectious diseases** range from a cold to the **Ebola virus**. Doctors use diagnostic tests to narrow down the causes of the various symptoms that a patient may present and, ultimately, to diagnose the cause of the patient’s symptoms and recommend appropriate treatment. The tests covered by this draft guidance represent how molecular technology in genetic sequencing can improve upon a more rudimentary diagnostic test, like a **strep culture test**. Particularly for severe and **emerging infectious diseases** like Ebola or **other infections**, rapid diagnosis is essential in order to act within a short time frame to benefit the patient and public health. These Infectious Disease NGS Dx devices can be developed to test the various specimens, such as blood, sputum, urine, etc., that may reveal an **infectious disease agent**. They can also identify markers of **antimicrobial resistance** and **virulence**, which would help the doctor select the treatment that will be the most effective.

**Genetic sequencing** can identify infectious disease agents by mapping their unique genetic makeup. At its most basic level, mapping an infectious disease pathogen’s DNA sequence involves taking the segment of DNA strand available in a sample and “**amplifying it**,” using enzymes to react with the existing segment and thereby to create millions of copies. With a complete map and millions of copies of a pathogen’s DNA sequence, scientists can fully examine and understand any individual pathogen’s potential for spreading infectious disease. That way, upon sequencing the various pathogens in a specimen, the test can identify those pathogens that are agents of infectious disease.

This guidance covers two types of approaches that an Infectious Disease NGS Dx device would use: targeted or agnostic. A targeted approach means that the device can detect the presence or absence of a particular infectious disease agent or agents (or resistance markers)—by ‘targeting’ that agent. An agnostic approach means that the device has no particular infectious disease agent in mind. The agnostic approach relies more on comparing the **genetic sequences** of a specimen’s microorganisms to a database or library of genetic sequences, so that the benign microorganisms can be ruled out and the infectious agents can be pinpointed. Targeted devices will already have a specific pathogen or infectious disease agent in mind, and will test specimens for the presence or absence of that particular pathogen. In contrast, agnostic devices will aim to identify which pathogen among the several pathogens in a specimen is likely to spread an infectious disease (or to resist a particular treatment).

Because Infectious Disease NGS Dx devices are complex and specialized, this Draft Guidance relies on **systems science** to understand and conceptualize the diagnostic process from beginning to end. “This approach will evaluate, in parallel, the system as a whole... and each individual step in the sequencing data pipeline as part of that system, from specimen collection to results report.”

CDRH classifies devices according to the level of control needed to assure their **safety and effectiveness**. This guidance’s Infectious Disease NGS Dx devices are considered **Class II**, which require the manufacturer to notify CDRH of the new device before marketing it and to meet quality controls. In contrast, Class III devices cannot be sold without pre-market application, review, and approval from CDRH; a device that diagnoses HIV, or a few other certain infectious diseases that have traditionally been treated as high-risk,
would accordingly require Class III premarket approval.

ENDORSEMENTS & OPPOSITION

Endorsements:

- In a Regulatory Affairs Professionals Society (RAPS) news article, industry players offer support, including Illumina, which “commend[s] the FDA for its ‘one system’ approach.” Roche, despite disagreeing about the one system approach, believes that FDA’s NGS guidances show “novel, innovative regulatory approaches.”
- In a news summary, attorneys at Hogan Lovells comment that the guidance “shows FDA’s willingness and flexibility” in facing challenges when it comes to regulating devices that “do not fit into the existing regulatory framework.”

Opposition:

- In the RAPS news article, above, Roche and AstraZeneca wish that FDA would apply the novel, innovative regulatory approach to all IVD [in vitro diagnostic] devices. Roche considers the one system approach to be “diametrically opposed to FDA’s expressed policies and precedent” and as “limiting the innovative tools that such specialized manufacturers could bring to the market.”
- In the same RAPS article, Illumina questions whether the guidance outlines a too-complex and onerous approach if “directed at relatively common pathogens or disease markers.”
- The Hogan Lovells news summary also comments that the guidance leaves unanswered questions about “how to use a regulatory database as a comparator” (emphasis added). Similarly, in the RAPS news article, above, Illumina “also calls for more of an explanation for how the ARGOS database will be developed” and argues that “the scope of [the database’s] use should be described in a more clear and transparent manner.”

STATUS

This guidance was released in draft form on May 13, 2016. Public comments were initially due on August 11, 2016. On August 11, 2016, the public comment period was extended to September 12, 2016. After receiving public comment, the agency may reissue an updated version of the guidance.

RELATED POLICIES

FDA has issued other draft guidances about Next Generation Sequencing Diagnostic Devices in other contexts, including "Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing Based In Vitro Diagnostics used for diagnosing Germline Diseases" and "Use of Public Human Genome Variant Databases to Support Clinical Validity for Next Generation Sequencing Based In Vitro Diagnostics."

PRIMARY AUTHOR

Lizzie Brown, JD Candidate

EDITOR(S)

Jacqueline Robinson-Hamm, PhD Candidate, & Aubrey Incorvaia, MPP

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