Leveraging Post-Approval Studies to Support Earlier FDA Approval

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Discussion Points

Overview of FDA's guidance

Building a regulatory strategy to leverage post approval studies (PAS)

A case study

Overview of FDA Guidance

Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval

Issued April 2015 (draft April 2014)

"…this guidance outlines how FDA considers the role of postmarket information in determining the extent of data that should be collected in the premarket setting to support premarket approval while still meeting the statutory standard of reasonable assurance of safety and effectiveness."

Not a new concept…

Section 513(a)(3)(C) of the FD&C Act specifically requires FDA to consider the use of postmarket controls in lieu of collecting and reviewing all effectiveness data prior to PMA approval.

Postmarket controls include, but not limited to:

- Adverse event reporting
- Special labeling requirements
- Restrictions on sale/distribution
- Postmarket studies or surveillance
- Periodic (annual) reports; including numbers sold and distributed
- Unique Device Identifier (UDI)
- Patient registries

Works because FDA has authority to withdraw PMA approval for which FDA later determines that there is insufficient data demonstrating reasonable assurance that the device is safe or effective under the conditions of use.

Deciding Factors

How does FDA determine when it is appropriate for a sponsor of a PMA to collect some data (clinical or non-clinical) in the postmarket setting instead of in the premarket setting?

Risk vs. Benefit

Risk Benefit Determination

FDA considers

- Degree of certainty of the probable benefits of device (i.e., potential impact on public health)
- Probable risks of the device and if they can be mitigated

FDA may accept greater uncertainty of benefits and risks of Class III devices at approval if there is

- Potential to address unmet medical needs
- Premarket data to support a reasonable assurance of safety and effectiveness
- Ability to sufficiently balance any uncertainty by other factors, including postmarket controls

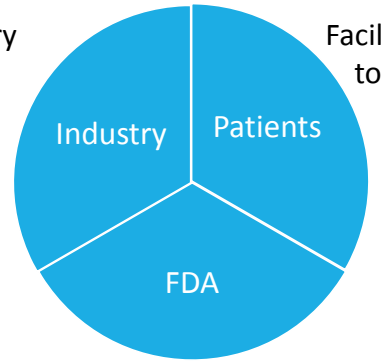
Related Guidance

"Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications," issued on March 28, 2012 ("Benefit-Risk Guidance")

"Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need,"3 issued on April 13, 2015 ("EAP Guidance")

Importance

Supports industry and business objectives



Facilitates timely patient access to new technology without incurring patient risk

Enables FDA's mission to "assure that patients and providers have timely and continued access to safe and effective and high quality medical devices," and to "facilitate medical device innovation."

Building a regulatory strategy to leverage Post Approval Studies (PAS)

Consider at start of product development process

Model existing products (look at approval orders and guidances)

Important to consider as part of clinical trial planning

- Will the PAS be a separate protocol or continuation of pre-market, pivotal study?

Provide evidence and discuss with FDA as part of Pre-Sub process

- Potential of device to address unmet medical needs
- Premarket data that will be gathered and/or available to support a reasonable assurance of safety and effectiveness at approval
  - Emphasize analytical studies
  - Consider data collected outside US also
- Plan to execute postmarket controls to balance any remaining uncertainty

Examples of when PAS is appropriate

- Mature Technology
- Urgent public health need
- IVD Platform migration
- To confirm effectiveness of a safety mitigation to a known risk
- To modify warnings, contraindications, precautions in approved labeling
- **Approval for an intended population beyond what was evaluated in the pivotal trial**
- To assess long-term performance or rare adverse events
- To bridge where data collected outside the US is available but not sufficient

A case study

Approval for an intended population beyond what was evaluated in the pivotal trial

Aptima HPV Assay (Gen-Probe/Hologic, Inc.)

Approved: October 28, 2011

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=5499

Aptima HPV Assay

An in vitro nucleic acid amplification test for the qualitative detection of e6/e7 viral messenger RNA (mRNA) from 14 high-risk types of human papillomavirus (HPV) in cervical specimens.

Cervical specimens in thinprep pap test vials containing preservcyt solution and collected with broom-type or cytobrush/ spatula collection devices may be tested with the Aptima HPV assay.

The use of the test is indicated:

1. To screen patients 21 years and older with atypical squamous cells of undetermined significance (ASC-US) cervical cytology results to determine the need for referral to colposcopy. The results of this test are not intended to prevent women from proceeding to colposcopy.

2. In women 30 years and older, the Aptima HPV assay can be used with cervical cytology to adjunctively screen to assess the presence or absence of high-risk HPV types. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.

Regulatory Strategy

- Goal was to get both claims at approval of PMA
- Longest item was need for 3 years of follow-up data for adjunctive screening
- Started negotiations with FDA* early in planning (prior to final clinical protocol)
- Implemented 2 separate protocols and clinical reports (one for each study)
- Provided all available information at time of PMA submission
- Continued open dialog with FDA during PMA review
- Amended PMA during review to continue to provide status updates on study
- Towards end of PMA review, worked with FDA to finalize wording in approval order
- **PAS becomes condition of approval with required reporting schedule!!**
- **Results of PAS were required to be added to labeling**

*** prior to any product specific guidance – HPV guidance issued Nov 2011**

Approval Order includes PAS Requirements

In addition to the Annual Report requirements, **you must provide the following data in postapproval study reports (PAS).** Gen-Probe must conduct a post-approval study to continue the follow-up of women 30 years and older with NILM cytology from the premarket study who had a consensus histological diagnosis of less than cervical intraepithelial neoplasia2 (CIN2) or no consensus histology results. **The study should be conducted as per approved protocol No. 2007HPVASCUS30 located in PMA Volume 7 Appendix 7-04**.

The objectives of the post-approval study are to evaluate APTIMA HPV Assay performance for detecting high-risk HPV types in subjects ≥30 years of age with negative (NILM) cytology results from routine Pap testing. This will be accomplished by evaluating the assay performance compared to known cervical disease status based on consensus histology at baseline and at a 3-year follow-up period.

Please be advised that the results from these studies should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.

FDA would like to remind you that you are required to submit PAS Progress Reports every six months during the first two years post-approval and annually thereafter. The reports should clearly be identified as Post-Approval Study Report.

http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100042A.pdf (Emphasis added)

From FDA's Web-site

Trade Name	APTIMA HPV ASSAY
Classification Name	Kit, Rna Detection, Human Papillomavirus[24]
Applicant	GEN-PROBE INCORPORATED
PMA Number	P100042
Date Received	11/05/2010
Decision Date	10/28/2011
Product Code	OYB [Registered Establishments With OYB[25]]
Docket Number	11M-0792
Notice Date	11/04/2011
Advisory Committee	Microbiology
Clinical Trials	NCT00973362[26]
Expedited Review Granted?	No
Combination Product	No
Information About:	Labeling, Approval Order, Summary Of Safety And Effectiveness[27]

Approval Order Statement

Approval for the aptima hpv assay. Aptima hpv assay indications for use: the aptima hpv assay is an in vitro nucleic acid amplification test for the qualitative detection ofe6/e7 viral messenger rna (mrna) from 14 high-risk types of human papillomavirus (hpv) in cervical specimens. The high-risk hpv types detected by the assay include: 16, 18,31,33,35, 39,45,51,52,56,58,59,66, and 68. The aptima hpv assay does not discriminate between the 14 high-risk types. Cervical specimens in thinprep pap test vials containing preservcyt solution and collected with broom-type or cytobrush/ spatula collection devices* may be tested with the aptima hpv assay. The assay is used with the tigris dts system. The use of the test is indicated: i. To screen patients 21 years and older with atypical squamous cells of undetermined significance (asc-us) cervical cytology results to determine the need for referral to colposcopy. T results of this test are not intended to prevent women from pro to colposcopy. 2. In women 30 years and older, the ap na h can be used with cervical cytology to adjunctively scre presence or absence of high-risk hpv types. This infor with the physician's assessment of cytology history, o and professional guidelines, may be used to guide pa ment. * broom-type device (e. G. , wallach pipette) or end brush/spatula.

Approval Order	Approval Order[28]
Post-Approval Study	Show Report Schedule And Study Progress[29]
Supplements:	S001[30] S002[31] S003[32] S004[33] S005[34]

Link to Post-approval study schedule and status as part of approval on FDA's web-site

Logistics for Successful PAS

Follow FDA guidance "Procedures for Handling Post-Approval Studies Imposed by PMA Order," issued June 15, 2009 ("post-approval guidance")

- Follow template exactly
- Follow-up reports should be cumulative and clearly account for subjects and changes to protocol
- FDA reviewers will call with questions

Need infrastructure within company to support timely, accurate submissions

- Need information from clinical affairs and study monitors
- Involve marketing and submit final labeling supplement as soon as final PAS report approved by FDA

Check FDA's post-approval study web-site to ensure your status is accurate

- http://www.accessdata.fda.gov/scripts/ cdrh/cfdocs/cfPMA/PMA_pas.cfm

From FDA's Post-Approval Study Web-site

Aptima HPV Assay Schedule

Report Schedule	Report Date Due	FDA Receipt Date	Reporting Status
six month report	04/27/2012	04/26/2012	On Time
one year report	10/27/2012	10/16/2012	On Time
18 month report	04/27/2013	04/11/2013	On Time
two year report	10/27/2013	10/10/2013	On Time
three year report-FINAL REPORT	10/27/2014	05/01/2014	On Time

Everyone will know if you're late!!

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?c_id=583&t_id=458860

From FDA's Post-Approval Study Web-site

General	
Application Number	P100042
Current Protocol Accepted	10/28/2011
Study Name	APTIMA HPV Assay
Study Status	Completed
General Study Protocol Parameters	
Study Design	Prospective Cohort Study
Study involve follow-up of premarket cohort (Y/N)	Yes
Data Source	New Data Collection
Comparison Group	Concurrent Control
Analysis Type	Analytical
Study Population	Adult: >21

Final Study Results

Actual Number of Patients Enrolled	10,545
Actual Number of Sites Enrolled	13
Patient Followup Rate	96.76%
Final Safety Findings	No issues concerning the safety of the APTIMA HPV Assay on either TIGRIS or PANTHER
Final Effectiveness Findings	The absolute risk of cervical disease is greater in subjects with positive APTIMA HPV Assay
Study Strengths and Weaknesses	This study was able to demonstrate that the APTIMA HPV assay-s postmarket performance is characterized
Recommendations for Labeling Changes	Yes

PAS data required to be added to final labeling

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?c_id=583&t_id=458860

Outcome

Aptima HPV Assay FDA approved October 28, 2011

- Included both claims and a PAS requirement

PAS progress reports submitted to FDA on schedule and final labeling updated at conclusion of study

Final labeling supplement approved June 5, 2015

Post-approval study enabled use of HPV adjunctive claim **3.5 years** sooner

without risk to patients!!

Why it worked

Human papillomavirus (HPV) testing devices have two distinct intended use populations with inherently different risk levels for cervical pre-cancer and cancer.

Approval of PMA for both populations was based on full analytical data and agreement of clinical samples against a valid comparator, and clinical evidence of safety and effectiveness for the high risk population.

A post-approval study assessed the longitudinal risk of cervical cancer in the population with lower risk.

Pivotal study continued and collected patient information at follow-up visits.

On-time, accurate and correctly formatted PAS reports.

Final labeling supplement submitted immediately after last PAS report was approved by FDA.

Conclusions

To successfully leverage post-approval studies to support earlier FDA approvals

- Start planning early in product development process
- Model existing product approvals and guidances
- Engage FDA on PAS options during Pre-Sub process
- Enable FDA to accept greater uncertainty of benefits and risks of Class III devices at approval by showing
  - Potential to address unmet medical needs
  - Premarket data to support a reasonable assurance of safety and effectiveness
  - Ability to sufficiently balance any uncertainty by other factors, including postmarket controls
- Be diligent to submit PAS reports in proper format and on-time!