UNIVERSITY of MARYLAND

# Platform to Improve Transparency for Biomarker Integration in Accelerated Approval Pathway


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|---|---|---|
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**FDA Mentor**

Shashi Amur, Ph.D.

Office of Translational Sciences

“Speeding the availability of drugs that treat serious diseases are in everyone's interest, especially when the drugs are the first available treatment or if the drug has advantages over existing treatments.”

-FDA

# Opportunity for Innovation

## Dissemination of information

### OCALIVA (obeticholic acid) tablets

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**Company: Intercept Pharmaceuticals, Inc.**
**Application No.: 207999**
**Approval Date: 05/27/2016**

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- Approval Letter(s) (PDF)
- Printed Labeling (PDF)
- Summary Review (PDF)
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- Medical Review(s) (PDF)
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- Statistical Review(s) (PDF)
- Clinical Pharmacology Biopharmaceutics Review(s) (PDF)
- Risk Assessment and Risk Mitigation Review(s) (PDF)
- Proprietary Name Review(s) (PDF)
- Other Review(s) (PDF)
- Administrative Document(s) & Correspondence (PDF)

**Where is the information showing the relationship of the biomarker to clinical benefit?**

# Opportunity for Innovation

## Communication between sponsor and FDA

"The FDA's determination of the acceptability of a biomarker endpoint for Accelerated Approval is occurring too late in the [drug development] process, typically at the End-Of-Phase 2 meeting." This poses a barrier to the development of and access to novel drugs for rare diseases that lack treatment.

| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>Food and Drug Administration<br><br>**NOTICE OF BIOMARKER USE AS SURROGATE ENDPOINT FOR ACCELERATED APPROVAL** | Form Approved:<br>Expiration Date:<br><br>Note: |
|---|---|

**Section 1: Administrative & Background Information**

| 1. Name of Sponsor | 2. Date of Submission (mm/dd/yyyy) |
|---|---|
| 3. Sponsor Address | 4. Telephone Number (Include country code if applicable and area code) |
| Address 1 (Street address, P.O. box, company name c/o) | |
| Address 2 (Apartment, suite, unit, building, floor, etc.) | |
| City / State/Province/Region | |
| Country / ZIP or Postal Code | |
| 5. Name(s) of Drug (Include all available names: Trade, Generic, Chemical, or Code) | |
| 6. IND Number (If previously assigned) | 7. (Proposed) Indication for Use |
| 8. Justification for The Use of a Surrogate Endpoint | |

**Section 2: Biomarker Specific Information**

| 9. Biomarker Identity | 10: Thresholds Used to Define Biomarker as a Surrogate Endpoint |
|---|---|
| 11. Has the Surrogate Endpoint Described Above Been Used for Drug Approval? If yes, please provide when it was used, and in what context. | Yes<br>No |
| 12. Justification of Use of Biomarker as Surrogate Endpoint | |

Selected Snapshot of the NOTICE OF BIOMARKER USE AS SURROGATE ENDPOINT FOR ACCELERATED APPROVAL form and instructions for filling out the form

## INSTRUCTION FOR FILLING OUT FORM FOR SURROGATE ENDPOINT EVALUATION

This is a voluntary form for submitting information regarding a proposed surrogate endpoint for review. Fill out all fields in SECTION 1 and any applicable fields in SECTIONS 2-5.

- **SECTION 1: ADMINISTRATIVE & BACKGROUND INFORMATION**
  - **Field 1: NAME OF SPONSOR**
    - The sponsor is the person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual, pharmaceutical company, governmental agency, academic institution, private organization or other organization.
  - **Field 2: DATE OF SUBMISSION**
    - Enter the date the submission is being submitted to the FDA.
  - **Fields 3 – 4: SPONSOR ADDRESS AND TELEPHONE NUMBER.**
    - Provide the address and telephone number of the sponsor identified in field 1
  - **Field 5: NAME(S) of DRUG**
    - For name(s) of drug , list the generic name(s) and trade name, if available. Also, provide the dosage form(s), and the unique ingredient identifier (UNII) term and code for active substances (if applicable). Use the Continuation Page if additional space is needed.
  - **Field 6: IND NUMBER**
    - Provide the IND number if it was previously assigned. If an IND number has not been assigned, leave the field blank. For IND numbers less than six digits, the IND number should be preceded using zeros (i.e., for IND 12345 enter 012345).
  - **Field 7: (PROPOSED) INDICATION FOR USE**
    - The proposed indication should be provided.
  - **Field 8: JUSTIFICATION FOR THE USE OF A SURROGATE ENDPOINT**
    - Explain as to why the disease state in question warrants the utilization of a surrogate endpoint rather than a clinical outcome (e.g. Sample size too small or disease course too long)
  - **SECTION 2: BIOMARKER SPECIFIC INFORMATION**
  - **Field 9: BIOMARKER IDENTITY**
    - [illegible] measurable biological substance that will be used as an indicator of the disease
  - **Field 10: THRESHOLDS USED TO DEFINE BIOMARKER AS A SURROGATE ENDPOINT**
    - What [illegible] of change in the biomarker level/amount will be defined as significant prior to treatment improvement
  - **Field 11: HAS THE SURROGATE ENDPOINT DESCRIBED ABOVE BEEN USED FOR DRUG APPROVAL [YES OR NO]**
    - If yes, please provide when it was used, and in what context
  - **Field 12: JUSTIFICATION OF USE OF BIOMARKER AS SURROGATE ENDPOINT**
    - What clinical benefit do you postulate is tied to the proposed surrogate endpoint
    - What are the current clinical uses and/or insights on the surrogate endpoint
    - Why is this the relative best endpoint to use? What other biomarkers exist that could have the same context of use, and why has the proposed surrogate endpoint been chosen over them?
  - **Field 13: CONTEXT OF USE**
    - A comprehensive and clear statement that describes the manner of use, interpretation, and purpose of use of a biomarker in drug development.
  - **Field 14: BASELINE MEASUREMENT IN TARGET PATIENT POPULATION**
    - Report the mean value of the biomarker presence and/or level(s) in the target disease patient population. Explain the behavior of the biomarker in this patient population.
  - **Field 15: BIOMARKER VARIABILITY**
    - Explain factors that indicate the biomarker is unlikely to have variability due to other causes than the intervention
      - **Is there variability in the biomarker level depending on the stage of the disease in question? [Yes or No]**
        - **If yes, please explain.**
      - **Is there variation in the biomarker level amongst relevant subgroups e.g. age, ethnicity, lifestyle? [Yes or No]**
        - **If yes, please explain.**

# Potential Impact

- Improved communication between FDA and Sponsor
- Improved access to relevant information for clinicians making decisions about drugs approved through Accelerated Approval

# The Process

**Systematic Literature Review**

- FDA documents from Drugs@FDA
- Editorials

**Semi-structured interviews of relevant stakeholders of Accelerated Approval Pathway**

**Thematic analysis**

# Themes

| | | |
|---|---|---|
| Justification for the use of a surrogate endpoint | **Biomarker Variability** | Preclinical data |
| Biomarker identity | Drug class | Literature review |
| Thresholds used to define biomarker as a Surrogate Endpoint | Impact of drug on biomarker from a biochemical perspective | Retrospective cohort studies |
| Has the surrogate endpoint described above been used for drug approval | Disease pathway | External Advisory Committee and Key Opinion Leader Surrogate Recommendations |
| **Justification of use of biomarker as surrogate endpoint** | Place of biomarker in disease pathway | Committee request |
| Context of use | Biomarker impact on symptomatology | **Classification of Biomarkers** |
| Baseline measurement in target patient population | Methods of measuring biomarker | |

# Theme

## Classification of Biomarkers

| Section 5: Sponsor Conclusion |
| --- |
| 27: Classification of Biomarker as a Surrogate Endpoint<br><br>☐ Level 1: A true clinical-efficacy measure<br>☐ Level 2: A validated surrogate endpoint (for a specific disease setting and class of interventions)<br>☐ Level 3: A non-validated surrogate endpoint, yet one established to be “reasonably likely to predict clinical benefit” (for a specific disease setting and class of interventions)<br>☐ Level 4: A correlate that is a measure of biological activity but that has not been established to be at a higher level |

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| Form | Date | Description | Format | Contact Info |
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| 0356h | 08/2015 | Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use (PDF) (Recommended for use with Adobe Acrobat 8 or 9) | (PDF - 2.5MB) | CBER MATT at 240-402-8020 CDER Drug Info at 301-796- |

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- Other Review(s) (PDF)
- Administrative Document(s) & Correspondence
- Biomarker use as a surrogate endpoint (PDF)

Implementation

**Where is the information showing the relationship of the biomarker to clinical benefit?**

# Key Points of our Proposal

- Communicate the characteristics of a biomarker that may be used as a surrogate endpoint

- The use of this form is voluntary

Questions?

# Supplement A: Notice of Biomarker Use as Surrogate Endpoint for Accelerated Approval form

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
Food and Drug Administration

**NOTICE OF BIOMARKER USE AS SURROGATE ENDPOINT FOR ACCELERATED APPROVAL**

Form Approved:
Expiration Date:

Note:

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|---|---|
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| Address 1 (Street address, P.O. box, company name c/o) | |
| Address 2 (Apartment, suite, unit, building, floor, etc.) | |
| City / State/Province/Region | |
| Country / ZIP or Postal Code | |
| 5. Name(s) of Drug (Include all available names: Trade, Generic, Chemical, or Code) | |
| 6. IND Number (If previously assigned) | 7. (Proposed) Indication for Use |
| 8. Justification for The Use of a Surrogate Endpoint | |

| Section 2: Biomarker Specific Information | |
|---|---|
| 9. Biomarker Identity | 10: Thresholds Used to Define Biomarker as a Surrogate Endpoint |
| 11. Has the Surrogate Endpoint Described Above Been Used for Drug Approval? If yes, please provide when it was used, and in what context. | ☐ Yes ☐ No |
| 12. Justification of Use of Biomarker as Surrogate Endpoint | |

12. Justification of Use of Biomarker s Surrogate Endpoint (*Continued*)

| 13. Context of Use | 14. Baseline Measurement in Target Patient Population |
| --- | --- |

15. Biomarker Variability

| Section 3: Drug and Disease Information in Relation To Biomarker | |
|---|---|
| 16. Drug Class | 17: Impact of Drug on Biomarker from a Biochemical Perspective |
| 18. Disease Pathway | |
| 19. Place of Biomarker in Disease Pathway | |
| 20: Biomarker Impact on Symptomatology | 21: Methods of Measuring Biomarker |

**Section 4: Information on Supporting Data**

22. Preclinical Data

- ☐ Bioinformatics and Modeling studies
- ☐ Human tissue cell studies
- ☐ Imaging studies

23. Literature Review ☐ Yes ☐ No

24: Retrospective Cohort Studies ☐ Yes ☐ No

25. External Advisory Committee and Key Opinion Leader Surrogate Recommendations

26. Committee Request

| Section 5: Sponsor Conclusion |
| --- |
| 27: Classification of Biomarker as a Surrogate Endpoint<br><br>☐ Level 1: A true clinical-efficacy measure;<br>☐ Level 2: A validated surrogate endpoint (for a specific disease setting and class of interventions);<br>☐ Level 3: A non-validated surrogate endpoint, yet one established to be "reasonably likely to predict clinical benefit" (for a specific disease setting and class of interventions);<br>☐ Level 4: A correlate that is a measure of biological activity but that has not been established to be at a higher level. |

# Supplement B: Instruction for Filling out Form for Surrogate Endpoint Evaluation

# INSTRUCTION FOR FILLING OUT FORM FOR SURROGATE ENDPOINT EVALUATION

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    - Provide the address and telephone number of the sponsor identified in field 1
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  - **Field 7: (PROPOSED) INDICATION FOR USE**
    - The proposed indication should be provided.
  - **Field 8: JUSTIFICATION FOR THE USE OF A SURROGATE ENDPOINT**
    - Explain as to why the disease state in question warrants the utilization of a surrogate endpoint rather than a clinical outcome (e.g. Sample size too small or disease course too long)
- **SECTION 2: BIOMARKER SPECIFIC INFORMATION**
  - **Field 9: BIOMARKER IDENTITY**
    - Name the measurable biological substance that will be used as an indicator of the disease.
  - **Field 10: THRESHOLDS USED TO DEFINE BIOMARKER AS A SURROGATE ENDPOINT**
    - What range of change in the biomarker level/amount will be defined as significant primary endpoint improvement
  - **Field 11: HAS THE SURROGATE ENDPOINT DESCRIBED ABOVE BEEN USED FOR DRUG APPROVAL [YES OR NO]**
    - **If yes, please provide when it was used, and in what context**
  - **Field 12: JUSTIFICATION OF USE OF BIOMARKER AS SURROGATE ENDPOINT**

- What clinical benefit do you postulate is tied to the proposed surrogate endpoint
- What are the current clinical uses and/or insights on the surrogate endpoint
- Why is this the relative best endpoint to use? What other biomarkers exist that could have the same context of use, and why has the proposed surrogate endpoint been chosen over them?

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  - Report the mean value of the biomarker presence and/or level(s) in the target disease patient population. Explain the behavior of the biomarker in this patient population.
- **Field 15: BIOMARKER VARIABILITY**
  - Explain factors that indicate the biomarker is unlikely to have variability due to other causes than the intervention
    - **Is there variability in the biomarker level depending on the stage of the disease in question? [Yes or No]**
      - **If yes, please explain.**
    - **Is there variation in the biomarker level amongst relevant subgroups e.g. age, ethnicity, lifestyle? [Yes or No]**
      - **If yes, please explain.**
    - **Are there any variations of the biomarker due to where it is obtained from within the body i.e. is the biomarker site specific? [Yes or No]**
      - **If yes, explain if it found in an appropriate place.**

- **SECTION 3: DRUG AND DISEASE INFORMATION IN RELATION TO BIOMARKER**
  - **Field 16: DRUG CLASS**
    - Report the group of medicines that consist of similar chemical arrangements, the same mode of action, and are used to resolve the same disease state as the molecule used for this context of use
  - **Field 17: IMPACT OF DRUG ON BIOMARKER FROM A BIOCHEMICAL PERSPECTIVE**
    - Describe how the drug affects the chemical or substance that is defined as the biomarker
  - **Field 18: DISEASE PATHWAY**
    - Explain the pathophysiology process and the series of biological actions that leads to a product of the disease, is there variability in disease pathway, and is the etiology fully understood
  - **Field 19: PLACE OF BIOMARKER IN DISEASE PATHWAY**
    - How does the biomarker play a role plays in the disease pathophysiology?
  - **Field 20: BIOMARKER IMPACT ON SYMPTOMATOLOGY**
    - How does changes in the biomarker impact symptoms of the disease?
  - **Field 21: METHODS OF MEASURING BIOMARKER**

- Explain the process and devices used in order to measure a biomarker. Explain the validity of the analytical methods used to measure the biomarker.

- **SECTION 4: Information on Supporting Data**
  - **Field 22: PRECLINICAL DATA**
    - Check all applicable. What type of data has been gathered preceding the clinical stage? Attach all study documents with this submission.
      - **Bioinformatics and Modeling studies**
      - **Human tissue cell studies**
      - **Imaging studies**
  - **Field 23: LITERATURE REVIEW [YES OR NO]**
    - What type of data has been gathered from available peer reviewed literature supporting the biomarker use as a surrogate endpoint in this context of use. Attach all study documents with this submission.
  - **Field 24: RETROSPECTIVE COHORT STUDIES [YES OR NO]**
    - What type of data has been gathered from any retrospective cohort studies conducted by the sponsor or a third party supporting the biomarker use as a surrogate endpoint in this context of use.
  - **Field 25: EXTERNAL ADVISORY COMMITTEE AND KEY OPINION LEADER SURROGATE RECOMMENDATIONS**
    - Cite any external expert opinions or recommendations from key opinion leaders or external advisory committees
  - **Field 26: COMMITTEE REQUEST**
    - What committees to be requested to consult on this surrogate endpoint validation? Refer to Index for list of all active committees.
- **SECTION 5: SPONSOR EVALUATION**
  - **Field 27: CLASSIFICATION OF BIOMARKERS**
    - Select the position of the proposed surrogate endpoint in the hierarchy of outcome measures based on the data presented in this notice. This subjective classification is intended to assess preliminarily the degree of agreement regarding the validity of the biomarker as an endpoint between the FDA and the sponsor.
      - **Level 1: A true clinical-efficacy measure;**
      - **Level 2: A validated surrogate endpoint (for a specific disease setting and class of interventions);**
      - **Level 3: A non-validated surrogate endpoint, yet one established to be "reasonably likely to predict clinical benefit" (for a specific disease setting and class of interventions);**
      - **Level 4: A correlate that is a measure of biological activity but that has not been established to be at a higher level.**