FDA Draft Panel Questions

November 30, 2017
Blood Products Advisory Committee (BPAC) Devices Panel
HLA, HPA and HNA Device Classification

1. Following the review of relevant literature, medical device reports and recalls related to HLA, HPA and HNA devices, FDA has identified the following risks to health when these devices are used for transfusion, transplantation or disease diagnosis:

   Patient injury or death due to:

   - Poor graft survival or function due to transplantation of incompatible hematopoietic cells, tissue or organ.
   - Graft rejection because of the transplantation of incompatible hematopoietic cells, tissue or organ.
   - Graft-versus-host disease because of the transplantation of incompatible immune system cells.
   - Incorrect or delayed diagnosis of medically related conditions because of incorrect HLA, HPA or HNA test results.
   - Transfusion reaction (e.g. Transfusion Associated Lung Injury, Post Transfusion Purpura) due to incorrect HLA, HPA or HNA test results.
   - Platelet refractoriness because of incorrect HLA or HPA typing or antibody detection results.

   a. Do you agree that this is a complete and accurate list of the risks to health presented by HLA, HPA and HNA devices?

   b. If you disagree, please comment on what additional risks should be included or explain which, if any, of the risks listed are not part of the overall risk assessment of HLA, HPA and HNA devices.

2. Section 513 of the Food, Drug, and Cosmetic Act (FD&C Act) states:

   A device should be **Class III** if:

   - Insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls would provide such assurance,

     AND

   - The device is life-supporting or life sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

A device should be **Class II** if:

- General controls by themselves are insufficient to provide a reasonable assurance of safety and effectiveness,

  AND

- There is sufficient information to establish special controls to provide such assurance.

A device should be **Class I** if:

- General controls are sufficient to provide reasonable assurance of the safety and effectiveness,

  OR

- Insufficient information exists to determine that general controls are sufficient or special controls can be established to provide a reasonable assurance of safety and effectiveness, but the device type is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health and does not present a potential unreasonable risk of illness or injury.

  General controls may include:
  - Prohibition against adulterated or misbranded devices,
  - Good Manufacturing Practices (GMPs),
  - Registration of manufacturing facilities,
  - Listing of device types,
  - Recordkeeping, etc.

a. FDA believes that general controls alone are not sufficient to provide a reasonable assurance of safety and effectiveness for HLA, HPA and HNA devices.

   i. Do you agree with this assessment?

   ii. If not, please discuss how general controls alone are sufficient to provide a reasonable assurance of safety and effectiveness for HLA, HPA and HNA devices.

b. Under the Federal Food, Drug, and Cosmetic Act, a device is potentially class III if it is "life-supporting or life-sustaining, or of substantial importance in preventing impairment of human health." FDA believes that HLA, HPA and HNA devices are not life-supporting or life-sustaining,

   i. Do you agree with this assessment?

ii. If not, please explain why HLA, HPA and HNA devices are life-supporting or life-sustaining.

c. Under the Federal Food, Drug, and Cosmetic Act, a device is potentially class III if it is "of substantial importance in preventing impairment of human health." FDA believes that HLA, HPA and HNA devices are of substantial importance in preventing impairment of human health.

i. Do you agree with this assessment?

ii. If not, please explain why HLA, HPA and HNA devices are not of substantial importance in preventing impairment of human health.

d. Under the statute, a device is potentially class III if it presents a "potential unreasonable risk of illness or injury." Considering the risks and benefits of these devices, FDA believes that HLA, HPA and HNA devices present a potential unreasonable risk of illness or injury. (Note that such a device may still be classified as class II if application of special controls would provide reasonable assurance of its safety and effectiveness.)

i. Do you agree with this assessment?

ii. If not, please explain why HLA, HPA and HNA devices are not for a use which presents a potential unreasonable risk of illness or injury.

e. FDA believes sufficient information exists to establish special controls for HLA, HPA and HNA devices. FDA is proposing the following as special controls that would provide reasonable assurance of safety and effectiveness:

1) Premarket submissions must include detailed documentation of the following information:
    i. Device accuracy study using well-characterized samples representing as many targets as possible.
    ii. Precision studies to evaluate possible sources of variation that may affect test results
    iii. Comparison studies to evaluate the device's performance compared to a predicate.
    iv. Specific information that address or mitigate risks associated with false positive antibody reactivity e.g., reactivity with denatured/cryptic epitopes, if applicable.
    v. Description of how the assay cut-off was established and validated as well as supporting data.
    vi. Documentation for device software, including, but not limited to, software requirement specifications, software design specification, e.g., algorithms, alarms and device limitations; hazard analysis, traceability matrix, verification and validation testing, unresolved anomalies, hardware and software specifications; electromagnetic compatibility and wireless testing.

vii. For multiplex assays in which large numbers of probes and/or primers are handled during manufacturing process, premarket submissions should provide the design specifications that are in place to prevent incorrect reactivity assignment.
viii. Description of a plan on how to ensure the performance characteristics of the device remain unchanged over time when new {HLA, HNA or HPA} alleles are identified, and/or reactivity assignments are changed from the assignments at the time the device was evaluated.

2) The device labeling must include:

i. A limitation statement that reads, "The results should not be used as the sole basis for making a clinical decision."

ii. A warning that reads "The use of this device as a companion diagnostics, has not been established."

f. Based on the information presented today, please discuss whether you believe that sufficient information exists to establish special controls that can provide a reasonable assurance of safety and effectiveness of HLA, HPA and HNA devices. If not, please explain why not.

g. Do you agree that the list in e.1) is a complete and accurate list of the special controls needed to provide reasonable assurance of safety and effectiveness for HLA, HPA and HNA devices?

If you disagree, please comment on what additional special controls are needed or explain which, if any, of the proposed special controls are not needed.

h. Do you agree that the Agency's proposed classification for HLA, HPA and HNA devices as Class II with special controls will provide reasonable assurance of safety and effectiveness?

If you disagree, please discuss why special controls are not adequate to assure safety and effectiveness of HLA, HPA and HNA devices.