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Final guidance provides additional clarity to the Humanitarian Device Exemption program

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On 6 September 2019 the U.S. Food and Drug Administration (FDA or the agency) issued its final guidance document entitled "Humanitarian Device Exemption (HDE) Program." The guidance replaces the 13 June 2018 draft guidance and supersedes the 8 June 2010 "Guidance for HDE holders, Institutional Review Boards (IRBs), Clinical Investigators, and Food and Drug Administration Staff, Humanitarian Device Exemptions (HDE) Regulation: Questions and Answers."

The final guidance is largely consistent with the draft version of the guidance, formally incorporating updates to account for changes to the law made by the 21st Century Cures Act. The final guidance contains clarifying language on types of evidence appropriate to support an HDE application and probable benefit-risk assessment.

Types of evidence

The agency's acceptance of a broad range of types of evidence to support an HDE application is made more explicit in the final guidance; these include "investigations using laboratory animals, investigations involving human subjects, nonclinical investigations, and analytical studies for in vitro diagnostics," and retains FDA's prior stated recognition that there may be little or no clinical experience with humanitarian use devices (HUDs).

Probable benefit-risk assessment

While reaffirming that probable benefit-risk will be assessed using the same factors applied to premarket approvals and De Novo requests, the final guidance also affirms that the weighting of the factors and the nature of the evidence will differ in the HDE context. Specifically, the guidance underscores the expectation that "there will generally be greater uncertainty surrounding the benefit-risk profile based on the evidence submitted in an HDE application." The final guidance adds an example of such a case, noting that FDA would expect a greater amount of uncertainty from smaller patient populations, due to the challenges of obtaining clinical data regarding the device. Finally, the draft guidance includes language encouraging HDE applicants to collect and submit patient preference information as available to assist in the probable benefit-risk assessment.

HDE filing review checklist

The updated checklist is very similar to the checklist found in the draft guidance, and remains consistent with the general approach used in other premarket applications, such as the recently released guidance document, "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications" (benefit-risk guidance). Similarly, the attention to quantifying uncertainty aligns with recent agency efforts to clarify the extent of uncertainty in premarket review. See our analysis of the new benefit-risk guidance and the role of uncertainty in premarket reviews.

Per the final guidance, FDA will notify the HDE applicant of the filing decision within 30 calendar days from the date the HDE application was received, with a "not filing letter" considered a request for submission of an HDE amendment.

IRBs and local committees

The final guidance provides nuanced clarification around FDA's interpretation of the statutory provisions governing HDEs. Specifically, the agency has clarified that its prior position with respect to the IRB or local committee review and approval on a per facility basis is grounded on its interpretation of the relevant statutory language. In addition, the final guidance provides further insight into the criteria FDA would consider in assessing whether a local committee is "appropriate" to review use of HDEs in clinical care.

Conclusion

The final guidance remains largely consistent with the draft guidance, as well as FDA's approach to HUD designations and HDE applications per the 21st Century Cures Act. The specificity of language included in the final guidance around the types of evidence considered appropriate to support HDEs is certainly welcome, although it remains to be seen how the agency will approach this issue in practice going forward. FDA has considerable discretion in the types of data considered acceptable to demonstrate probable benefit in support of HDEs for devices intended to treat small, orphan populations. Despite this discretion and the practical challenges presented by conducting clinical trials in such small populations, in practice we have seen a clear preference for clinical data, and even where clinical data are available from small nonrandomized studies, questioning of applicants ability to conduct randomized controlled trials in these small populations. Recently, we have seen instances of FDA requesting post-approval registry studies to gain more long-term data for HUD devices in an effort to provide access to needed devices with more limited clinical data.

On 21 October 2019 FDA will host a webinar to discuss this final guidance.

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