Moving Points in Nephrology

FDA Regulatory Perspectives for Studies on Hemodialysis Vascular Access

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Abstract

In an effort to foster innovation and new product development, the American Society of Nephrology and the US Food and Drug Administration partnered to form the Kidney Health Initiative in 2012. Part of the Kidney Health Initiative's mission is to foster development of therapies by creating a collaborative environment where the US Food and Drug Administration and the greater nephrology community can interact to optimize product evaluation. This particular Kidney Health Initiative project focused on products related to hemodialysis vascular access, with the goal of clarifying appropriate trial end points that could subsequently inform clinical, regulatory, and coverage decisions. Both the lack of common definitions and the lack of consensus on trial end points have been viewed as barriers to innovation in this area. Toward this end, the Kidney Health Initiative convened teams of expert stakeholders to address these issues for each major vascular access category (arteriovenous grafts, arteriovenous fistulas, and central venous catheters), and each team provided recommendations. This commentary provides an overview of the US Food and Drug Administration centers that regulate hemodialysis vascular access and certain laws and regulations that affect these products as well as our perspectives on some of the issues raised and end points proposed by the Kidney Health Initiative teams. The standardized definitions and clinical trial end points proposed by the teams represent an important step forward to improve innovation in this area.

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Introduction

In an effort to foster innovation and new product development, the American Society of Nephrology and the US Food and Drug Administration (FDA) partnered to form the Kidney Health Initiative (KHI) in 2012. Part of the KHI's mission is to foster development of therapies by creating a collaborative environment where the FDA and the greater nephrology community can interact to optimize evaluation of drugs, devices, biologics, and food products (1). As many have noted, vascular access is the lifeline of patients on hemodialysis (HD), and better treatments are needed to address the problems associated with HD vascular access, which greatly affect patients' quality of life. Both the lack of common definitions and the lack of consensus on appropriate trial end points have been viewed as barriers to innovation in this area. Accordingly, the aim of this KHI project was to clarify appropriate trial end points that could subsequently inform clinical, regulatory, and coverage decisions. Toward this end, the KHI teams authored manuscripts presented in this issue (2,3) related to the main categories of vascular access.

Within the FDA, different centers have responsibility for evaluating the safety and effectiveness of medical products being developed for the three categories of HD vascular access: arteriovenous graft (AVG), arteriovenous fistula (AVF), and central venous catheter (CVC). These products are governed by specific laws and regulations that specify different requirements for clearance, approval, or licensing depending on which medical product definition a certain product meets (*i.e.*, devices, drugs, and biologics). This manuscript provides an overview of these centers and certain laws and regulations that affect how the FDA regulates these products. It also provides our perspectives on some of the issues raised and end points proposed in the KHI manuscripts.

FDA Center Regulations

Center for Devices and Radiologic Health

As part of the agency's public health mission, the FDA's Center for Devices and Radiologic Health (CDRH) is responsible for providing the United States public with timely and continued access to safe, effective, and high-quality medical devices. The CDRH uses a risk-based classification of devices, which determines the applicable regulatory requirements (examples of vascular access devices are included in Table 1). The lowest risk devices are class 1, which are typically exempt from FDA premarket review but subject to general controls, such as adherence to good manufacturing practices. Class 2 devices are generally subject to premarket notification, also referred to as the 510(k) pathway, and may be subject to special controls. For a 510(k) clearance, a device must be determined to be "substantially equivalent" (4) (as safe and as effective) to a predicate (legally marketed) device in the United States. Most 510(k) submissions do not require clinical data, acknowledging that there is a body of knowledge regarding the risks and benefits for similar devices already on the market. However, there

Table 1. Center for Devices and Radiologic Health device risk classification with hemodialysis vascular access device examples

Device Class	Risk Level	Device Class Requirements	HD Vascular Access Example	Regulatory Pathway (for Example)	Comments
1	Low	General controls[a]	Manual surgical instrument (*e.g.*, scalpel, hemostat)	Exempt from premarket notification	Regulation (21 CFR 878.4800)[b]
2	Low to moderate	General controls[a]; special controls[c]	Vascular graft prosthesis	Premarket notification [510(k)]	Regulation (21 CFR 870.3450)[d]; the special control for this device is the FDA guidance document entitled "Guidance Document for Vascular Prostheses 510k Submissions"[e]
3	High	General controls[a]; PMA[f]	Bovine carotid artery arterial graft prosthesis[g]	PMA[f]	PMA approval is on the basis of a determination by the FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s)[f]

HD, hemodialysis; CFR, Code of Federal Regulations; FDA, US Food and Drug Administration; PMA, premarket approval.
[a]General controls are regulatory requirements authorized by the Federal Food, Drug, and Cosmetic Act under sections 501 (adulterated devices), 502 (misbranded devices), 510 (registration and listing), 516 (banned devices), 518 (notification and other remedies), 519 (records and reports), and 520 (general provisions). General controls apply to all medical devices, unless exempted by regulations. If a device is exempted from one of the general controls, such exemption is stated in the classification regulation for that device.
[b]https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=878.4800.
[c]Special controls are regulatory requirements for class 2 devices, for which general controls alone are insufficient to provide reasonable assurance of the safety and effectiveness of the device and there is sufficient information to establish special controls to provide such assurance. Special controls are usually device specific (*e.g.*, performance standards, postmarket surveillance, patient registries, special labeling requirements, premarket data requirements, and guidelines).
[d]https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=870.3450.
[e]https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073681.htm.
[f]https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm.
[g]https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=FZC.

are instances where clinical data are needed (for example, to address technologic differences [compared with the predicate] or ensure that a specific device complies with identified special controls). The highest risk devices are class 3, which typically require premarket approval (PMA). To receive approval, a PMA application must show that there is a "reasonable assurance that the device is safe and effective" (5) for its intended use. Typically, this requires robust clinical data, although the design and size of the study will vary depending on the product. In weighing this information, the FDA will consider whether the probable benefits of use outweigh the probable risks (6).

Center for Drug Evaluation and Research

The Center for Drug Evaluation and Research (CDER) is responsible for ensuring that safe and effective drugs are available to the United States public. The CDER regulates prescription drugs, including therapeutic proteins, as well as generic drugs and over the counter medications.

For drugs to be approved by the FDA, they must be shown to be safe and effective for their intended use. The effectiveness requirement for drug approval was added to the Federal Food, Drug, and Cosmetic Act in 1962 (7). According to this act, "substantial evidence" of effectiveness, consisting of evidence from adequate and well controlled investigations, is needed to support approval. Biologics, including therapeutic proteins, are licensed under section 351 of the Public Health Service Act. According to this act, products must show "continued safety, purity, and potency"; the "potency" of a product has been interpreted to include effectiveness.

Drugs may be approved on the basis of an effect on a clinical outcome (*i.e.*, how an individual feels, functions, or

survives). Alternatively, drugs may be approved on the basis of an effect on a surrogate end point, an end point that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. Surrogate end points do not measure the clinical benefit of primary interest; they are, however, expected to predict the clinical benefit (8). In the United States, validated surrogate end points—surrogate end points that are known to predict clinical benefit—can be used as the basis for traditional approval, whereas "reasonably likely surrogate endpoints"—surrogate end points that are reasonably likely to predict clinical benefit—can be used as the basis for accelerated approval of drugs and biologics intended to treat a serious or life-threatening diseases. The latter approval pathway comes with a requirement to conduct postmarketing trials verifying the predicted benefit. The FDA's guidance document on expedited programs provides an overview of some of the factors to consider in identifying and assessing surrogate end points in the context of accelerated approval (9). With regard to the evidence required to show that a surrogate end point has been "validated," the FDA has stated that "robust" scientific evidence is needed because of the risk to public health associated with falsely concluding that a therapy provides benefit when it does not. To date, surrogate end points have been widely used as a basis for approval of therapies intended to treat CKD and its complications. As an example, a doubling of serum creatinine has long been used as a surrogate end point for assessing a drug's efficacy in reducing the risk of progression to ESRD, and more recently, on the basis of the results of a scientific workshop, lesser changes in renal function are also being used (10,11).

Combination Products

As in other therapeutic areas, there has been significant interest in the development of combination products for HD vascular access. The FDA defines combination products on its website as "a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product" (12). The regulatory definition is more detailed and relates to how the constituent parts are combined, copackaged, or distributed (13). Regulatory oversight and coordination are provided by the FDA's Office of Combination Products.

Because of the inherent complexity of combination products, diverse expertise is needed to fully assess their safety and effectiveness and may necessitate involvement of multiple centers in the review of the combination product. The different laws and regulations governing drugs, devices, and biologics add another layer of complexity associated with the regulation of combination products. The FDA is currently taking a number of steps to improve coordination by enhancing our internal processes and clarifying regulatory requirements (14).

Although the evaluation of combination products may be completed by a team of experts from multiple centers, the medical product review is led by the center responsible for the constituent part of the combination product that provides the product's primary mode of action (15). As an example, CVCs with antimicrobial coatings are a combination product, including both drug and device constituents. The FDA has determined that the primary mode of action is attributable to the device component's role in providing central venous access, whereas the drug component plays a secondary role (*e.g.*, reducing the risk of catheter-related infections by inhibiting bacterial growth on the catheter's surface) (16,17).

Product Jurisdiction: Review of Vascular Access Type by FDA Center

The FDA centers involved in the regulation of the various HD vascular access products are described in Table 2. Examples of specific regulatory and scientific considerations for AVG and CVC are included below:

Arteriovenous Grafts

The data required to market a vascular graft or related device vary depending on the unique risks and benefits of that device and its novelty compared with other devices on the market. For instance, synthetic AVGs are class 2 devices; because they have been on the market for many years, their risks and benefits are relatively well understood, and their premarket submissions typically do not require clinical data. The FDA's expectations for nonclinical testing are outlined in our Guidance Document (18). However, animal (*e.g.*, bovine carotid artery) tissue AVGs (19) are class 3 devices requiring a PMA application, because their risks and performance characteristics are less well defined.

Central Venous Catheters

CVCs are class 2 devices and include both nonimplanted (*i.e.*, short-term) and implanted (*i.e.*, long-term or cuffed) designs. Additional details on the regulatory requirements and testing recommendations for "implanted" CVCs can be found in our Guidance Document (20). As stated in the guidance document, clinical evidence is generally not warranted for these devices. Some exceptions include fully subcutaneous port catheter systems; catheters with certain coatings; or catheters with novel designs, technologies, or claims. Some examples where clinical data were included to support safety and efficacy are the addition of a third lumen (21) and a fully subcutaneous HD port catheter system (22).

Regulatory Perspective Regarding the Recommendations Made by Content Development Teams

The aim of the KHI project on vascular access was to clarify appropriate trial end points that could subsequently inform clinical, regulatory, and coverage decisions. As part of this effort, the authors generated a concise set of standard definitions, an important step forward for innovation in any area. The manuscripts also contain a number of recommendations regarding trial end points; we address some of these recommendations below.

It is important to note that a range of end points can be used to evaluate the efficacy/benefits of HD vascular

Table 2. Vascular access products by the Food and Drug Administration center with regulatory jurisdiction

FDA Center and Review Entity	Dialysis Access–Related Product
Center for Devices and Radiologic Health	
Office of Device Evaluation, Division of Cardiovascular Devices, Vascular Surgery Devices Branch	Synthetic (*e.g.*, PTFE) AVGs; tissue AVG derived from animal (usually bovine) origin or human umbilical veins; stent grafts (covered stents); devices intended to assist in creating new AVF (*e.g.*, *via* an endovascular approach); devices to assist in AVF maturation; devices to maintain or restore AV access patency
Office of Device Evaluation, Division of Reproductive, Gastro-Renal and Urological Devices, Renal Devices Branch	Central venous catheters intended for hemodialysis; needles for AVF (and AVG); implanted needle guide devices
Center for Drug Evaluation and Research	
Division of Cardiovascular and Renal Products	Drugs and therapeutic proteins intended to improve AVF maturation and function and reduce complications
Center for Biologics Evaluation and Research	
Office of Tissues and Advanced Therapies	Tissue-engineered AVG (*e.g.*, extracellular matrices developed through cell culture); cellular-, gene-, and tissue-based therapies intended to improve AVF maturation and function and reduce complications

FDA, US Food and Drug Administration; PTFE, polytetrafluoroethylene; AVG, arteriovenous graft; AVF, arteriovenous fistula; AV, arteriovenous.

access products, and ultimately, study designs and trial end points should be tailored to a specific product and its intended use. The FDA provides mechanisms for sponsors to obtain feedback on appropriate end points and study designs. For medical devices reviewed in the CDRH, this can be done through the presubmission process (23). Meetings related to the development and review of a drug or biologic can also be scheduled with the CDER or the Center for Biologics Evaluation and Research (24).

Arteriovenous Grafts and Arteriovenous Fistula

The arteriovenous dialysis access manuscript discusses the phases of the arteriovenous access life cycle and the potential problems that can arise in each phase. The manuscript then addresses potential trial end points on the basis of trial categories that reflect a particular phase of arteriovenous access development or complication. In the manuscript, table 1 outlines how trial end points will vary on the basis of which phase of the arteriovenous access life cycle is under study, and more concrete end point suggestions are offered in table 3 (2). These suggestions clearly recognize that flexibility in outcome measures is required given that the effectiveness and safety end points will vary from trial to trial depending on the unique features of the specific access type and the intervention under investigation. Whatever particular end points are selected for a given trial, these should allow for an adequate assessment of the safety, effectiveness, and benefit-risk profile of the product.

These trial categories provide a useful construct for thinking about potential targets for intervention, and the proposed end points for the different trial categories would likely be acceptable for a device. However, as previously discussed, the legal and regulatory requirements for drugs differ from those of devices. Specifically, drugs are approved on the basis of an effect on a clinical outcome or surrogate end point that is considered validated (basis for traditional approval) or reasonably likely (basis for accelerated approval). For some of the end points proposed by the group, more data may be needed to provide reassurance that a drug's effect on the end point will reliably predict a drug's effect on long-term AVF outcomes. An example of such an end point is physiologically mature AVF (*i.e.*, internal diameter $\geq$0.5 cm and access blood flow $\geq$500 ml/min). However, in registration trials of drugs intended to improve AVF suitability for dialysis, it may be reasonable to use such a definition to assess suitability for dialysis in the subset of patients enrolled in the trial who do not initiate dialysis during the time course of the trial.

This manuscript also discusses secondary end points for the different trial categories. These end points reflect other potential benefits or harms of a therapy. Regardless of whether an end point is categorized as a secondary end point, it is important for trials to collect information on a spectrum of arteriovenous access–related complications and adverse events from both an efficacy and a safety perspective. Clinical trials to evaluate a variety of novel intraluminal and extraluminal devices, drugs, and biologic products and their potential unintended and adverse effects, such as the effect of subsequent treatment failure on the ability to salvage a failing or occluded arteriovenous access, must be considered. For instance, the ability to extend secondary patency may not be significantly affected after treatment failure of a stenotic lesion with a drug-coated balloon, because nothing permanent is left behind that may complicate future efforts to retreat the target lesion. However, implantation of a stent graft in an AVF may have very different consequences for the patient when that device fails. Abandonment of an AVF related to the

failure of an implanted device is likely to have a significant effect on affected subjects. Considering the consequences of failure is an essential component of the risk-benefit analysis that the FDA makes when evaluating access-related devices.

Central Venous Catheter

The CVC manuscript provides standardized definitions for trial end points for catheter-related bloodstream infection (CRBSI), catheter dysfunction, and central vein obstruction; discusses areas of uncertainty regarding proposed end points; and recommends studies that are needed to resolve outstanding questions related to end point definitions (3).

As an example, the Infectious Diseases Society of America (IDSA) CRBSI definition (25) has not been validated for CVCs in patients on HD. As pointed out by the authors, it may not always be possible to meet the IDSA definition in this population for various reasons, including patient factors (lower basal temperature or inadequate peripheral veins) and HD clinic logistics (lack of phlebotomy services or physicians not present during symptom presentation). We acknowledge that obtaining peripheral blood samples may be technically challenging and could imperil the integrity of blood vessels for future access. However, there is minimal evidence showing that dialysis circuit samples accurately identify CRBSI. Therefore, we agree with the high-priority studies proposed by the authors to validate the alternate CRBSI definition, including studies to validate the checklist for excluding non-catheter sources of infection.

The CVC manuscript also describes special pediatric considerations. Although there are challenges associated with conducting vascular access clinical trials in pediatric patients, there is also significant need for innovation in this space. There are unique vascular access issues and considerations in children. For example, pediatric patients may need multiple types of access over the course of their lives; transplant rates, wait times, and vessel sizes also differ from those in adults (26). These as well as the other issues described by the authors may have bearing on the design and conduct of vascular access clinical trials in this population. Further discussions are needed with the larger nephrology community regarding barriers to innovation in this space and how to overcome these barriers.

Summary

Better treatments are needed to improve HD vascular access. The standardized definitions and clinical trial end points proposed by the work groups represent an important step forward. Ultimately, study designs and trial end points are generally tailored to an individual product; the documents produced by the KHI workgroups provide a valuable resource for doing so. We thank the workgroup members and hope that their efforts facilitate advances that will ultimately improve the lives of patients with kidney failure.

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Disclosures

None.

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See related articles, "Clinical Trial End Points for Hemodialysis Vascular Access: Background, Rationale, and Definitions," "Recommended Clinical Trial End Points for Dialysis Catheters," and "Definitions and End Points for Interventional Studies for Arteriovenous Dialysis Access," on pages 490–494, 495–500 and 501–512, respectively.