

The FDA and the State of Chronic Diseases: Cardiovascular, Endocrine, Pulmonary, and Renal Diseases

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Abstract

Despite needs for new therapies and improvements in existing approaches in cardiovascular, pulmonary, endocrine, and renal disease, investment in these areas is lagging relative to other specialties. This article summarizes a meeting of key stakeholders of U.S. Food and Drug Administration (FDA) officials, representatives from academia, national organizations, and patients and caregivers. The purpose was to identify and discuss high-priority issues, establish areas of common interest, and explore opportunities for collaboration. During the meeting (September 2016), the construct of a “multimorbidity continuum” emerged, in which chronic diseases are understood as their effects on the whole rather than individual organ systems. Cross-disciplinary priorities included: 1) the need to generate greater high-quality evidence at lower cost; 2) the imperative to develop and implement patient-centered approaches to clinical investigations; 3) the importance of trial participation in under-represented populations, particularly with comorbid conditions, and 4) the need for progress in tobacco regulation. Representatives from each therapeutic area reported on their consensus priorities, and FDA representatives discussed the agency’s role in facilitating broader approaches to therapeutic development and evaluation of disease as linked across organ systems rather than in isolation, and emphasized the importance of patient engagement, collaboration and communication across stakeholders.

Introduction

Diseases related to cardiovascular, endocrine, pulmonary, and renal disorders remain the leading causes of death in the United States.¹ Collectively, these diseases create tremendous burdens for patients, caregivers, families, and the U.S. healthcare system. But despite the need for new therapies and improvements in existing treatments and preventive approaches, investment in these therapeutic areas is lagging relative to other conditions.² We previously reported these concerns relative to cardiovascular development,³ which is also true of the other major chronic diseases outlined here (Figure 1).⁴ Although investment and development has declined, there is still a pipeline of novel R&D therapeutics, contradicting the notion that there is a relative shortage of new basic scientific ideas to underpin clinical advances. In oncology, better understanding of the genetics of cancer has been essential in moving the development of new therapeutic agents forward. In cardiovascular, renal, endocrine and pulmonary diseases, these advances have only mostly led to incremental developments in therapeutics. While the issues are multifactorial, the challenge is finding a balance between generating needed evidence for safety and efficacy, despite the burden of cost and efficiency that may drive innovation into other therapeutic areas.

This article summarizes a meeting of key stakeholders, including the Commissioner of the U.S. Food and Drug Administration (FDA), other FDA officials, and organizations focusing on cardiovascular, endocrine, pulmonary, and renal disciplines. Its purpose was to identify and discuss priority issues, establish areas of common interest, and explore opportunities for collaboration (Appendix).

Cross-Disciplinary Themes

There was widespread recognition that multiple priorities were broadly shared (Table 1).

Because many therapies are only partially effective, there is a need for clear evidence that the benefits of a treatment outweigh its risks, evaluating comparative effectiveness, and implementing treatment strategies for subpopulations. Accordingly, there was consensus that a much more efficient, high-volume system is needed to generate reliable evidence at lower cost and encourage investment in new developments as well as treatment alternatives.

Data from clinical registries and patient experiences is one option to generate meaningful evidence. Although traditional randomized controlled trials (RCTs) are the gold standard for marketing and labeling approval, real-world evidence (RWE) generated from data collected during routine care and in other settings, coupled with methods spanning cluster randomization, individual randomization, and observational analysis, can supplement RCT findings in important ways.⁵ Such evidence can be used to support expanded indications for use; understand therapeutic effects on populations (including pediatric populations) who are underrepresented or absent from traditional RCTs; to establish long-term safety and effects of therapies beyond usual trial follow-up; and in selected cases, to less expensively generate large sample sizes for pre-registration trials when traditional methods have already collected data on thousands of patients exposed to a new product.

Novel study designs, including Bayesian, adaptive, and seamless clinical trial designs; *a priori* responder analyses; endpoint relationship modeling; and disease subtype information synthesis can also improve overall study efficiency and accelerate the matching of treatments to specific populations.^{6,7} FDA encourages a flexible approach to trial design, prioritizing efficiency while also considering disease severity and rarity and degree of unmet need.⁸

However, research in chronic diseases lags oncology and rare-disease specialties in applying novel methods.

A harmonized legal schema (encompassing statutory, regulatory, and subregulatory authority) will allow patient data to be used for multiple purposes without imposing excessive burdens on researchers while also facilitating patients' control over their data. Although use of data from clinical registries may be limited due to current regulations, a re-evaluation of such use provides value for regulatory decision-making and is a point for further discussion with other collaborators, including the FDA. Additionally, professional societies⁹ and government entities should work together to ensure that EHR companies include appropriate, useable, and interoperable data fields to support evidence generation. As such companies' primary customers, large health systems should collaborate on requiring these qualities from their vendors.

In addition, implementing a learning health system that supports RWE and existing data sources to guide regulatory decision-making and practice guidelines is essential to improving outcomes. This would create an ecosystem that provides sustainability for registries by embedding registries into the fabric of care documentation.

Patient-Centered Approaches

Patient perspectives should be incorporated when creating clinical practice guidelines. This should include development of shared decision-making tools and steps to foster engagement with regulatory processes so that patient perspectives can be thoughtfully integrated. Ultimately, this would result in a two-way model of engagement in which the FDA serves as a convener. The 21st Century Cures Act,¹⁰ which instructs the FDA to work with industry, researchers, and patients to

develop methods and guidance for incorporating patient perspectives in the development process, offers additional impetus.

Incorporating patient-reported outcomes in trial designs will allow novel endpoints beyond traditional “hard” outcomes to be collected. The FDA’s Patient-Focused Drug Development (PFDD) program, an important step in this process, is intended to more systematically obtain patients’ perspectives on a disease and its impact on their daily lives, the types of treatment benefit that matter most to them, and the adequacy of available therapies. The FDA is holding ≥ 20 public meetings over the course of PDUFA V, each focused on a specific disease area, and plans to call for patient groups to scale this effort by taking the methods into their own organizations using approaches developed by the PFDD program.¹¹

Expanding Trial Participation

Recruiting diverse populations in clinical trials, including those with comorbid conditions (such as end-stage renal disease [ESRD] or diabetes) in trials is also a priority. Chronic cardiovascular, pulmonary, endocrine, and renal conditions have common underlying risk factors, including smoking, diabetes, dyslipidemia, and hypertension. Engaging with patients to better understand their concerns, quality-of-life (QOL) issues, needs and preferences regarding the use of technology, and real-world outcomes will yield more meaningful results for millions of Americans.

Professional societies can support FDA by educating the workforce about regulatory science and emphasizing the importance of participating in trials. Evidence demonstrates that the vast majority of patients would participate in trials if asked, but clinicians are not asking. This would also help address the lack of demographic diversity among investigators.

Tobacco Regulation

The FDA deeming rule on tobacco regulation, which extends the agency's authority to regulate products such as electronic cigarettes, hookahs, selective cigars, and pipe tobacco, is strongly supported across therapeutic specialties.¹² Given rapid increases in electronic nicotine delivery systems (ENDS) use among middle-school and high school students, youth access to these products is concerning.¹³⁻¹⁶ Whether ENDS may serve as a harm-reduction strategy for adult smokers is unresolved, but research directly addressing this issue will require substantial time¹⁷ while ENDS, hookah, and little cigar/cigarillo use among adolescents and teenagers continues.¹⁸ From 2012-2014, there were >7,500 distinct flavorings available for e-cigarettes on the Internet, with >200 added every month.¹⁹ The FDA is encouraged to accelerate research efforts funded by the Tobacco User Fees to guide regulation of ENDS.

A related issue is the need to ban mentholated cigarettes. Two FDA advisory councils found that menthol additives make cigarettes less harsh and more palatable, increase the numbers of children and young adults who start smoking, make cigarettes more addictive and quitting more difficult, and have disproportionate effects on youth, African-Americans, and women.²⁰⁻²²

A last point of interest involves 2 WHO-supported strategies for tobacco control that have proven effective in >75 countries: graphic health warnings and plain packaging.^{23,24} A recent RCT emphasizes the effectiveness of graphic warnings in smoking cessation.²⁵ Despite recent legal rulings, FDA is encouraged to redouble efforts to use meaningful graphical information to assist tobacco cessation efforts.

Biomarker Development/Qualification

Biomarkers can identify persons with disease, stratify risk, and direct therapy to the most appropriate patients;²⁶ further, they are critical for developing effective therapies. Although validation of a biomarker as a surrogate is a high bar to clear, surrogates are often used while definitive long-term outcome data are collected. A recent compilation of success factors by FDA concluded that high-quality biomarkers led to a much higher rate of successful drug development. Thus, development of high-quality, validated surrogate biomarkers is a critical priority.

The FDA's Accelerated Approval pathway allows use of unvalidated surrogate endpoints considered reasonably likely to predict a clinical benefit in conjunction with the totality of evidence about a drug or biologic. Identification of markers for patients who are refractory to available therapies should also lead to qualification for expedited review or accelerated approval. However, because the major chronic diseases have established therapies that are partially effective, more traditional pathways are still needed in these contexts.

Well-established surrogate endpoints are often used for traditional approvals: of 94 new drugs approved from 2010-2012, 45% were approved based on either a validated or unproven surrogate endpoint in conjunction with other data.²⁷ Once a surrogate is established to predict clinical benefit, it can be used in traditional approvals and accelerated approval is no longer required (e.g., HbA1c is commonly used for approval of new diabetes therapies).

The FDA's Clinical Outcome Assessment Drug Development Tool Qualification Program and related Biomarkers Qualification Program were designed to facilitate biomarker use in drug development.²⁸ Qualification assures a sponsor that a measure, within a specific context of use, can be used for that purpose. Recent examples in pulmonary disease include the

qualification of several DDTs, such as fibrinogen, which can be used to enroll participants at high risk for moderate/severe chronic obstructive pulmonary disease (COPD) exacerbations and/or death.²⁹ The COPD Biomarker Qualification Consortium organized by the COPD Foundation³⁰ sponsored the fibrinogen qualification, providing an example of the broad medical community collaborating to pool resources in creating tools that will be freely available and advance the field. Additional biomarkers are being explored to address crucial unmet needs: 1) recruitment and stratification for clinical trials for risk and to identify subjects who might benefit from specific treatments, 2) indicators of disease activity (e.g., active inflammation or alveolar destruction) as opposed to disease severity,³¹ and 3) novel outcome measures assessing aspects of disease not well captured with traditional measures such as airflow or health status.

Halting CKD progression to ESRD requiring dialysis or transplantation remains the primary aspiration of the renal community. The development and qualification of biomarkers that could be used as surrogate endpoints³² within an accelerated approval process for anti-CKD progression agents could enable rapid availability of effective therapeutic agents targeting this critical unmet need.

The FDA has created a mechanism that allows promising biomarkers to be evaluated for fitness-for-use in regulatory decision-making.²⁸ The medical community has responded by organizing consortia to acquire and evaluate data required for regulatory review. Progress will depend on adequate resourcing so that novel tools can be evaluated, reviewed, approved, and used in timely fashion. The 21st Century Cures legislation and user fees include substantial support for FDA to contribute its part. The communities for these diseases now need to respond by building consortia and developing needed evidence.

Specific Therapeutic-Area Priorities

Cardiovascular Disease

The cardiovascular community has prioritized other initiatives such as implementing new healthcare delivery systems to provide access to novel therapies and evidence-based practice; reauthorization of user fees to support funding for medical product review, regulatory science, and evidence generation; and creating an innovation-friendly environment with appropriate patient protections (Table 2).

Cardiovascular groups support efforts to lower sodium intake toward a goal of <2300 mg/day. Given controversy regarding optimal sodium intake (especially for patients with cardiovascular disease) and the absence of high-quality RCTs measuring major cardiovascular outcomes,³³ a mortality-based RCT of sodium reduction advice should be a priority. Mandatory sodium limits in prepared and processed foods should also be considered.

Endocrine Health

Recent FDA actions have benefited endocrine health, including a public workshop³⁴ that better identified outcomes that matter to patients. Additional outcomes, such as hypoglycemia, hyperglycemia, time in range, diabetic ketoacidosis, QOL, and patient-reported outcomes, that better reflect glucose control and have beneficial effects on how patients feel, function, and survive should be incorporated into decision-making. Earlier intervention is key to preventing long-term complications of endocrine disorders.

One important example of effective partnership is the recent approval of the first artificial pancreas device system. FDA and JDRF have collaborated on artificial pancreas device systems for over a decade,³⁵ resulting in the development of pathways for early feasibility studies, jointly

sponsored workshops, and a guidance document within the context of sustained engagement,³⁶ which yielded clear, reasonable regulatory expectations that catalyzed industry to engage in device development.³⁷ FDA and other stakeholders must continue to collaborate efficiently on next-generation artificial pancreas systems and ensure patient needs are prioritized.

Multiple biologics have been approved to treat endocrine diseases (e.g., recombinant insulin, erythropoietin, human growth hormone), but cost places these therapies out of reach for many patients. The development of a regulatory framework to implement the Biologics Price Competition and Innovation Act of 2009, as well as guidance on interchangeability and traceability of specific products, were critical steps toward expediting approval of treatment options and improving patient access.³⁸ Despite this, the first nonendocrine biosimilars are only now becoming available, and interchangeability and naming conventions continue to present challenges. Until these issues are resolved, lifesaving or life-changing products may remain inaccessible for many patients.

Simple language on nutrition labels and technologies such as smartphone apps that can help explain this information in the context of dietary guidance is needed. Endocrine patients depend on understandable information to make wise choices in conjunction with guidance from their healthcare teams. Better characterization of the impact of obesity is likewise important: focusing on BMI does not mirror clinical practice, and other measures that reflect outcomes important to patients should be identified. Additional priorities include expanding label indications for metformin; including sex as a biological variable in clinical evaluations; engaging patients in treatment decisions during long-term treatment, and patient education.

Pulmonary Diseases

Pulmonary diseases comprise diverse conditions including restrictive, obstructive, developmental, and vascular disease states affecting millions of Americans, with an overall annual economic impact of >\$100B.³⁹ COPD affects approximately 16 million Americans⁴⁰ and comprises pathogenic conditions including airway inflammation/obstruction, emphysema, and chronic bronchitis. Recent studies suggest that significant clinical COPD symptoms occur in smokers with normal spirometry^{41,42} and that an estimated 35 million current/former US smokers are at risk for COPD;^{43,44} many would not be diagnosed using spirometric criteria only. Available therapies provide modest symptom relief but do not address underlying inflammatory processes, modify or prevent disease progression, address extrapulmonary problems, or restore lost function. Furthermore, there is almost no pipeline of novel COPD therapies. Smoking cessation is essential but not sufficient for reducing COPD progression. The FDA is invited to participate in developing the COPD National Action Plan, which seeks to develop precision medicine for COPD based on differing pathogenesis and clinical heterogeneity.⁴⁵

Although disease pathophysiology differs between pediatric and adult patients,^{46,47} Safety and efficacy data often are not generated for children, which affects treatment recommendations and access to therapy. For example, there are 14 FDA-approved targeted therapies for pulmonary arterial hypertension in adults but none approved for long-term pediatric use. Effective approaches to encouraging and incentivizing pediatric pulmonary drug development are needed.

A third area of concern is the impact of multidrug-resistant tuberculosis and resistant pathogens leading to severe pneumonias and sepsis. The growth of antibiotic resistance is outpacing new antibiotic development, and addressing different resistance mechanisms will require multiple new antibiotics in a wide variety of classes.

Renal Disease

The American Society of Nephrology, the FDA, and >75 member organizations and companies established the Kidney Health Initiative (KHI), a public-private partnership seeking to enhance innovation and patient safety in kidney care.⁴⁸⁻⁵¹ In 2014, Medicare paid \$26.1B to care for 428,000 hemodialysis patients.⁵² However, the current 5-year survival rate for these patients is only 41.5%, significantly worse than most forms of cancer. Hemodialysis currently adds only a fraction of the possible value to overall healthcare, with value defined as outcomes/cost.

Accordingly, the construct of care within hemodialysis units (HDUs) presents opportunities to perform high-quality studies that could improve hemodialysis value. The HDU may be an ideal setting for pragmatic trials focused on process-of-care issues, such as those related to potassium flux, fluid removal, anticoagulation, and sudden cardiac death. Important advantages of the HDU for such an approach include: 1) thrice weekly patient availability, 2) low dropout rate, 3) ease of drawing blood samples during hemodialysis, 4) data collection that is reasonably uniform across dialysis providers, and 5) the ability to perform cluster randomization at the level of the HDU itself, which may or may not require formal written informed consent.

This approach is illustrated by the Time to reduce Mortality in End-stage renal disease (TiME) trial. TiME used cluster randomization at the HDU level to evaluate whether increasing hemodialysis duration from 4-4.25 hours could show benefit for mortality, hospitalization, and health-related QOL. This information is routinely collected in HDUs, thus substantially reducing research costs.^{49,53}

Morbidity and mortality is primarily driven by causes indirectly triggered by renal disease, particularly cardiovascular disease.⁵² Despite this, 57% of cardiovascular outcome studies excluded patients with CKD.^{54,55} Efforts by the community and patient groups to

highlight this disconnect, combined with recommendations from federal agencies on the need to include CKD/ESRD patients in trials (similar to those governing inclusion of women, children, and minorities) could change prevailing mindsets on this issue.⁵⁶ In some cases, joint enrollment in cardiovascular outcomes trials is reasonable, while in other cases, specific trials in this growing population of CKD patients at risk of poor cardiovascular outcomes will be necessary.

“Dialysis keeps you alive but does not allow you to live.” The renal community, particularly our patients, believes this to be a true characterization of dialysis, which has remained essentially unchanged for 2 decades. KHI and the FDA submitted a commitment statement to the White House Organ Summit on Organ Transplantation⁵⁷ in June 2016 to “initiate the development of a roadmap that will describe scientific, technical, and regulatory milestones needed to achieve the goal of creating a bio-artificial or bioengineered alternative to dialysis as renal replacement therapy.” This roadmap engages all stakeholders to incentivize innovation and financial investment in this neglected area.⁵⁸

Although the nutrition facts label announced by FDA in May 2016 includes information on potassium and calcium, further attention should be paid to phosphorous. High phosphorous levels are linked to mortality in hemodialysis patients,⁵⁹ that now appears to extend to persons with normal kidney function.⁶⁰ A problematic issue is high levels of phosphorous resulting from use as an additive in processed food.⁶¹ Because processed foods are typically cheaper, and many patients with CKD/ESRD are economically disadvantaged, including phosphorous on food labels could provide particular benefit for such patients, as well as for the general population.

Involving renal patients throughout the product development lifecycle, from identification of patient-centric issues, to patient-reported outcomes, to postmarketing input, is

critically important. For example, the ability to travel while on hemodialysis often scores at the top of a list of important issues for patients, while ranking near the bottom on physician lists.⁶²

Although initiatives such as the KHI's Patient Preference Workshop on Renal Devices⁵⁸ and the FDA's PFDD Program¹¹ represent important steps, more should be done to ensure that patient-centered development becomes standard. Patients are members of the governance structure for KHI, and a Patient and Family Partnership Council provides necessary feedback, training, and mentorship to patients interested in supporting this area of focus.

FDA Role

The FDA supports an increasing emphasis on new approaches spanning organ systems and characterized by cross-center collaboration and communication. The agency has long been concerned about the relative lack of investment in therapeutic development in chronic diseases.³ Adapting to a new information ecosystem that includes electronic health records, claims data, quality registries, and wearable devices presents critical issues in terms of ensuring evidence generation at costs that encourage investment in innovation. FDA can also play a role in stimulating new therapies through novel initiatives, such as biomarker qualification, use of novel or patient reportend endpoints, or expedited pathways for approval.⁶³ With regard to tobacco, the FDA has made great progress in finalizing the deeming rule; however, much remains to be done. Finally, patient engagement is a high priority, as highlighted by the Center for Devices and Radiologic Health designating this as a strategic focus in 2016.⁶⁴ These discussions underscore the importance of including all stakeholders in efforts to strengthen science and advance new therapies.

Conclusions

Although the groups represented in this meeting focused on specific disease areas, the concept of a “multimorbidity continuum” emerged. Risk factors such as smoking, lack of exercise, obesity/diabetes, dyslipidemia, hypertension, and environmental toxins produce disease manifestations in 4 different organ systems. Rather than considering each area in isolation, there is value in identifying shared themes across noncommunicable diseases. Such an approach mirrors evolving thinking about global health, in which noncommunicable diseases are outstripping infectious diseases as causes of death and disability. In addition, there is consensus about the desirability of increased participation of patients with chronic diseases in clinical trials, inclusion of patients in therapeutic development, and collaborative efforts for evidence generation. An engaged ecosystem comprising academia, industry, patients and caregivers, providers, and government agencies is critical to progress in research, therapeutic advancement, and clinical practice.

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References

1. Centers for Disease Control and Prevention. National Center for Health Statistics. FastStats. Leading causes of death. <https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm>. Accessed October 9, 2017.
2. Fordyce C, Roe M, Ahmad T, et al. Cardiovascular drug development: is it dead or just hibernating? *J Am Coll Cardiol*. 2015;65(15):1567-1582.
3. Fiuzat M, Stockbridge N, Califf R. Resourcing drug development commensurate with its public health importance: The road ahead. *JACC: Basic to Translational Science*. 2016;1:309-12.
4. Thomas D, Wessel C. Emerging therapeutic company investment and deal trends. BIO Industry Analysis. Available at: <https://www.bio.org/sites/default/files/BIO%20Emerging%20Therapeutic%20Company%20Report%202007-2016.pdf>. Accessed January 22, 2018.
5. Sherman RE, Anderson S, Dal Pan G, et al. Real-World Evidence - What is it and what can it tell us? *N Engl J Med*. 2016; 375(23):2293-2297.
6. Berry DA. Emerging innovations in clinical trial design. *Clin Pharmacol Ther*. 2016;99(1):82-91.
7. Berry DA. Bayesian clinical trials. *Nat Rev Drug Discov*. 2006;5(1):27-36.
8. Sherman RE, Davies KM, Robb MA, Hunter NL, Califf RM. Accelerating development of scientific evidence for medical products within the existing US regulatory framework. *Nat Rev Drug Discov*. 2017;16(5):297-298.
9. Hicks K, Tchong J, Bozkurt B, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Am Coll Cardiol*. 2015;66(4):403-469.

10. H.R. 6. 21st Century Cures Act. US Congress. <https://www.congress.gov/bill/114th-congress/house-bill/6>. Accessed October 9, 2017.
11. US Food and Drug Administration. Center for Drug Evaluation and Research. Prescription Drug User Fee Act (PDUFA) - Public meeting on patients who have received an organ transplant. <https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm495933.htm>. Accessed October 9, 2017.
12. U.S. Food and Drug Administration. Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products. *Fed Regist.* 2016;81:28973-9106.
13. Singh T, Arrazola RA, Corey CG, et al. Tobacco use among middle and high school students--United States, 2011-2015. *MMWR Morb Mortal Wkly Rep.* 2016;65(14):361-367.
14. Goriounova NA, Mansvelder HD. Short- and long-term consequences of nicotine exposure during adolescence for prefrontal cortex neuronal network function. *Cold Spring Harb Perspect Med.* 2012;2(12):a012120.
15. Mantey DS, Cooper MR, Clendennen SL, Pasch KE, Perry CL. E-cigarette marketing exposure is associated with e-cigarette use among US youth. *J Adolesc Health.* 2016;58(6):686-690.
16. McCarthy M. E-cigarette companies target youth, US congressional study finds. *BMJ.* 2014;348:g2871.
17. Sharfstein JM. Electronic cigarettes: gateway to understanding the FDA? *Milbank Q.* 2015;93(2):251-254.
18. Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev.* 2016;9:CD010216.

19. Zhu S-H, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tob Control* 2014;23 Suppl 3:iii3-9.
20. Lee YO, Glantz SA. Menthol: putting the pieces together. *Tob Control*. 2011;20 Suppl 2:ii1-7.
21. US Food and Drug Administration. Preliminary scientific evaluation of the possible public health effects of menthol versus nonmenthol cigarettes. 2016.
<http://www.fda.gov/downloads/UCM361598.pdf>. Accessed October 9, 2017.
22. US Food and Drug Administration. Menthol cigarette and public health: Review of the scientific evidence and recommendations.
<http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/tobaccoproductsscificadvisorycommittee/ucm269697.pdf>.
23. Hughes N, Arora M, Grills N. Perceptions and impact of plain packaging of tobacco products in low and middle income countries, middle to upper income countries and low-income settings in high-income countries: a systematic review of the literature. *BMJ Open*. 2016;6(3):e010391.
24. Starr MA, Drake K. Graphic warning labels and the demand for cigarettes. *Tob Control*. 2017;26(2):169-174.
25. Brewer N, Hall M, Noar S, et al. Effect of pictorial cigarette pack warnings on changes in smoking behavior: A randomized clinical trial. *JAMA Intern Med*. 2016;176(7):905-912.
26. FDA-NIH Biomarkers Working Group. Biomarkers, EndpointS, and other Tools (BEST) Resource. 2016. <https://www.ncbi.nlm.nih.gov/books/NBK326791/>. Accessed October 9, 2017.
27. US Food and Drug Administration. 21st-Century Cures: Modernizing Clinical Trials and Incorporating the Patient Perspective. Statement of Janet Woodcock, MD.
<http://docs.house.gov/meetings/IF/IF14/20140711/102451/HMTG-113-IF14-Wstate-WoodcockJ-20140711.pdf>. Accessed October 9, 2017.

28. US Food and Drug Administration. Center for Drug Evaluation and Research. Drug Development Tools (DDT) Qualification Programs. <https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/>. Accessed October 9, 2017.
29. Mannino DM, Tal-Singer R, Lomas DA, et al. Plasma fibrinogen as a biomarker for mortality and hospitalized exacerbations in people with COPD. *Chronic Obstr Pulm Dis*. 2015;2(1):23-34.
30. Casaburi R, Celli B, Crapo J, et al. The COPD Biomarker Qualification Consortium (CBQC). *COPD*. 2013;10(3):367-377.
31. Vestbo J, Rennard S. Chronic obstructive pulmonary disease biomarker(s) for disease activity needed--urgently. *Am J Respir Crit Care Med*. 2010;182(7):863-864.
32. Levey AS, Inker LA, Matsushita K, et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kidney Dis*. 2014;64(6):821-835.
33. Fiuzat M, Mayne S, Stockbridge N, Zuckerman B, Califf R. JACC: Heart Failure Series: FDA in the 21st Century: Focus on nutrition and heart failure prevention. *JACC Heart Fail*. 2017;5(3):229-231.
34. U.S. Food and Drug Administration. News & Events - Public Workshop: Diabetes Outcome Measures Beyond Hemoglobin A1c (HbA1c). <https://www.fda.gov/drugs/newsevents/ucm499281.htm>. Accessed October 9, 2017.
35. JDRF International. JDRF Celebrates FDA Approval of Artificial Pancreas System. Press release. September 28, 2016. <http://www.jdrf.org/press-releases/jdrf-celebrates-fda-approval-of-artificial-pancreas-system/>. Accessed October 9, 2017.
36. US Food and Drug Administration. Center for Devices and Radiological health. The Artificial Pancreas Device System.

<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ArtificialPancreas/default.htm>. Accessed October 9, 2017.

37. Hamburg, MA. Inspiring young voices on type 1 diabetes. FDA Voice. July 11, 2013. <https://blogs.fda.gov/fdavoices/index.php/2013/07/inspiring-young-voices-on-juvenile-diabetes/>. Accessed October 9, 2017.
38. US Food and Drug Administration. Implementation of the Biologics Price Competition and Innovation Act of 2009. <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm>. Accessed October 9, 2017.
39. National Heart, Lung and Blood Institute. Fact Book: Fiscal Year 2012. <https://www.nhlbi.nih.gov/about/documents/factbook/2012>. Accessed October 9, 2017.
40. Wheaton AG, Cunningham TJ, Ford ES, Croft JB; Centers for Disease Control and Prevention (CDC). Employment and activity limitations among adults with chronic obstructive pulmonary disease--United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2015;64(11):289-95.
41. Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and radiologic disease in smokers with normal spirometry. *JAMA Intern Med*. 2015;175(9):1539-1549.
42. Woodruff PG, Barr RG, Bleecker E, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med*. 2016;374(19):1811-1821.
43. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System. Smoking exposures in the United States. 2013. https://www.cdc.gov/brfss/annual_data/annual_2013.html. Accessed October 9, 2017.
44. U.S. Census Bureau. Statistical Abstract of the United States: 2012. Table 7: Resident population by sex and age: 1980 to 2010. <https://www2.census.gov/library/publications/2011/compendia/statab/131ed/tables/pop.pdf>. Accessed October 9, 2017.

45. National Heart, Lung, and Blood Institute. COPD National Action Plan. http://www.nhlbi.nih.gov/health/educational/copd/get-involved/COPD-Action-Plan-Draft-FINAL_508.pdf. Accessed October 9, 2017.
46. Barst RJ, Ertel SI, Beghetti M, Ivy DD. Pulmonary arterial hypertension: a comparison between children and adults. *Eur Respir J*. 2011;37(3):665-677.
47. Bush A, Menzies-Gow A. Phenotypic differences between pediatric and adult asthma. *Proc Am Thorac Soc*. 2009;6(8):712-719.
48. Archdeacon P, Shaffer RN, Winkelmayr WC, Falk RJ, Roy-Chaudhury P. Fostering innovation, advancing patient safety: the Kidney Health Initiative. *Clin J Am Soc Nephrol*. 2013;8(9):1609-1617.
49. Dember LM, Archdeacon P, Krishnan M, et al. Pragmatic trials in maintenance dialysis: Perspectives from the Kidney Health Initiative. *J Am Soc Nephrol*. 2016;27(10):2955-2963.
50. Linde PG, Archdeacon P, Breyer MD, et al. Overcoming barriers in kidney health-Forging a platform for innovation. *J Am Soc Nephrol*. 2016;27(7):1902-1910.
51. Nolin TD, Aronoff GR, Fissell WH, et al. Pharmacokinetic assessment in patients receiving continuous RRT: Perspectives from the Kidney Health Initiative. *Clin J Am Soc Nephrol*. 2015;10(1):159-164.
52. United States Renal Data System. 2016 Annual Data Report. <https://www.usrds.org/adr.aspx>. Accessed October 9, 2017.
53. Kraybill A, Dember LM, Joffe S, et al. Patient and physician views about protocolized dialysis treatment in randomized trials and clinical care. *AJOB Empir Bioeth*. 2016;7(2):106-115.
54. Ishida JH, Johansen KL. Exclusion of patients with kidney disease from cardiovascular trials. *JAMA Intern Med*. 2016;176(1):124-125.

55. Konstantinidis I, Nadkarni GN, Yacoub R, et al. Representation of patients with kidney disease in trials of cardiovascular interventions: An updated systematic review. *JAMA Intern Med.* 2016;176(1):121-124.
56. Rossignol P, Pitt B, Thompson A, Zannad F. Roadmap for cardiovascular prevention trials in chronic kidney disease. *Lancet.* 2016;388(10055):1964-1966.
57. FDA White House Organ Summit Fact Sheet.
https://obamawhitehouse.archives.gov/sites/whitehouse.gov/files/documents/White_House_Organ_Summit_Fact_Sheet_FINALv2.pdf. Accessed October 9, 2017.
58. American Society of Nephrology. Kidney Health Initiative (KHI) - Current Projects.
<https://www.asn-online.org/khi/projects-current.aspx>. Accessed October 9, 2017.
59. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol.* 2004; 15(8):2208-2218.
60. Chang AR, Lazo M, Appel LJ, Gutierrez OM, Grams ME. High dietary phosphorus intake is associated with all-cause mortality: results from NHANES III. *Am J Clin Nutr.* 2014;99(2):320-327.
61. Carrigan A, Klinger A, Choquette SS, et al. Contribution of food additives to sodium and phosphorus content of diets rich in processed foods. *J Ren Nutr.* 2014;24(1):13-19, 9e1.
62. Evangelidis N, Tong A, Manns B, et al. Developing a set of core outcomes for trials in hemodialysis: An international Delphi survey. *Am J Kidney Dis.* 2017;70(4):464-475.
63. Stockbridge N, Miller K, Amur S, Hillebrenner M, Zuckerman B, Fiuzat M, Califf RM. The FDA in the 21st Century: How is the FDA responding to the new world? A focus on cardiovascular drug development. *JACC Heart Fail.* 2017;5(1):67-70.
64. Hillebrenner M, Zuckerman B, Fiuzat M, Stockbridge N, Califf R. The FDA in the 21st Century: How is the FDA responding to the new world? A focus on heart failure devices. *JACC Heart Fail.* 2016;4(12):974-977.

Figure Legend

Figure 1. US venture capital by disease area, 2007-2016. Adapted from: Chart 6. Total venture funding for each major disease area from 2007-2016. Funding is represented as investment toward R&D of novel molecular entities (blue) vs. improvements of approved drugs (red).

Thomas D, Wessel C. Emerging therapeutic company investment and deal trends. BIO Industry Analysis. 2017. Available at:

<https://www.bio.org/sites/default/files/BIO%20Emerging%20Therapeutic%20Company%20Report%202007-2016.pdf>. Accessed January 22, 2018.

Tables

Table 1. Cross-Disciplinary Consensus Themes

Theme	Proposed Steps
Improve cost-efficient evidence generation	<ul style="list-style-type: none"> • Leverage and expand use of existing data resources, including “real-world” data from EHRs and other sources, to guide clinical treatment, guideline development, and regulatory decisions • Foster use of clinical and claims data for multiple purposes and support measures that ensure data interoperability • Sustain and expand quality and disease-area registries • Employ novel/flexible trial designs as appropriate
Foster patient-centered approaches	<ul style="list-style-type: none"> • Incorporate patient perspectives in guidelines development • Create tools to support shared decision-making • Prioritize patient engagement activities, with FDA playing a key role as a convener • Continue building on efforts such as FDA’s PFDD program in order to incorporate PROs as novel endpoints in trial design
Expand trial participation	<ul style="list-style-type: none"> • When appropriate, broaden inclusion criteria to ensure a more diverse, representative trial population, especially regarding patients with relevant comorbid conditions such as ESRD or CKD • Engage with professional societies in fostering greater awareness of “regulatory science” among clinicians and educate them about the importance of proactively offering clinical trials to patients
Continue to strengthen measures against tobacco use	<ul style="list-style-type: none"> • Build on progress in Tobacco Deeming Rule by gathering additional data on health effects of ENDS, flavored tobacco products, and tobacco use among youth • Explore incorporation of WHO-recommended approaches such as graphic warning labels and plain packaging for tobacco products
Prioritize biomarker development & qualification	<ul style="list-style-type: none"> • Continue to leverage FDA’s accelerated approval pathway for the development and approval of biomarkers • Provide support and resources through existing research consortia to apply advanced biological, computational, and statistical methods in identifying biomarkers that can be integrated into the regulatory framework

CKD=chronic kidney disease; EHR=electronic health record; ENDS=electronic nicotine delivery systems;

ESRD=end-stage renal disease; FDA=US Food and Drug Administration; PFDD=Patient-Focused Drug

Development; PRO=patient-reported outcome; WHO=World Health Organization

Table 2. Specific Priorities by Therapeutic Area

Therapeutic Area	Key Priorities
Cardiovascular	<ul style="list-style-type: none"> • Continued progress enabled by tobacco deeming rule • Inclusion of UDIs for cardiovascular devices in billing records to facilitate safety surveillance and quality registries • Reauthorization of user fees to support medical product review, regulatory science, and evidence generation • Focus on nutrition, especially elimination of trans fats and reduction of sodium intake toward a goal of <2300 mg/day
Endocrine	<ul style="list-style-type: none"> • Adoption of outcomes including hypoglycemia, hyperglycemia, time in range, diabetic ketoacidosis, QOL, and patient-reported outcomes • Fostering partnerships among FDA and other stakeholders to further develop outcome measures important to patients • Continued development of artificial pancreas systems in partnership with FDA • Further progress in developing efficient programs for development and approval of biologic/biosimilar products • Improved labeling/guidance for nutrition/diet • Better characterization of the impact of obesity on endocrine health • Expanded labeled indications for metformin • Inclusion of sex as biological variable in clinical evaluations • Engaging patients in treatment decisions and expanding patient education
Pulmonary	<ul style="list-style-type: none"> • Prioritization of novel drug development for COPD, including precision medicine approaches as described in the COPD National Action Plan • Focus on incentives for generating safety and efficacy data for children to support expanded pediatric drug development • Develop new antibiotics and antibiotic classes to counter growth of resistant pathogens
Renal	<ul style="list-style-type: none"> • Engaging hemodialysis units as hubs for pragmatic clinical research • Including patients with CKD/ESRD in cardiovascular clinical trials, where appropriate and feasible • Development of bioartificial alternatives to dialysis • Inclusion of phosphorus information on nutrition facts labeling

- Engagement with patients to solicit feedback and perspectives throughout the medical products lifecycle

CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; ESRD=end-stage renal disease;
FDA=US Food and Drug Administration; UDI=unique device identifier

Fig. 1

US Venture Capital by Disease Area, 2007-2016

