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Volume 3 • Number 4

Introduction: 2023 RAPS Convergence

Renée Matthews

Welcome to the December issue of RF Quarterly, featuring selected presentations from RAPS 2023 Convergence and including articles on pediatric drug development, the FDA's proposed ACNU rule, clinical evidence from a notary body perspective, submission content considerations for combination products, and attributes for successful regulatory leadership.

Among the themes emerging from discussions during this year's Convergence was that change and greater collaboration will become increasingly important definers of the regulatory profession, especially with the rapid advances in artificial intelligence and machine learning and other new technologies. Within that context, we hope these selected articles will serve as useful guidance and resources for global regulatory professionals. As always, we thank the authors for their generosity in sharing their real-world knowledge and expertise with the RAPS community.

Drug development

Pediatric drug development is complex and requires multifaceted strategic considerations to achieve success. In **Pediatric drug development: Essential insights for success** (p. 4). **Kimberly Belsky, Karl-Heinz Huemer,** and **Linda McBride** examine the key factors in establishing a global pediatric drug development strategy. They address the changes in regulatory requirements and clinical study design and highlight the importance of monitoring and responding quickly to change. Early engagement with health authorities is a strategic imperative to ensure alignment on selecting study end point(s), the age ranges for the study groups, and the formulation needs of pediatric patients, while also achieving the company goals. Failure to do so can lead to delays in clinical study conduct, compliance issues, and missed opportunities for new and enhanced pediatric treatment options.

Significant portions of the US population are undertreated or not treated at all for their medical conditions despite the availability of branded and generic drugs and having medical insurance. In **Facilitating self-directed care: The FDA's proposed ACNU rule** (p. 12), **Paul Wardle, Alfred Whitehead,** and **Erin Oliver** discuss a novel regulatory pathway proposed by the US Food and Drug Administration (FDA) for expanding the types of drug product available directly to patients without a prescription. The pathway would establish a nonprescription drug with an additional condition for nonprescription use (ACNU), which would increase options for those submitting new drug applications (NDAs) to increase patient self-directed access to medications and improve public health. At the time of publication, this novel proposed rule is intended to be finalized in April 2024.

Notified bodies, and drug-device combinations

In **Clinical evidence under the EU MDR: A notified body perspective** (p. 24) **Matthias Fink, Tonia Jeiter, Richard Holborow,** and **Christoph Ziskoven** examine clinical evaluation under the new regulation based on their respective experience working at notified bodies. New guidance on clinical evaluation is anticipated, with an update of MEDDEV 2.7/1, rev. 4, and a definition of orphan devices that will include clarification on their use in the EU. In addition, the expanding use of real-world data and evidence is expected to gain traction in confirming the safety and performance of medical devices, especially during postmarket clinical follow-up. The authors emphasize the importance of continuous exchange between industry and notified bodies outside of the normal conformity assessment process and a steady need to understand the notified bodies' interpretation of topics related to clinical evidence and the clinical evaluation process.

Drug-device combination products can play a critical role in enhancing the therapeutic benefit of drugs, ensuring patient convenience, and reducing costs to the healthcare system, write **Chin-Wei Soo** and **Niedre Heckman** in **Drug-device combination products: Device regulatory submission content and considerations** (p. 33). However, the electronic common technical document (eCTD) is a traditionally drug-and-biologic–oriented structure, not geared to medical devices. In the US regulatory framework, where a single application can be used for both the drug/biologic and the device for a combination product, the FDA has provided a basic structure for the inclusion of device- and combination product–specific information in the eCTD. However, the EU and most other countries and regions require two applications – one for the drug or biologic and one for the device. Soo and Heckman address that requirement by providing practical guidelines for the inclusion of medical devices in the eCTD for European submissions. They also address regulatory considerations associated with notified body opinion in accordance with the EU Medical Devices Regulation (EU MDR) .

Building strong leadership

In **Seven attributes for success as a regulatory leader** (p. 41), **Monika McDole-Russell** examines seven aspects of leadership that could help regulatory leaders succeed as both people leaders and business partners. The attributes are leadership style, the ability to be both a people leader and business partner, having an executive presence, understanding corporate politics, having a passion-driven vision, and being a lifelong learner – all of which are distinct from soft skills such as communication, emotional intelligence, and collaborating. McDole-Russell contextualizes each attribute within the workplace setting and draws on her own leadership experience in detailing how each attribute contributes to effective leadership.

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Upcoming in RF Quarterly during 2024

- Quality in the regulatory setting (March)
- Global clinical trial design (June)
- Artificial intelligence (September)
- 2024 RAPS Convergence (December)

Previous issues

- Leadership in regulatory affairs (September 2023)
- Global health agencies and regulatory practice (June 2023)
- Patient-focused regulatory practice (March 2023)
- Artificial intelligence (December 2022)

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From X-Rays to AI

Navigating US Regulations in Radiological Health

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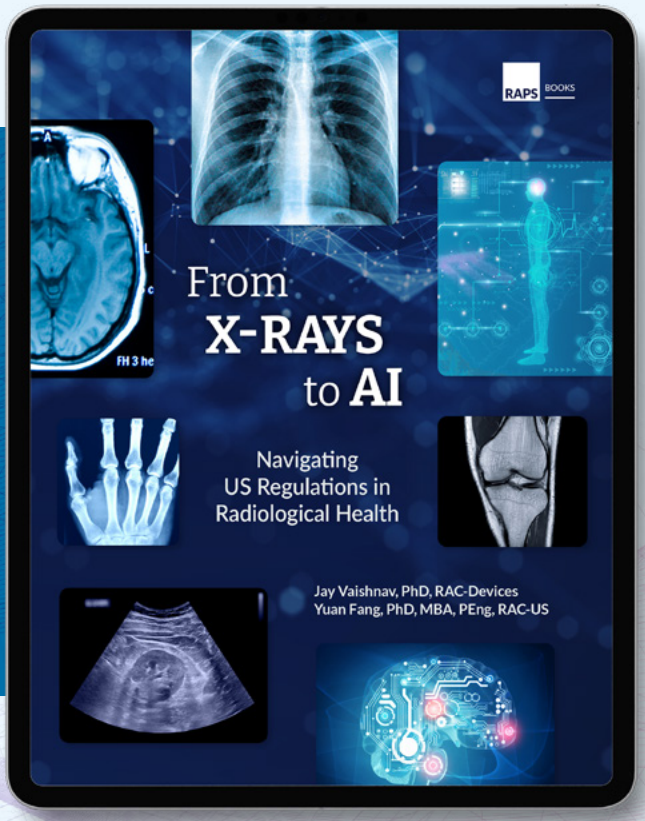

Given the lifelong use and impact of radiological health devices, it has never been more vital to stay up to date with US Food and Drug Administration regulations with ***From X-Rays to AI: Navigating US Regulations in Radiological Health.*** Boasting 18 well-regarded author-experts offering cutting-edge information and sound advice over a breezy eight chapters, this one-of-a-kind book removes the mystery behind the FDA's approach to regulating radiological health devices. Readers will discover the history behind radiological health regulations and learn how radiation products enter the US market.

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RF Quarterly

Volume 3 • Number 4

Pediatric drug development: Essential insights for success

Kimberly Belsky, MS, FRAPS

Karl-Heinz Huemer, MD, PhD

Linda McBride, RPh, RAC

This article describes some of the key considerations in establishing a global pediatric drug development strategy, including changes in regulatory requirements and clinical study design, and includes case studies and examples.

Keywords – pediatric drug development, strategy, precedent, study design

Introduction

Pediatric drug development in the US and EU is subject to the continual evolution in local, regional, and global regulatory requirements and guidelines. While these changes may take time to implement, it is paramount that regulatory professionals routinely monitor regulatory changes and shifts in precedent to ensure the development of robust strategies that include risk and mitigation plans for pediatric drug development. Failure to do so can lead to delays in clinical study conduct, compliance issues, and missed opportunities for new and enhanced pediatric treatment options.

Monitoring changes in the regulatory environment

Regulations and guidance

There were several important proposed changes in the EU and US regulatory environments during 2023, each of which could affect pediatric drug development programs and warrants monitoring for finalization and implementation of specific regulations.

In April 2023, the European Commission published a proposal to reshape the regulation of the EU pharmaceutical sector[1] by addressing inequities around new medicines, including their availability to patients, drug pricing, transparency related to public funding of drug development, environmental sustainability, drug shortages, and global competitiveness.[2] The proposal amends and replaces the existing EU directive and regulation and the regulation of pediatric and orphan drugs and includes recommendations for:

- Revision of data protection periods, exclusivity, and incentives;
- The introduction of a new pediatric investigation plan that will evolve and become more defined as more evidence becomes available; and
- Simplifying the EMA's delegate structures by discontinuing the orphan, pediatric, and advanced therapy medicinal products committees and retaining just two scientific committees – the Committee for Medicinal Products for Human Use, for approving human medicines, and the Pharmacovigilance Risk Assessment Committee, for assessing human safety data.

In May 2023, the FDA issued two important draft guidance documents addressing the regulatory[3] and scientific[4] considerations in pediatric drug development. The documents are intended to clarify the agency's approach to requirements and incentives related to drug development for this population, though obtaining pediatric exclusivity could become more challenging.

The draft guidance on regulatory considerations[3] describes the process for qualifying for pediatric exclusivity under the Best Pharmaceuticals for Children Act (BPCA),[5] including the intent to limit the scope of studies eligible for pediatric market exclusivity under the BPCA. Historically, the FDA has periodically granted pediatric market exclusivity to sponsors conducting studies already required under the Pediatric Research Equity Act (PREA),[6] even if no new indications were expected in a pediatric population. The guidance notes that written requests from the agency would be reserved only for sponsors who need to conduct additional studies beyond PREA requirements to demonstrate a drug's health benefits in the pediatric population.[3] Thus, under the final document, the FDA will likely not issue written requests for drugs for studies or planned studies required under the PREA.

The draft guidance on scientific considerations[4] clarifies the clinical, scientific, and ethical issues related to the development of pediatric drugs and biologics under the BPCA and PREA, specifically regarding formulation development, clinical and nonclinical information, safety information, and the conditions under which sponsors may extrapolate pediatric data from studies of drugs intended for adult use.

End points and data acceptability

The EMA and FDA share many similarities in their evaluation processes, but there can be instances in which they may not accept the same end points and outcomes. This divergence can occur because of differences between EU and US regulatory priorities, patient populations, and healthcare systems. For example, the EMA might be more open to accepting certain clinical end points or surrogate markers as valid indicators of a drug's efficacy, especially in cases in which there is a significant unmet medical need or the benefits outweigh the risks for the European patient population.

One such example was the June 2021 expanded indication authorization in the EU for Aubagio (teriflunomide)[7] as a first-line treatment for relapsing-remitting multiple sclerosis (RRMS) in patients aged 10 to 17 years. The EU approval came after the FDA had issued the company a complete response letter[8] for the same patient population. The FDA deemed the submitted data were not sufficient for obtaining approval of an indication in the pediatric population, and the Aubagio label[9] was updated in 2021 to include safety data from the pediatric clinical study program. Specifically, Subsection 5.11 of the label's Warnings and Precautions section was revised to include a warning for pancreatitis in pediatric patients, and Subsection 8.4 of the Use in Specific Populations section was revised to reflect that the drug's safety and effectiveness had not been demonstrated in the clinical study evaluating pediatric patients with RRMS.[10]

> *Sponsors might consider using the EMA-FDA parallel scientific advice program to ensure potential strategies align with the preferences of the two agencies.*

Such differences between the EU and US underscore the importance of carefully navigating the regulatory requirements and understanding the regulatory flexibility of the respective authorities to ensure successful drug approval in both places. Sponsors should engage with all relevant agencies early in the drug development phase to proactively identify and address potential problems. They might consider using the EMA-FDA parallel scientific advice program to ensure potential strategies align with the preferences of the two agencies. In general, staying informed and adapting to regulatory

changes is integral to any pediatric drug development program.

Rare diseases with simultaneous approval in adults

A company can request the FDA assign a pediatric drug any of the following designations, which could facilitate its development and have a positive impact on final product approval:

- **Orphan drug,** introduced in the Orphan Drug Act of 1983;[11]
- **Fast track,** introduced in the Food and Drug Administration Modernization Act;[12]
- **Regenerative medicine advanced therapy (RMAT),** introduced in the 21st Century Cures Act;[13] and
- **Rare pediatric disease (RPD),** introduced in the Food and Drug Administration Safety and Innovation Act.[14]

As of November 2023, the FDA has approved several products for rare diseases with indications for both pediatric and adult patients. The following approvals are examples of how FDA designations had a positive effect, facilitating the development and path to approval:

- **Vyjuvek (beremagene geperpavec-svdt),** approved on 19 May 2023,[15] was granted designations of orphan drug, fast track, RMAT, and RPD. The biologics license application (BLA) received priority review, and the manufacturer, Krystal Biotech, received a priority review voucher (PRV) upon approval. The approval was the first for a topical gene therapy for treating epidermolysis bullosa in patients six months or older.[16]
- **Skyclarys (omaveloxolone),** approved on 28 February 2023,[17] was granted designations of orphan drug, fast track, and RPD. The new drug application (NDA) received priority review, and the manufacturer, Reata Pharmaceuticals, received a PRV upon approval. The approval was the first for treating Friedreich's ataxia in patients aged 16 years or older.[18]
- **Veopoz (pozelimab-bbfg)** was approved on 18 August 2023 for treating CHAPLE disease in patients one year old or older.[19] It was granted designations of orphan drug, fast track, and RPD. The NDA received priority review, and the manufacturer, Regeneron, received a PRV upon approval.
- **Daybue (trofinetide)** was approved on 10 March 2023[20] for treating Rett syndrome in adults and pediatric patients aged two years or older. It was granted designations of orphan drug, fast track, and RPD. The NDA received priority review, and the manufacturer, Acadia Pharmaceuticals, received a PRV upon approval.
- **Joenja (leniolisib)** was approved on 24 March 2023[21] for treating activated phosphoinositide 3-kinase delta syndrome in adults and pediatric patients 12 years or older. It was granted designations of orphan drug and RPD. The NDA received priority review, and the manufacturer, Pharming Technologies, received a PRV upon approval.

Understanding the benefits, criteria, and timing for the various avenues provided by the FDA is critical to the overall drug development program and corporate objectives.

Receiving an RPD designation and the subsequent receipt of a PRV upon approval is a lucrative benefit. The company can use the PRV in future NDA or BLA submissions to facilitate a priority review rather than the standard review, reducing the review from 10 months to six months. A PRV can also be sold to another company – one company recently sold its PRV for $102 million.[22] Understanding the benefits, criteria, and timing for the various avenues provided by the FDA is critical to the overall drug development program and corporate objectives.

Clinical study design

There are numerous challenges in designing a clinical study (or studies) for approving a drug in the pediatric population, especially for products that have already been approved. A hypothetical example would be an investigational product with a potential topical analgesic effect (based on its mechanism of action). In this example, the following considerations would need to be addressed:

- **The effects of administration route and duration of treatment.** A locally or topically treated indication will likely require short-term treatment (e.g., for simple surgical procedures or local infections). Long-term conditions would more likely require a systemic treatment. These short- and long-term considerations should have a role in defining and justifying an appropriate patient population for inclusion in the study, bearing in mind that the planned label should always address whether the new therapy will meet an unmet therapeutic need in this target population. When developing drugs for children, it is important to strike a balance between limiting development to an older population and expanding the scope of the study to include all ages, despite the challenges of doing so. Early discussion with the regulatory agency about approaches to age inclusivity is recommended.
- **Appropriate outcome measures in different age ranges.** In the current example, the study design for a locally acting analgesic in children poses specific problems, such as which end points would be appropriate if younger children were included in the patient population. Established adult outcome measures, such as the visual analog or Likert scales, are not applicable in the pediatric setting. Instead, an innovative approach would be required, such as involving healthcare providers in reporting pediatric patient outcomes by, for example, noting their patients' behavioral or even autonomic reactions to pain.
- **Disease progression patterns.** For recurrent and multiple lesions (e.g., in epidermolysis bullosa), it would be important to ensure that patients' current standard-of-care and other adjunctive treatments, such as antiseptics or those for wound healing, are not interrupted. This can be addressed by isolating treatment with the study drug/topical analgesic to an established number of predefined target lesions or predefined area(s) of the body that are tracked for comparison with untreated lesions or body areas. One should also consider whether comparative data for other established analgesics might be required in the study. Pediatric-specific problems will also have to be addressed, for example, compliance with often burdensome wound management or nonspecific reporting of disease symptoms.

> *When developing drugs for children, it is important balance limiting development to an older population and expanding the scope of the study to include all ages.*

In conclusion, pediatric studies will require some specific considerations in addition to the aspects that usually have to be taken into account for adult-only trials.

Age-appropriate formulations

Another important aspect of pediatric drug development is the establishment of age-appropriate formulations for the age ranges in which the product will be used. Both US and EU regulations specify that this can be imposed.[3,23]

It is important to start such considerations early. This would include a critical review of all excipients planned for use in the pediatric formulations to assess their possible risks if included. Only essential excipients should be included and, where warranted, replaced with those

that have better-established safety profiles in children. These products could include dyes, sweeteners, stabilizers, parabens, alcohol, and flavorings. Requirements for excipients in pediatric drug development are much stricter than in other regulated industries, for example, those in prepared foods. It should be noted that considerations around excipients in the pediatric setting may also be relevant to adult formulations of the same drug and that a formulation appropriate for children might also be preferable for adults.

Tablet size should be age appropriate so that younger children can easily and safely swallow the tablet and to ensure accurate dosing. Other formulation options – such as microtablets, granules, or liquids – that will ensure ease and safety of swallowing and accurate dosing may also need to be considered. Acceptability of the formulation will require supporting data in the target population, mainly as a secondary objective in the clinical study. There may be a need for more than one additional formulation. This could include having smaller tablet sizes or strengths for more accurate dosing and/or to allow easier swallowing in smaller children or microgranules for sprinkling on food or adding to liquid formulations for infants. The microgranular formulation would also need proof of appropriate bioavailability.

Conclusion

Pediatric drug development is complex and requires multifaceted strategic considerations to achieve success. Early engagement with health authorities is a strategic imperative and requires internal collaboration to ensure alignment on selecting the end point(s), the age ranges for the study groups, and the formulation needs of pediatric patients while also achieving the company goals. This strategy encompasses an understanding of the current and evolving global regulatory requirements and incentives and an assessment of current precedent to ensure success.

Abbreviations

BLA, biologics license application; **BPCA,** Best Pharmaceuticals for Children Act; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration [US]; **NDA,** new drug application; **PREA,** Pediatric Research Equity Act; **PRV,** priority review voucher; **RMAT,** regenerative medicine advanced therapy; **RPD,** rare pediatric disease.

About the authors

Kimberly (Kim) Belsky, MS, FRAPS, is an experienced regulatory professional skilled in innovative and strategic thinking as it relates to a range of medical products and functional areas. Her global roles include regulatory policy and intelligence and advertising and promotion. Her passion is the assessment of changes in the regulatory environment to identify opportunities and challenges. Belsky holds a master of science degree in chemistry from State University of New York at Stony Brook and has several scientific publications. She served as chair for the 2022 and 2023 RAPS Convergence meetings and on the RAPS board of directors during 2021-2023. She can be reached at belskyk@yahoo.com

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The Medical Device Validation Handbook

Third Edition

EDITOR
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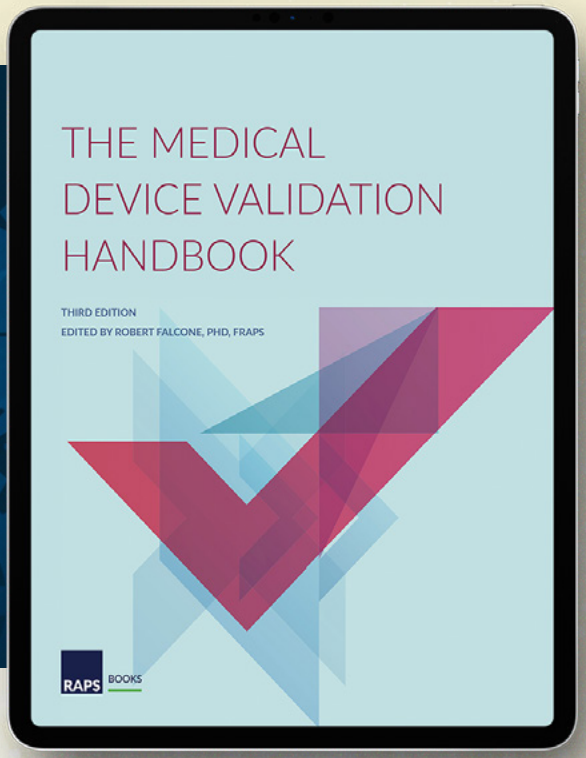

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Facilitating self-directed care: The FDA's proposed ACNU rule

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This article discusses a novel regulatory pathway proposed by the US Food and Drug Administration (FDA) intended to improve public health by expanding the types of drug product available directly to patients without a prescription. As proposed, the pathway would establish a nonprescription drug with an additional condition for nonprescription use (ACNU),[1] and increase options for those submitting new drug applications (NDAs) to develop innovative solutions to engage patients in appropriate healthcare treatment. Significant portions of the population remain undertreated or untreated for their medical conditions despite the availability of branded and generic pharmaceutical medicines and higher numbers of people with medical insurance. Individual circumstances such as financial, geographic, physical, psychological and/or behavioral reasons can exacerbate barriers to accessing treatment. A number of these barriers might be addressed with this ACNU pathway.

Keywords – ACNU, nonprescription, patient access, patient engagement, self-directed care, unmet need

Introduction

In 2012, in an effort to address the undertreatment of common diseases and conditions in the US, the FDA began shaping the foundation of a regulatory framework to increase direct patient access to drug products, such as some that are currently prescription-only and treat chronic diseases or conditions.[1] The intent was to enable the direct selection and/or use of these medicines without the intervention of a healthcare professional and thereby address the demands being placed on an overly burdened healthcare system. Given the potential implications of expanded access, the FDA solicited feedback from multiple stakeholders including representatives from the medical establishment, academic institutions, pharmaceutical industry, patient advocacy groups, and the payor community. After a public hearing and multiple workshops, the FDA proposed a rule in June 2022 to establish this new regulatory framework.[1]

The ACNU is a condition that must be fulfilled for a consumer to gain direct access to a drug without the need for a prescription. An ACNU drug may be marketed at the same time as the identical prescription drug product and development may be initiated at any point in the drug product lifecycle, thus increasing access to patients who might not otherwise be able to or might prefer not to visit a healthcare provider.

The proposed rule does not create a new class of drugs or change the expectations

for appropriate treatment. As proposed, an ACNU drug is distinct from other nonprescription drug products. Patients appropriate for direct access without a consultation with a healthcare provider must complete a required condition before gaining or continuing access to the drug product. For example, an ACNU may be implemented to conduct a self-assessment (similar to telehealth via a technology platform) to assist the patient or consumer in determining the appropriate diagnosis and conditions for use before gaining access to the drug product. As another example, the ACNU might be a mechanism to assess diagnostic results before receiving continued product refills.

Because an ACNU may only be approved when nonprescription labeling alone is insufficient for consumers to accurately self-select or use the drug product, behavioral studies must be conducted to justify the necessity of an ACNU. These studies must also demonstrate that consumers exhibit appropriate behavior without the involvement of a healthcare provider. As such, when labeling alone presents challenges for adequate communication of information, technology solutions may resolve these challenges and reduce barriers for consumers.

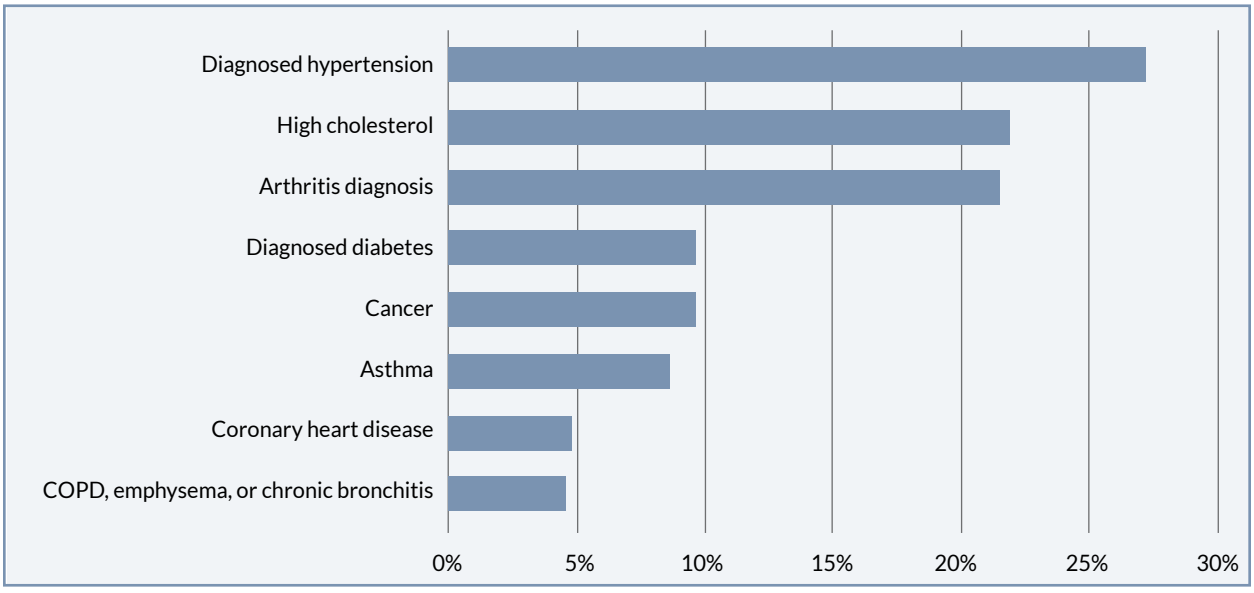
This novel proposal has significant implications for the development of initiatives to increase access among the intended target population for a medication. As of this article's publication, the proposed rule is intended to be finalized in April 2024.

Rationale and public health need

Despite the increased number of people with medical insurance in the US, there are well-documented shortages in healthcare providers.[2,3] In addition, almost three quarters of pharmacists do not think they have sufficient time to safely perform patient care and clinical duties.[4] Given these shortages and the health disparities or inequities across the US, novel strategies are necessary to meet the prevalent unmet healthcare needs.

More than 50% of the US adult noninstitutionalized population lives with at least one chronic disease, and more than one quarter is living with multiple chronic conditions.[5] This burden of multiple chronic health illnesses is highest among women, non-Hispanic white adults, older adults, adults on public health insurance, and adults in rural areas.[5] **Figure 1** summarizes the prevalence among adults of the most common chronic illnesses within the US.[6]

Figure 1. Prevalence of adults diagnosed with certain chronic diseases 2019-2022



Source: Centers for Disease Control and Prevention[6]

Beyond any limited or lack of access to a healthcare provider, many individuals encounter financial and nonfinancial barriers that reduce their access to needed healthcare and medications. These unmet needs result in both poorer health outcomes and reductions in quality of life. For example, heart disease remains the leading cause of death of adults in the US, with an adult dying from cardiovascular disease every 34 seconds.[7] This disease is largely preventable with medicinal agents that have been broadly available for decades.

Notably, uncontrolled hypertension is the largest single contributor to all-cause and cardiovascular mortality,[8] and yet 37.3% of patients had undiagnosed hypertension, and 27.0% of patients with diagnosed hypertension were without a prescribed antihypertensive medication for one day or more.[9] In addition, about half of patients prescribed an antihypertensive drug stop taking it within one year.[10,11] Further, 45.5% of adults older than 21 years who might benefit from statin use are not taking them. For statins, adherence rates are less than 50% just one year after starting therapy, declining to 30% at two years.[12]

More than 60% of survey respondents said they were 'always looking' for new ways to manage their health on their own; a third wished it were easier to access the medication they needed to manage their health.

There is also evidence of undertreatment across many other therapeutic categories, such as menopause, where 50% of women delayed seeking care of their symptoms for more than six months and almost 40% who had no documentation of prescription medication[13] or similarly, known treatment gaps among individuals with asthma, diabetes, mental health care, arthritis, etc.

Individual medical needs and patient perspectives

Patient needs are diverse because of inherent differences in medical history, potential comorbidities, and stage of disease or condition progression. In addition, patient desires and motivations will vary within or across therapeutic categories. As such, potential solutions will likely need to differentiate between individuals who can appropriately self-manage their circumstances and those who may be better served with integrated support from a healthcare provider.

In an online survey[14] conducted among a broad representation of adults with chronic medical conditions, more than 60% of participants reported they were always looking for new ways to manage their health on their own. Each respondent reported having high blood pressure and a range of other personal medical conditions, including anxiety, arthritis, depression, high cholesterol, and obesity. In addition, more than one third said they wished it were easier to access the medication they needed to manage their health. Patient sentiment, barriers to care, motivations, and expressed needs varied along the patient journey. Preferences for method of medication access – from initial diagnosis to drug refills as well as to potential changes in medication – also varied.

Barriers to medication access and adherence include a range of factors, including financial limitations, geographical location, inflexible daily schedules due to work or caregiving commitments, and psychological considerations or motivations. However, some of these barriers may be addressed with nonprescription access. As a proxy for the potential gains of self-directed access, there is an average increase of approximately 30% in therapeutic category use when a first-in-class drug transitions from prescription to nonprescription.[15]

Over the past few decades, US consumers have become adept at searching for healthcare information, and most US adults have engaged in healthcare in new ways. These new ways include use of diagnostic self-tests, such as those that surged during the COVID-19 pandemic; use of digital self-assessment tools; reference to personal test or diagnostics results through digital platforms; or use of telehealth and online ordering.[14] This information indicates that patients are willing and

able to incorporate novel technologies into self-directed healthcare solutions.

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Classes of drugs in the US

There are two classes of drugs in the US. In 1951, the Durham-Humphrey amendment to the Federal Food, Drug, and Cosmetic Act (FDCA) established two regulatory classes of medication: prescription and nonprescription. Essentially, the FDCA mandated that a product should only be prescription if it is not safe for use except under the supervision of a healthcare practitioner because of toxicity, method of use, or other collateral measures necessary for use, such as required monitoring.

In contrast, a drug is nonprescription if it can be used safely and effectively by a consumer without the supervision of a healthcare practitioner. Because there is no practitioner involvement, nonprescription drugs must be labeled with adequate directions for use so that consumers can self-select and use the nonprescription drug products on their own.

Historically, the term *nonprescription* was synonymous with "over the counter" (OTC). However, as efforts are made to apply the nonprescription status to an expanded array of drug products, then the vocabulary may need to be updated to distinguish among the products. It is important to note that the proposed ACNU rule does not create a third class of drug; however, as proposed, it is a type of nonprescription drug distinct from conventional OTCs (**Table 1**).

The role of nonprescription labeling

The content and format of nonprescription drug labeling is specified in the regulations to help inform consumers and assist them in making decisions about a product. As set forth in 21 CFR 201.66,[16] the drug facts label (DFL) provides a highly structured format for the consistent presentation of required labeling. This standard template facilitates navigation to help consumers appropriately self-select and use nonprescription drugs safely and effectively (**Figure 2**, p. 16).

In some instances, supplemental educational information may be needed and the FDA may approve additional labeling, such as a consumer package insert.

For many drugs, the DFL is sufficient. However, for some drugs or certain conditions, the DFL may not adequately communicate all the necessary information, particularly for drugs treating more complex conditions that were previously managed exclusively by a healthcare professional. For example:

- Space limitations may make it difficult to accommodate the necessary information,
- Users may find it difficult to navigate lengthy or complex labels,

Table 1. US drug classification

Prescription	Nonprescription	
	ACNU	OTC
Healthcare provider must write prescription for patient to gain access to drug DFL	Patient determines individual appropriateness for drug use leveraging the DFL and successfully completing a required additional condition to gain access to the drug product	Patient has direct access to the drug, and is able determine individual appropriateness for drug use leveraging just the

ACNU, additional condition for nonprescription use; **DFL,** drug facts label; **OTC,** over the counter.

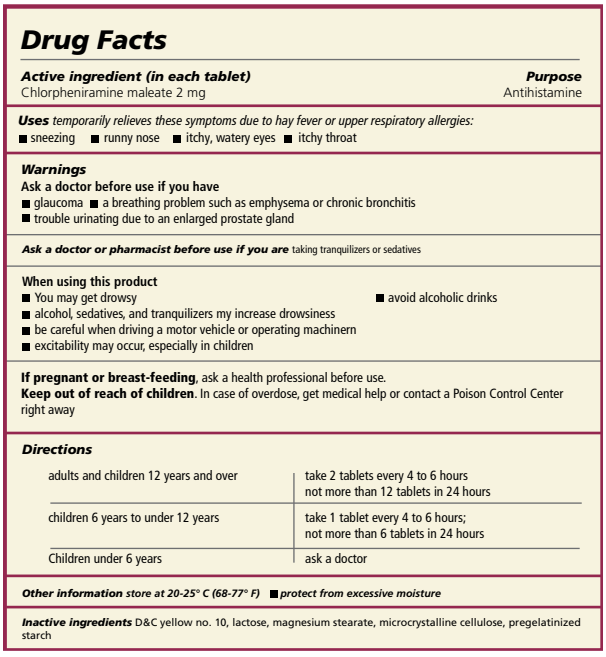
- Users may find it difficult to integrate multiple different pieces of information when deciding on whether to use a product, and/or
- Users may need to complete certain actions or input diagnostic information to determine product eligibility.

In trying to address the limitations of the DFL's ability to adequately guide consumer behavior for more complex medical conditions, the FDA considered two key questions in developing the proposed ACNU rule:

- In what other ways can sponsors deliver information to consumers to ensure appropriate self-selection and appropriate use of nonprescription drug products?
- How can sponsors leverage technology to develop innovative approaches to facilitate consumers' self-care and autonomy over their medical treatment?

The agency considered how to increase options for applicants to develop and market safe and effective non-prescription drug products and how to improve public health by broadening the types of nonprescription drug products available to consumers.

Figure 2. Example of a drug facts label



Drug Facts

Active ingredient (in each tablet) — **Purpose**
Chlorpheniramine maleate 2 mg — Antihistamine

Uses *temporarily relieves these symptoms due to hay fever or upper respiratory allergies:*
■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat

Warnings
Ask a doctor before use if you have
■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis
■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

When using this product
■ You may get drowsy ■ avoid alcoholic drinks
■ alcohol, sedatives, and tranquilizers my increase drowsiness
■ be careful when driving a motor vehicle or operating machinern
■ excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away

Directions

adults and children 12 years and over	take 2 tablets every 4 to 6 hours not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
Children under 6 years	ask a doctor

Other information *store at 20-25° C (68-77° F)* ■ *protect from excessive moisture*

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

Source: Food and Drug Administration[17]

Proposed ACNU pathway for self-directed access

On 28 June 2022, the FDA published a proposed rule for the nonprescription drug product with an additional condition for nonprescription use[1] that is intended to increase options for applicants to develop and market safe and effective nonprescription drugs.

In addition to the general regulatory requirements for nonprescription products currently regulated through the NDA pathway, the proposed rule,[1] if finalized, would establish additional considerations and application requirements for a nonprescription drug product with an ACNU, including:

- **Refuse-to-approve provisions –** the FDA would be able to refuse to approve an application if it fails to meet the applicable requirements.
- **Simultaneous marketing allowance –** a prescription drug and a nonprescription drug with an ACNU that contains the same active ingredient can be marketed simultaneously even if they do not have other meaningful differences, such as different indications or strengths. The prescription and nonprescription drug with an ACNU are two different products because the ACNU would constitute a meaningful difference.
- **Exemption from adequate directions for use –** a nonprescription drug with an ACNU would be exempt from the statutory requirement to be labeled with adequate directions for use.
- **New labeling requirements –** the drug product would comply with all existing applicable labeling requirements and specific new labeling requirements.
- **Other postmarket reports –** the proposed rule includes additional postmarket reporting requirements.

Status of the proposed rule

The FDA opened a public docket to solicit feedback from external stakeholders when the proposed rule was published. Public comments had to be submitted by

6 October 2022. The comments to the proposed rule can be viewed in the docket;[1] however, the FDA cannot approve a nonprescription drug product with an ACNU until the rule is finalized. A target finalization date for the rule has been set for April 2024 and has been included on the spring 2023 unified agenda.[18]

About the ACNU

The proposed rule defines the term *additional condition for nonprescription use* as one or more FDA-approved conditions that an applicant of a nonprescription drug product must implement to ensure consumers' appropriate self-selection or appropriate actual use, or both, of the nonprescription drug product without the supervision of a healthcare practitioner.

An ACNU is not labeling, even though the condition of use may include labeling. Rather, the ACNU involves a further measure to ensure safe and proper product use by the patient or consumer. For example, the ACNU could be a requirement that the consumer take a self-selection test on a mobile app before purchasing a drug product to determine whether the drug is "appropriate" for use by them. The list of questions in a self-selection test is labeling, but the requirement for the consumer to answer them represents the ACNU. Another example of the distinction between labeling and the ACNU would be a requirement for the consumer to watch a video describing how the drug should be used and then respond to a question to confirm before they can purchase the drug that they understand how to use it.

The proposed definition is intentionally broad to give applicants flexibility regarding the types of additional conditions that may be proposed and how they can be implemented. However, an ACNU will be considered only after an applicant has optimized the DFL and other labeling with iterative testing, and the applicant demonstrates that labeling is not sufficient.

When is an ACNU appropriate?

The evidentiary standards for a drug product to demonstrate safety and effectiveness for FDA approval remain unchanged; however, the proposed pathway requires additional data to demonstrate the necessity of the ACNU. That is, an ACNU is appropriate only when the DFL alone is not sufficient to guide appropriate consumer behavior.

Sponsors of nonprescription drugs conduct rigorous testing to design and develop an appropriate label. The DFL must convey the necessary information to support the safe and effective use of the product in a manner that can be understood by a layperson. The three types of studies typically performed using the DFL are label comprehension, self-selection, and actual use. A human factors study may also be necessary if a device is part of the product (**Table 2**). These studies do not measure the effect of the drug on the body; instead, they measure the ability of lay users to meet key safety

Table 2. Typical behavior studies to support the safe, effective use of a nonprescription NDA product

Type of study or testing	Objective
Label comprehension	To assess consumer understanding of major communication objectives
Self-selection	To assess consumer's ability to make appropriate choices as to whether a product is right for them
Human factors	To assess a consumer's interaction with a device and understanding of how to use it
Actual use	To evaluate whether consumers can use a product safely and effectively in a non-prescription setting (naturalistic clinical study)

NDA, new drug approval

and effectiveness objectives. Although the studies are typically conducted in sequence, they are iterative in nature, often requiring multiple rounds of testing to optimize language.

There are no limitations for when an ACNU may be considered within a product lifecycle. As a result, an NDA with an ACNU may extend the drug reach in the intended target audience by permitting self-directed access to a subset of patients who otherwise might not seek prescription treatment. This direct consumer access may help extend the branded lifecycle of the product.

Developing an ACNU solution

A nonprescription drug with an ACNU may be brought to market at any point in the lifecycle for a previously approved prescription drug or directly as a nonprescription product. When weighing whether to pursue the ACNU pathway, it is important to consider numerous issues, both regulatory and nonregulatory. Drugs with ACNUs are not like conventional OTC drugs in that they require additional development steps; may touch on other regulations within and outside of the FDA's purview (e.g., device regulations); and may have a complex relationship with concurrently marketed prescription products. The regulatory affairs professional will need to navigate these issues to achieve a successful approval.

> *The three types of studies typically performed using the DFL are label comprehension, self-selection, and actual use, although a human factors study may also be necessary if a device is part of the product.*

The condition: Addressing the correct problem

The ACNU proposed rule is primarily concerned with imposing a condition that a prospective user of the product must fulfill before, or as part of, its use.[1] The condition allows the user to use the product safely and effectively by addressing challenges in self-selection, actual use, or both. In this context, the challenges are the gap in safe and effective use behavior observed when testing a solution based on the DFL alone.[19] Understanding these barriers and behaviors in detail is the vital first step to resolving the issue for the prospective user.

Prospective users of the drug must be able to correctly decide when and when not to use the product. The potential user must also understand when to consult a doctor (or pharmacist) before using the product and when to stop use and talk to a doctor. In this sense, the selection process is a screening function that allows the appropriate users through and keeps the unintended users out. Users with an "ask a doctor (or pharmacist) before use" situation should be able to determine if this instruction applies. Deselection, or screening out, is as important as selection from a safety standpoint.

Any challenges that prevent users from meeting key safety and effectiveness objectives, whether those challenges stem from the label itself or from perspectives that the consumer carries from experience, are necessarily related to elements mentioned in Table 2: comprehension of the information provided (label comprehension), decision making when applying that information to oneself (self-selection or deselection), and behavior (actual use).

Identification of the potential challenges a prospective user may encounter allows for the development of an effective countermeasure, or condition. Issues with actual use are usually detected in human factors studies or in actual use trials. In either case, the problem is typically a need to train the user on proper procedure or to screen out those users who lack the ability to perform it.

When diagnosing the underlying challenges facing the prospective user, it is important to remember that the population of prospective users is not a monolith. There are often multiple subpopulations within it, each of whom have their own specific challenges. The ACNU condition must be designed to address all these disparate needs.

The condition: Design considerations

Once the challenges facing the prospective users have been understood, a sponsor can proceed to design of the ACNU condition. Sponsors need to determine:

- The supports needed for the challenges faced by prospective users, and
- The mechanism of delivery for these supports.

When determining how to deliver the ACNU support solutions, there is a natural tendency to gravitate toward digital and other technological solutions. Sponsors should take the time to consider solutions that resolve the cognitive or behavioral challenges for the DFL alone but require less technology, as the goal of the proposed rule is to improve access to drugs and the requirement to use technology imposes a soft barrier. In general, the goal of the sponsor should be to minimize the burden on prospective users and to therefore use the most accessible possible solution.

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Nevertheless, digital technologies such as websites provide an effective way to deliver logic that supports decision making to prospective users. These technologies bring together a variety of supports into a cohesive experience that dynamically guides the prospective user through self-selection and/or actual use. Properly constructed websites can be made available on desktop, mobile, and kiosk systems to provide multiple points of access.

Sponsors should consider whether websites are the most appropriate method of providing access, or if alternative methods could apply. Alternative methods include telephone support or support by mail.

When enforcing the mandatory nature of the additional condition, sponsors will often need to work with other stakeholders, such as retailers, to succeed. Although the proposed regulatory rule does not dictate how a particular ACNU may be operationalized in practice, practical implementation measures are also key to effective utilization and commercialization. Involving these stakeholders in the design and execution of the ACNU condition (called "operationalization" in the proposed rule[1]) is an important prerequisite to success.

The development process: Studies and controls

Conceptualizing the solution is an important achievement, but a successful approval requires demonstration of safe and effective use under controlled conditions. Formal validation of the solution is needed, but often the concept can be effectively refined through small, and often informal, formative evaluations with prospective users. Smaller studies with prospective users facing challenges can provide insights that lead to effective and better ACNU solutions.

In terms of formal validation, sponsors should plan to conduct:

- Comprehension studies, demonstrating that prospective users understand the information presented in both labeling and any ACNU system;
- Human factors studies, demonstrating that prospective users can use the ACNU system without significant errors;
- Self-selection studies, in which users supported by the ACNU system can make correct decisions around use and nonuse or to seek professional input without any other external supports; and
- An actual use study, in which users select the product and make use of it in a naturalistic setting.

Sponsors are strongly advised to confer with the FDA on the unique circumstances for each potential program and to keep the FDA informed as to important DFL, ACNU, and study design decisions.

Many ACNU solutions will, by their nature, become medical devices in a drug-led combination drug-device product. The FDA's quality system regulation[20] applies to these ACNU solutions. Sponsors should prepare to comply fully with the requirements for design controls and risk management during the development process.

Regulations beyond the FDA

ACNU conditions would apply to members of the public who are considering purchasing a drug product. This fact means that consumer protection laws and regulations, at both the federal and state levels, may apply to ACNU solutions. Regulatory affairs professionals should consult with legal counsel and the privacy and compliance functions within their firms to ensure that the ACNU solution created meets these legal and regulatory requirements.

Reimbursement, generics, and the business case

Unlike the requirements for traditional OTC products, the proposed rule indicates that nonprescription products approved through the ACNU pathway may be simultaneously marketed with prescription products using the same active ingredient, dose, and indication.[1] In this case, the ACNU applied to the nonprescription product is considered to constitute a clinically meaningful difference sufficient to allow its dual marketing with the prescription version. In cases where the product's period of exclusivity due to FDA approvals and/or patent lifetime has lapsed, there may also be abbreviated new drug application holders marketing generic products. In many ways, the ACNU can be thought of as an alternative *safety system* to the prescriber, potentially reaching new patients unwilling or unable to seek assistance from the prescriber.

Simultaneous marketing may or may not impact the reimbursement of the product by insurers and employee plans depending on the health economic benefits of self-directed access. Sponsors should consider this when evaluating the business case around pursuing an ACNU approval.

Conclusion

This proposed ACNU rule has the potential to increase patient self-directed access to medications and improve public health. The intent is to broaden the types of medication that are available without a prescription, such as those for chronic health conditions. Generating the necessary support from behavioral studies will require careful and diligent patient understanding and be necessary to secure FDA approval. The proposed rule allows for simultaneous marketing with an existing Rx license and can be pursued at any point in the lifecycle of a medication. As such, this novel pathway has the potential to accelerate medication adoption, increase utilization, and extend the product lifecycle. The FDA cannot approve a nonprescription drug product with an ACNU until the rule is finalized.

Abbreviations

ACNU, additional condition for nonprescription use; **DFL,** drug facts label; **FDA,** Food and Drug Administration [US]; **NDA,** new drug application; **OTC,** over the counter.

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Clinical evidence under the EU MDR: A notified body perspective


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This article examines clinical evaluation under the EU MDR from the perspective of clinical experts from three notified bodies. They anticipate new guidance on clinical evaluation, with an update of MEDDEV 2.7/1, rev. 4, and a definition of orphan devices and clarification on their use in the EU. The article provides useful information for manufacturers and highlights published expert scientific opinions aimed at notified bodies. It also discusses the expanding use of real-world data and evidence (RWD and RWE) for confirming the safety and performance of medical devices, especially in postmarket clinical follow-up (PMCF).

Keywords – EU MDR, notified bodies, clinical evaluation, expert panel, real-world evidence

Clinical evaluation in the EU

The EU Medical Devices Regulation (EU MDR), also known as Regulation (EU) 2017/745,[1] has more detailed and specific requirements for evaluating clinical data compared with the EU Active Implantable Medical Devices Directive (EU AIMDD; Directive 90/385/EEC)[2] and the EU Medical Devices Directive (EU MDD; Directive 93/42/EEC),[3] which were repealed under the EU MDR in May 2021.

There are many regulatory projects globally and in the EU that aim to harmonize the interpretation of the clinical evaluation across industry and notified bodies. Within the EU, there are planned updates to existing guidance and projects focused on new guidance to facilitate the implementation of the EU MDR. The most significant change in the EU relates to the update of the 2016 MEDDEV 2.7/1, rev. 4, guidelines for medical devices to align them with the requirements of the EU MDR. The updates are expected to be completed over two stages, with the date of completion currently set for the end of 2024.

The updates during the first stage are expected to clarify some common terms used in the EU MDR but not defined in Article 2 of the regulation, for example, *indirect clinical benefit*. The updates will also provide clarity on conducting clinical evaluations and using data from different types of clinical investigations, such as retrospective studies or the additional clinical studies mentioned in Article 82 of the EU MDR. Notified bodies are currently reviewing a high number of retrospective studies conducted by manufacturers trying to improve their sufficiency of data by analyzing retrospective data sets, such as patient chart reviews, to supplement the data required under the former EU MDD and EU AIMDD.

The second stage of updates to the document will further clarify the clinical

evaluation process and address the changing clinical evaluation landscape. The updates will include new information on sufficient clinical data for orphan devices and define the criteria mentioned in Article 61(10) of the regulation when clinical data are not deemed appropriate to show conformity with the general safety and performance requirements. These efforts should help align manufacturers and notified bodies in their interpretations of this clause.

Notified bodies now also have to assess medical devices that include artificial intelligence (AI) that go beyond machine learning and medical device software containing AI, including next-generation AI. One challenge is establishing sufficient clinical data levels for AI in learning models that will accurately reflect the target patient population and not increase exposure to risks that may not be evidenced within the data model sets. The updates to MEDDEV 2.7/1, rev. 4, are also expected to clarify the clinical evaluation process for devices using AI.

The EU-funded Coordinating Research and Evidence for Medical Devices (CORE-MD)[4] consortium is reviewing the methodologies for the clinical evaluation of high-risk medical devices and suggesting new designs to ensure patient safety and clinical effectiveness of the devices developed in this innovative and rapidly advancing landscape. Participants in the consortium include medical professional societies, notified bodies, academic institutions, manufacturer groups, regulators, and health agencies. The CORE-MD project was launched in April 2021 and will be completed in 2024. In essence, it is looking at the application of regulatory science methods to clinical evaluation of these devices.

The findings of the projects within CORE-MD are expected to raise awareness of the limitations of past methodologies and advise on how the limitations can be improved by establishing best practices in collecting pre- and postmarket evidence. Conclusions from the CORE-MD research are expected to result in significant updates to MEDDEV 2.7/1, rev. 4.

The increased regulatory burden for devices under the EU MDR and the potential low return on investment for manufacturers are usually cited as reasons for removing devices from the market.

The removal of devices for rare diseases from the EU market remains a central concern for the medical community. The increased regulatory burden for devices under the EU MDR and the potential low return on investment for manufacturers are usually cited as the reasons for removing these devices from the market.[5] The European Commission and the Medical Device Coordination Group (MDCG) have recognized these concerns, as outlined in an MDCG position paper on the transition to the EU MDR.[6] The two entities have initiated a task force to examine how best to manage the clinical evaluation of orphan devices, especially with the limited availability of clinical data and reduced opportunities for postmarket data collection because of the low usage of these devices. The task force's efforts have been prioritized, and a final guidance paper is expected to be released in early 2024.

Another development within the EU relates to the qualifying criteria for having a contract between manufacturers when one seeks product equivalency with another's device. Under the EU MDR, if a manufacturer of Class III and implantable devices wants to bypass premarket clinical investigations and instead claim equivalence with another manufacturer's device(s), there should be a valid contract between the two parties to ensure the manufacturer pursuing the equivalence route has ongoing access to the other manufacturer's technical documentation. This requirement has reduced the number of claims of equivalence under the EU MDR for these specific devices. In addition, manufacturers that successfully claimed equivalence under the former directives but could not complete their PMCF activities and gain sufficient data on their device at the time of

EU MDR application may not be able to transition to the EU MDR successfully. That is clearly a concern for regulators and industry regarding the availability of certain devices.

An MDCG draft guidance is currently available for comments and feedback from interested parties. The document addresses whether there is a need for a contract between manufacturers for devices that were certified under the former directives. It challenges requirements in Article 61(5) and whether legacy or well-established technology devices mentioned within Article 61(6) are exempt from a contract when claiming equivalence, given that they do not need to conduct clinical investigations to establish data sufficiency.

The International Organization for Standardization's ISO/AWI 18969[7] is a new standard in development for clinical evaluation that aims to provide a horizontal standard to the clinical evaluation approach. The anticipated standard, due for completion in 2024, will explain the scientific steps required to conduct a robust clinical evaluation of a medical device and is not expected to introduce any additional requirements. The hope is that the horizontal standard will be the basis for developing vertical standards for specific device groups to facilitate a more predictable clinical evaluation for common standard-of-care devices, similar to the EU MDR's common specification requirements.

Published scientific opinion from EC expert panels

The EU MDR has introduced an additional level of scrutiny with the clinical evaluation consultation procedure (CECP) in Article 54 and requirement for expert panels[8] to support and advise on the scientific assessment of medical devices and in vitro diagnostic medical devices. These additional steps are to enhance the transparency of clinical evaluation assessments of high-risk devices by notified bodies.

Only Class III implantable and Class IIb active devices that administer and/or remove medicinal products are applicable for CECP.[9,10] Legacy devices modified to comply with EU MDR requirements are exempted from CECP under Article 54(2)b. In addition, MDCG 2019-3, rev. 1, which provides an interpretation of Article 54(2)b, clarifies that the requirement does not apply to devices being modified outside of strict EU MDR compliance and that Article 54(1) applies to them.[9]

> *Thematic expert panels disagreed with 9 of the 10 most recent notified body assessments, noting concerns related to available clinical evidence, the evaluation methodology, and PMCF strategies and plans.*

The notification for a CECP is triggered after a notified body issues a final positive clinical evaluation assessment. The notification package includes the clinical evaluation assessment report (CEAR) and the manufacturer´s clinical documentation, including the clinical evaluation plan and report and the PMCF plan and report. In compliance with Article 54(3), CECP notification is done through the European Database on Medical Devices, or EUDAMED, to the European Medicines Agency. After a feasibility check of the submitted documentation, the file will be passed on to a screening panel, which will decide within 21 days of receipt of the notification whether a thematic expert panel should give a scientific opinion on the notified body's CEAR, based on three screening criteria[10] – the device's novelty and resulting impact; scientifically valid health concerns; and significantly increased incidents. If any of those criteria apply, a scientific opinion by the expert panel will be issued within 39 days of initial receipt of notification, making the CECP a 60-day process after receipt of the dossier. Scientific opinions will be published on the European Commission website, with anonymized manufacturer and device information.[11] The expert panel will then use the scientific opinion to decide whether to agree or disagree with the outcome of the notified body's clinical evaluation assessment of the device.

As of October 2023, 10 scientific opinions had been issued since 2021 under the CECP.[11,12] Of those 10 opinions, the thematic expert panels agreed with only 1 of the notified body assessments, meaning they disagreed with 9 assessments. The expert panels' key concerns were similar in all negative opinions and related to the clinical evidence available, the evaluation methodology in general, and the PMCF, specifically:

In most opinions, the expert panels disagreed with the notified body's assessment that the clinical data were quantitatively and qualitatively sufficient. They noted that patient numbers, study design, and level of evidence included with the studies were limited and did not substantiate the claimed indications. Furthermore, long-term follow-up data was found to be poor or completely absent.

> *The expert panels found essential aspects of the clinical evaluation methodology lacked systematic soundness, and that literature search methodologies were unsystematic and had inadequate search periods and search terms.*

Essential aspects of the clinical evaluation methodology, which a notified body had approved, were found to lack systematic soundness. The expert panels found that literature search methodologies were unsystematic and had inadequate search periods and search terms. They also found that inconclusive inclusion and exclusion criteria meant that current pivotal scientific publications were not included in the search, and their data were therefore excluded from analysis in the clinical evaluation report. In addition, the expert panels identified that state-of-the-art evaluations did not always reflect the most current state of the art for the device in question.

Lastly, PMCF strategies presented within the PMCF plan and considered appropriate by the notified body were found to lack a comprehensive description of the planned postmarket activities. The PMCF activities were also considered insufficient for meeting the PMCF objectives, including the generation of long-term follow-up data.

Apart from challenging the manufacturer's clinical evaluation and the notified body's assessment, the expert panels also challenged the documentation of the assessment results in the CEAR. In particular, they concluded that:

- The CEARs did not sufficiently focus on the device's novel aspects;
- The stratification of the clinical evidence to the individual indications was insufficient; and
- The methodology for collecting preclinical data with clinical relevance lacked transparency.

The expert panels also identified a lack of robust and plausible justifications for why limited clinical data available for specific claims should be acceptable in conjunction with suitable PMCF activities.[12] In conclusion, having clinical evaluation assessments of high-risk medical devices under the expert supervision of a third party imposes additional challenges for all stakeholders but needs to be seen as a significant asset in the continuous improvement and harmonization of clinical evaluation assessment provided by the notified bodies.

Real-world evidence as PMCF

RWD and RWE have been discussed as potential sources of clinical data for the clinical evaluation. Several countries have undertaken efforts to implement frameworks for gathering and using RWD and RWE for medical devices.[13,14] RWD are not new for medical devices, but they are known as a data source used in regulatory decision making for medicinal products. RWD are data related to a patient's health status or delivery of healthcare and that are collected during routine clinical practice and manifold sources other than traditional clinical trial settings.[15] Device registry data, patient self-reported data, data generated by mobile devices,

and data from medical insurance or hospital medical records could be categorized as RWD. In recent years, sources of clinical data obtained from patients using medical devices have expanded significantly with the evolution and digitalization of medical devices. RWE is the result of the analysis of RWD as part of the clinical evidence needed to comply with the EU MDR clinical evaluation requirements.

The need for quantifying the clinical benefit and safety of medical devices has been described in the MEDDEV 2.7/1, rev. 4, guidance document currently under revision. The emphasis on clinical evidence based on clinical data in the MEDDEV guidance has been carried over into the EU MDR, which also reinforces clinical evaluation to improve health and safety, among other aims. RWE may contribute to inform decisions in medicine, specifically in line with the clinical evaluation requirements of the EU MDR.

RWE is generally considered a complement to traditional clinical evidence and not a replacement of it.[16] In particular, for Class III and implantable devices, it is evident that RWD and RWE alone are not sufficient to fulfill all clinical evaluation–related EU MDR requirements when setting up the clinical development plan for such devices. RWD under the regulatory framework of the EU MDR has been mentioned in the MDCG 2020-6 guidance document[17] for legacy devices previously CE marked under the EU MDD and AIMDD and exhibiting an indirect clinical benefit (i.e., devices that require combined use with another device to achieve the intended purpose, such as guidewires).

RWD fill in data gaps and provide complementary data that can help answer remaining scientific questions related to the inherent limitations of premarket clinical investigations. These limitations could include selection bias or rare side effects that are unquantifiable because of the low number of participants; device interactions; and the evaluation of human factors, including learning curve effects. RWD and RWE may also deliver additional evidence for devices with limited premarket clinical evidence, for example, orphan, pediatric, and breakthrough devices. In summary, as part of the cumulative evidence gained during the pre- and postmarket phases, RWD can be expected to reinforce the robustness of the evaluation of clinical benefit, performance, and safety of the use of the device in question.

> *Any acquisition of clinical data, including RWD, should be methodologically sound and include, but not be limited to, protocol documentation and the identification and control of any risk for bias.*

RWD fitness for purpose must be appraised to evaluate the suitability of the data obtained. In this context, any limitations of the different data sources must be evaluated. Typical measures to control the risk for bias in a study, such as blinding, randomization, or including a control group, are missing in RWD and RWE. Therefore, any acquisition of clinical data, including RWD, should be methodologically sound and include, but not be limited to, protocol documentation and the identification and control of any risk for bias. As a general rule, the manufacturer must be able to justify the contribution of any clinical data used as part of the clinical evidence under the EU MDR in relation to the device's risk and use.

The EU MDR requires an analysis of all relevant clinical data to reach conclusions about safety and clinical performance. For devices that already have market experience in non-European markets, RWD and RWE may exist and be relevant when the initial application is lodged with the notified body. In such cases, the manufacturer may be required to justify not considering these data as part of the clinical evaluation under the EU MDR. For example, the appraisal of the data includes a review of regional factors, such as differences between healthcare systems, that may affect the transferability of the data obtained outside of Europe to the European market.

The use of RWD and RWE is expected to increase, given their greater availability and the potential benefits of using them for the clinical evaluation of medical devices. However, there are technical, ethical, and legal challenges in implementing the collection of RWD for clinical evaluation under the EU MDR, such as those related to the feasibility of data access and availability of hospital data sources. Furthermore, the EU General Data Protection Regulation (EU GDPR), in combination with national laws, limits the use of RWD. An EU GDPR-conforming complete anonymization might render the datasets unusable for confirming the safety and performance of medical devices – for example, age information or the medical history of the patient may be needed to evaluate observed side effects appropriately. As such, notified bodies will require substantiated demonstration of the feasibility and sustainability of planned postmarket data collection as part of their assessment of the PMCF plan for conformity with the EU MDR.

Notified bodies will require substantiated demonstration of the feasibility and sustainability of planned postmarket data collection as part of their assessment of the PMCF plan for conformity with the EU MDR.

In general, patient health data are sensitive and confidential and should be securely stored and protected and available only to users with permission to access them. That means that access to data may be limited, which could significantly limit the availability of RWE. The systematic evaluation of deidentified, but not anonymized, patient data requires adherence to data protection requirements and analysis and application of the relevant recognized ethical principles for medical research. To that end, an example of a standardized broad consent that is compliant with the EU GDPR has been developed to enable the secondary use of such data for regulatory purposes.[18]

The clinical evaluation requirements of the EU MDR include the consideration of suitable sources of postmarket clinical data, specifically mentioning registers as an example of RWD. This is part of the EU MDR's legal requirements, but access to such data for manufacturers and notified bodies is limited by administrative hurdles, access restrictions, and/or insufficient resources for healthcare providers to record clinical experience data systematically during clinical practice. Further efforts involving legislators, authorities, certification organizations, and device manufacturers might facilitate access to RWD in the future.

Additional takeaways

There were numerous takeaways from the question-and-answer session after the presentation, including:

- The European Association of Notified Bodies (Team-NB) has introduced regular meetings between notified bodies to ensure they align on the interpretation of clinical evidence and clinical evaluation as presented in the EU MDR. Speakers involved in these meetings noted the interpretative alignment between the notified bodies had improved through the meeting discussions.
- When conducting a pre- or postmarket clinical investigation, it is important to do a comprehensible sample size calculation that factors in different patient subpopulations and the different indications for a medical device during clinical investigations.
- Manufacturers planning to conduct specific PMCF activities, such as a PMCF study or high-level survey outside of the EU, must consider the transferability of the clinical data to the European population.
- Under the MDCG 2022-14 guidance, notified bodies and manufacturers are encouraged to have a structured dialogue before and during the conformity assessment process to facilitate the efficiency and predictability of the process.[6] The notified bodies are investigating how to set up the necessary internal processes for such dialogue with the manufacturers.

Conclusion

It is important that there is a continuous exchange between various stakeholders and notified bodies outside of the normal conformity assessment process. In the current transition phase from the EU MDD and AIMDD to the EU MDR, there is a steady need to understand the notified bodies' interpretation of topics related to clinical evidence and the clinical evaluation process. With the introduction of the CECP, the legislation introduced another level of scrutiny, specifically on the work of the notified bodies but also of information on the quality and quantity of clinical data through published scientific opinions. RWD and RWE are becoming increasingly relevant for medical devices and could reduce the number of patients and the follow-up time required for specific PMCF activities. Finally, there will be a long-awaited update of the MEDDEV 2.7/1, rev. 4, guidance on clinical evaluation that will also provide some clarification on uncertainties in the interpretation of some requirements of the EU MDR.

Abbreviations

AI, artificial intelligence; **CEAR,** clinical evaluation assessment report; **CECP,** clinical evaluation consultation procedure; **CORE-MD,** Coordinating Research and Evidence for Medical Devices; **EU AIMDD,** EU Active Implantable Medical Devices Directive; **EU GDPR**, EU General Data Protection Regulation; **EU MDD,** EU Medical Devices Directive; **EU MDR,** EU Medical Devices Regulation; **MDCG,** Medical Device Coordination Group; **PMCF,** postmarket clinical follow-up; **RWD,** real-world data; **RWE,** real-world evidence; **Team-NB,** European Association of Notified Bodies.

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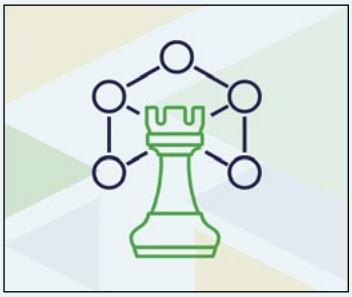

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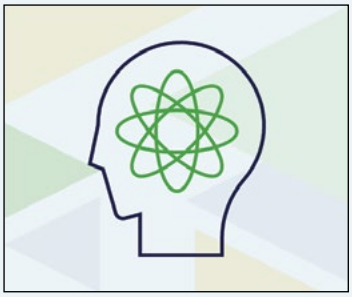

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Drug-device combination products: Device regulatory submission content and considerations

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This article aims to provide practical guidelines for the inclusion of medical devices in the electronic common technical document (eCTD), a traditionally drug-and-biologic-oriented structure. The article outlines an approach to describe information on device development for drug-led combination product submissions (e.g., the biologics license application [BLA] and new drug application [NDA]). It also addresses regulatory considerations associated with notified body opinion (NBOp) in accordance with Article 117 of the EU Medical Devices Regulation (EU MDR)[1] for medicinal products that incorporate a nonreusable medical device.

Keywords – combination products, submission contents, eCTD

Introduction

Drug-device combination products can play a critical role in enhancing the therapeutic benefit of drugs, ensuring patient convenience, and reducing costs to the healthcare system. Pharmaceutical companies are investing in the development of delivery devices (e.g., prefilled syringes, autoinjectors, and on-body injectors) in response to the increasing access needs of patients. For these products, the US and EU regulatory landscapes and requirements continue to evolve. In the US, device information for drug-led combination products is routinely submitted under a drug or biologics application pathway (e.g., BLA, investigational new drug, or NDA) through a single marketing application.

Under the single application pathway, the device submission content is reviewed by the US Food and Drug Administration's (FDA's) Center for Devices and Radiological Health (CDRH) through an intercenter consulting process. However, there is currently no single comprehensive FDA guidance that describes the device submission content for drug-led combination products. In the EU, Article 117 of the EU MDR requires a marketing authorization holder of a medicinal product that incorporates a nonreusable medical device (or integral drug-device combination product such as a prefilled syringe) to obtain an NBOp confirming the device part is compliant with the relevant general safety and performance requirements (GSPR)[2] in Annex I of the EU MDR.[1] The positive NBOp is then included in the marketing authorization application (MAA) or variation, as applicable.

This article will discuss the expectations for submission content and the best practices of the FDA and notified body (in accordance with EU MDR Article 117) for drug-led combination products and medicinal

products that incorporate a nonreusable medical device, respectively.

FDA device development submission content for drug-led combination products

Although regulatory submissions for drug-led combination products are becoming common, there is no comprehensive guidance that describes the device development submission content for drug-led combination products. Guidance and/or guidelines such as ICH MQ4 (R1)[3] and FDA guidance on pen, jet, and related injectors for drugs and biologic products[4] and eCTD conformance[5] are extremely helpful. However, these resources do not address the CDRH's current expectations for device development submission content. As a result, some companies may be forced to address requests for additional information that can result in delay in approvals.

Single-entity combination products such as prefilled syringes, autoinjectors, and on-body injectors are probably the most common combination products being developed by the pharmaceutical industry. The device development submission content for these products is commonly presented in Sections 3.2.P.2 and/or 3.2.R[3] of Module 3 in the eCTD submission structure, per CDRH expectations, because the content pertains to development of the device constituent part of the combination products (**Table 1**).

Similarly, the CDRH expects device submission content for copackaged combination products (e.g., vials and needles). However, the extent of the content varies greatly, depending on whether the device constituent has a marketing approval or clearance and, if it does, whether the device will be used according to its intended use. The device submission sections described in Table 1 can generally be adapted. In addition, there is other device constituent information that should be

Table 1. Device development information commonly presented in Sections 3.2.P.2 and/or 3.2.R3

Section	Description
Device description	Provide a description of the device constituent design and novel features and/or functionalities, and include drawings/diagrams, device components, principles of operation and intended use, and materials.
Relevant standards	Describe the applicable standards used.
Design and development (design controls)	Describe the design input specifications, necessary preconditioning as recommended be respective device standards and/or FDA guidance documents, sample sizes and justifications, test methods, acceptance criteria, design verification test results, and conclusions. Test protocols and reports may be provided, as applicable (e.g., when the methods do not conform to FDA-recognized consensus standards). Describe the device aging parameters (accelerated and/or real-time), and provide results to support the claimed shelf life of the combination product. Describe biocompatibility evaluation and human factors validation results.
21 CFR Part 46 (current GMP requirements for combination products)	Describe the quality system compliance approach. Include a discussion of each prespecified quality system provision.
Manufacturing and controls	Provide a high-level summary of the manufacturing, assembly, and packaging flow. Justify the overall device control strategy.
Risk management	Describe the risk management processes, activities, and the conclusion.

FDA, Food and Drug Administration [US]; **GMP,** good manufacturing practice

presented in applicable sections of the eCTD structure (e.g., Section 3.2.P.5 for control of the drug product), which are not discussed in this article.

In addition to the preceding guidance, there are numerous approaches to gaining further understanding of the FDA's current device content expectations for drug-led combination products. Specifically, a company may review the FDA's summary basis of approvals for recently approved combination products. The CDRH consulting reviewer memos, information requests, and associated responses, when made available, offer substantial insight into current regulatory expectations. A company can leverage these insights to inform the submission content, if applicable; to ensure a complete review; and to seek the agency's early input on submission content in a formal meeting (e.g., a Type C meeting). This practice is particularly important for complex or novel products.

If the NBOp will not be available in time for the drug submission, the company should obtain a pre-agreement with the EMA to facilitate NBOp submission during the drug review.

EU requirements for integral drug-device combination product: Article 117

Article 117 of the EU MDR[1] provides a mechanism for linking the device constituent assessment to the medicinal product approval when presented as a single integral, nonreusable product (e.g., prefilled syringe or pen). Article 117 amends the EU Medicinal Product Directive (Directive 2001/83/EC) such that the EMA looks for the result of a conformity assessment on the device constituent with the GSPR or for an NBOp on the conformity of the device part.

As integral administration devices are most often designed for use with the specific medicinal product and are typically not marketed separately bearing a CE mark, the relevant certificate from a notified body may not be available. Consequently, an NBOp must be obtained instead. If a sponsor has a device that meets the requirements of Article 117 and wishes to seek an NBOp to fulfill the requirements for seeking an MAA, then a GSPR checklist demonstrating conformance must be provided to the notified body for review. The NBOp is typically required with submission of the initial MAA.

Best practices for obtaining an NBOp

A successful NBOp requires early interactions with the notified body, diligent timeline planning between the NBOp and drug submission (MAA or variation), robust GSPR and harmonized standard assessments, and high-quality technical documentation (see section on eCTD structure).

- **Early interactions with the notified body.** Engage with the notified body early to discuss the product and the submission timeline, including that of the drug submission. It is important for the notified body to understand the product so that it can designate the review time slot and team members, especially when specialized expertise may be required (e.g., terminal sterilization).
- **Diligent timeline planning between the NBOp and the corresponding drug submission.** The timeline associated with the NBOp review and approval must be planned to enable the drug submission. If a company anticipates the NBOp will not be available in time for the drug submission, it should obtain a pre-agreement as early as possible with the EMA to facilitate NBOp submission during the drug review.
- **Robust GSPR and harmonized standard assessments.** Thoroughly assess the GSPR considering the intended use and labeling claim of the product. Ensure clarity on which requirements are applicable, which are not, and the reasons why. For each requirement that is applicable, state the method to demonstrate compliance and the appli-

cable harmonized standards as presented in **Table 2**. A notified body generally expects submission of technical documentation and the associated data or evidence that support compliance with the applicable GSPR. Similarly, the same assessment should be performed on applicable harmonized and current technical standards, which would be considered state of the art by the notified body; hence full compliance or partial compliance, along with the justification, must be clearly presented to the notified body.

The GSPR checklist

Part of the technical documentation required for medical devices includes evidence for compliance with the GSPR (see Section 4 of Annex II of the EU MDR[1]), addressing, for example, methods applied, use of harmonized standards, and data of compliance evidence. Using the GSPR checklist (see Annex I of the EU MDR[1]) allows for a systematic way to provide the required information. The checklist generally includes information under the headings shown in Table 2.

Best practices for completing the GSPR checklist

Creating or updating a GSPR checklist is an upstream undertaking that requires people resources and their time. When done well, the information compiled within the GSPR checklist can be leveraged to reduce regulatory burden downstream. Here are some ways to maximize benefits from the time spent:

- Assemble a cross-functional team of subject matter experts so that diverse perspectives are captured in each line item of the checklist. The best justifications will come from discussing perspectives and capturing the blend that best represents the medical device in relation to the overall product, disease state, and intended population. A cross-functional team will include representatives from both the medical device company and drug partner, as well as experts with quality, regulatory, drug safety, clinical, manufacturing engineering, pharmacovigilance, and human factors backgrounds.
- Provide justification for each of the GSPR

Table 2. Information headers in a GSPR checklist

Checklist heading	Example for prefilled syringe with a staked-in needle
GSPR line item number	8
GSPR description	Risks and side effects
GSPR applicability (Yes/No) and rationale	Yes
Method(s) used to demonstrate conformity	[Provide method description for the implementation of a risk management system and a usability engineering process, e.g., according to the indicated standards, which were applied to the product]
Harmonized standard(s) applied (incl. parts subparts, clauses, amendments, year)	EN ISO 14971 IEC 62366-1
Links to applicable supporting documents (title, revision)	• Risk management file, incl. risk management report, benefit-risk assessment[a] • Usability engineering file[a] • Information for safety, incl. residual risks

GSPR, general safety and performance requirements
[a]Applicable documents can be listed here.

Table 3. Sections of the eCTD containing information about medical devices[7a]

eCTD section	Description	Integral	Copackaged[b] or referenced[c]
Module 1 – Administrative and prescribing information	**Product information**	✓	✓
Module 3 – Quality			
3.2.P.1	Description and composition of drug producta	✓	✓
3.2.P.2	Pharmaceutical development	✓	✓
3.2.P.2.2	Drug producta	✓	✓
3.2.P.2.3	Manufacturing process development	✓	✓
3.2.P.2.4	Container closure	✓	
3.2.P.2.5	Microbial attributes	✓	✓
3.2.P.2.6	Compatibility	✓	✓
3.2.P.3	Manufacturer	✓	✓
3.2.P.3.1	Manufacturer	✓	✓
3.2.P.3.3	Description of manufacturing process and process controls	✓	✓
3.2.P.3.4	Controls of critical steps and intermediates	✓	✓
3.2.P.3.5	Process validation and/or evaluation	✓	✓
3.2.P.5	Control of drug producta	✓	✓
3.2.P.5.1	Specifications	✓	✓
3.2.P.7	Container closure system	✓	✓
3.2.P.8	Stability	✓	✓
3.2.A.2	Adventitious agents safety evaluation	✓	✓
3.2.R	Regional information [medical device]	✓	✓
Module 5 – Clinical study reports			
5.3.5.4	Other study reports, human factors (usability)	✓	✓

eCTD, electronic common technical document

[a]This table is intended to guide the placement of device information within the traditionally drug- or biologic-focused eCTD structure. For the purposes of this article, 'drug product' could be replaced with 'drug-device product' in this table. [b]In a copackaged combination product, the medical device and medicinal product are packed together.[7] [c]In a referenced combination product, the product information refers to the medical device that must be used with the medicinal product and the patient has to obtain the medical device separately.[7]

deemed inapplicable,. In some cases, the team will find it beneficial to document why a particular requirement applies.

- Append supporting documentation for each requirement. Supporting documentation should include standard operating procedures, technical

reports with raw data, and summaries of reports.
- Leverage the completed GSPR checklist with documentation for regulatory submissions in the US and other countries or regions. The completed GSPR checklist and associated documentation will serve as a strong starting point, and content can be modified as needed according to regional regulatory requirements.

Medical device information within the eCTD structure

The EMA has issued guidance for sponsors to use when they create dossiers for provision of device information within the eCTD.[7] **Table 3** (p. 37) provides a summary of where device information might be placed.

Best practices for providing medical device information in the eCTD

Discuss placement of the NBOp and other devices' information within the eCTD during the pre-MAA submission meeting. Irrespective of specific device content placement within the eCTD, a roadmap can help guide health authorities and other reviewers to device content throughout the document.

Conclusion

The US and EU each provide structural starting points for dossiers that will eventually be used global. Within the unique US regulatory framework, where a single application can be used for both the drug/biologic and the device when the sponsor's intention is a combination product, the FDA has provided a basic structure for the inclusion of device- and combination product–specific information in the eCTD.

The EU, as well as most other countries and regions, require two applications – one for the drug or biologic and one for the device.

While the EU has a two-application system, EU MDR Article 117 provides a conduit for integral drug-device combination products to be considered by the EMA in the approval of the medicinal product. For copackaged and referenced medical devices, the EMA, like the FDA, has provided guidance on where in the eCTD a sponsor could consider placing information. In all cases, the MAA administrative information form asks about whether a device accompanies the medicinal product and, if so, in what capacity.

In preparing regulatory submissions per US and EU guidelines for the products discussed in this article, sponsors should engage in these best practices to present streamlined, accessible information in the least burdensome way and to leverage information across multiple geographies.

Abbreviations

eCTD, electronic common technical document; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration [US]; **GSPR,** general safety and performance requirements; **MAA,** marketing authorization application; **MDR,** Medical Devices Regulation [EU]; **NB,** notified body; **NBOp,** notified body opinion.

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Seven attributes for success as a regulatory leader

Monika McDole-Russell, MS, RAC

This article examines seven aspects of leadership that, if developed intentionally and practiced regularly, can help regulatory leaders at all levels succeed as people leaders and business partners.

Keywords – leadership, management, professional development

Introduction

Leaders influence, motivate, and enable their teams to contribute to the success of the business. Regulatory leaders are also the translators of a very specialized function to business leaders who often have little knowledge of what, exactly, regulatory affairs does. When I first entered regulatory affairs 12 years ago, I quickly noticed a trend: regulatory affairs tends to attract talented, highly intelligent, technical people – who are also largely introverted and conflict averse. Yet this function is key to the success of any medtech company, large or small. Without regulatory, our products would never make it to the market. This means regulatory leaders are responsible for a powerhouse function that should be represented by a strong voice, from the earliest device development stages to the executive suite. Our business partners are aware of the clearances and approvals we gain, but beyond that, regulatory remains an enigma to many outside of the function, especially at the executive levels. Strong regulatory leadership helps other functions make better decisions at all levels of the business.

While there are certainly exceptions, I have worked with many regulatory leaders who are not comfortable acting as that bridge to the business by speaking up and advocating for a function that is every bit as critical as marketing or R&D. This results in regulatory often getting pushed into the background and losing that all-important place in the discussion.

It doesn't require the acquisition of a business degree or stacking the regulatory leadership deck with nontechnical people. All it takes is the deliberate development and consistent practice of a few good leadership habits. This article outlines the key skills and behaviors I have observed in successful leaders throughout the 20 years I have been in leadership.

Attribute 1: Know your leadership style

Ultimately, *why* you lead is *how* you lead, so take some time to figure out your "why." Learn what drives you, what motivates you; understand what you are trying to accomplish for yourself, your team, and your business. Personally and professionally, I am most fulfilled when I'm able to serve others, so I closely identify with servant leadership. This is a leadership philosophy that focuses heavily on the well-being and development of the team.

If you haven't identified a style yet or you are new to leadership, consider using any of the common and widely available personality tests to learn more about your leadership dynamic. View the test results as a way to help identify personal strengths and potential weaknesses; don't let any one test define how you lead. Most leaders are a blend of leadership styles, with one style that generally predominates.

You can also emulate past or current leaders. If you are fortunate enough to have access to them (even if they are not in your direct chain of command), you can learn from them by observing as they navigate obstacles and daily tasks. If you do not have a leader you would like to emulate, identify the traits of the kind of leader you would like to follow. Chances are, these traits will naturally resonate with you, so work on personally cultivating the qualities that already feel most genuine.

No matter how you discover it, once you identify your leadership style, own it. Be genuine because you will become who you portray. Your style will change and mature throughout your career, but you will always find yourself returning to the gravitational pull of what drives you. Also, the more deliberate you are about developing your style, the easier it is to adapt it to suit the situation and audience without losing your authenticity.

Attribute 2: The people leader

Experience has taught me that the most important leadership skills are soft skills. Productive communication, strong emotional intelligence, willing engagement, and confidence will make you a powerful leader. Being adept at communication is the bedrock of leadership, whether you are talking to your team or to your company's CEO. As a leader, you should constantly seek to improve your communication skills; effective communication engenders trust and alignment from those around you.

One way to learn how your communication style is perceived is to request a 360-degree assessment. These assessments allow your manager, reports, and peers to provide feedback on how you are perceived in your role, including your effectiveness in communication. The 360-degree feedback is helpful and informative; the critical feedback, while sometimes uncomfortable to read, is often the most valuable because it can reveal development areas you may not be aware of. Improving the way you communicate is always worth the effort, because strong communication skills allow you to know when and how to say difficult things tactfully and effectively.

A high level of emotional intelligence helps navigate challenging scenarios, from budget negotiations to difficult conversations with underperforming direct reports. Emotional intelligence is more than just empathy and social skills. It allows you to understand and manage your own emotions while also recognizing the emotions and experiences of the people around you. This helps you build trust and rapport with people who may be very different from you.

> *The most important leadership skills are soft skills – productive communication, strong emotional intelligence, willing engagement, and confidence will make a powerful leader.*

One of the best ways to build emotional intelligence is to practice active listening. In your next meeting, rather than just mentally preparing your reply when someone is speaking to you, focus on what the person is saying and how they are saying it, including nonverbal cues, such as facial expression and body language. Demonstrate your engagement in the conversation using your own nonverbal cues (nodding or leaning forward slightly, for example), and then paraphrase what the person said to ensure you understand. It has been estimated that only about 10% of people actually listen effectively,[1,2] so set yourself apart by being in that exemplary minority.

Being engaged and fostering engagement will build your team's morale and your reputation, both in your immediate circle and within the larger organization. Start by getting to know people at all levels of your team. In smaller teams, try to have skip-level meetings with your indirect reports at least twice a year. If you have a large group of indirect reports, try hosting virtual all-hands meetings every quarter or semiannually. You want to share what is going on at your level of the business (to the extent you can) and, if possible, to share good things about the business that are sparking your enthusiasm right now. In skip-levels, be intentional about seeking the opinions of those you are speaking to. How are they feeling about their role, your organization, and the company overall? Ask what you can do to help. At larger meetings, try a word cloud exercise using an audience interaction platform such as Slido to simply ask, "How engaged are you feeling right now?" and "What's one thing that would make you feel more engaged?"

Confidence in yourself, in your team, in your abilities, and in your business feeds into the all-important attribute of executive presence. Confidence is the Goldilocks of soft skills: too much and you're seen as cocky, too little and you're seen as indecisive or timid. A truly confident leader doesn't issue edicts and order people around; instead, they create cohesiveness within the team, lead by example, listen to understand, and share their knowledge along the way. One way in which leaders demonstrate confidence is by showing humility. Share stories of your successes to motivate your team and share some of your failures to show the value in learning from, and moving past, low points in your career. Seek feedback from your team and be open to criticism as a catalyst to your own continued growth. Finally, maintaining flexibility and agility during times of change requires great confidence. A leader who can lead through change with outward calm and confidence is of immeasurable value to their team and to their business.

Trustworthy leaders foster loyalty and provide stability. Teams feel empowered to speak up and to take initiative. Trust in leadership becomes particularly important during times of change or adversity, when the risk of disengagement is high. Trust is the foundation to a healthy and respectful work environment. Develop trust by communicating clearly. Follow up. Deliver on your promises. Establish a culture of growth and development within your team by developing and fostering the growth of your direct reports and setting the expectation that they will do the same with their teams.

Earning the trust of your team is critical because as a leader, you must be able to achieve business goals through the people on your team, and the higher you go in leadership, the truer this is. No matter your current level of leadership, do not just focus on getting the work done; focus on the people doing the work. Especially in a senior-level leadership position, you will inevitably begin distancing yourself from the day-to-day experiences of the people on your team as you focus on the bigger picture and broaden your view of the business.

> *Discomfort often leads to growth, so try to embrace what you learn from uncomfortable or awkward moments.*

Finally, discomfort often leads to growth, so try to embrace what you learn from uncomfortable or awkward moments. As a leader, you won't always be popular, you won't have the luxury of always being prepared, and there will be times when you aren't right. Just do your best to be humble and authentic. In other words, be worth following.

Attribute 3: The business partner

In many companies, regulatory affairs tends to be seen as all things to all people: expert, advocate, diplomat, and advisor. So the regulatory leader's role as business adviser should not be overlooked. Most importantly, you must understand the difference between leading a team and running a business. They are two sides of the same coin, but two separate skill sets. As a people leader, you focus on results at the functional, or micro, level. As a

business leader, you focus on results at the enterprise, or macro, level.

Your success as a regulatory leader hinges on your understanding that your business is more than your function. From the moment you step into a leadership role, you no longer just represent regulatory affairs, you are a partner in making your entire company a success. To understand how your work ties into the overall business, you need to understand how your business works. To do that, listen to your company's earnings calls, and read market intelligence – not just about what the competition is doing in regulatory affairs but about what the competition is doing overall. Set news alerts to flag when articles about your company and its main competitors are in the news. Attend your organization's town halls, and when you do, really listen to understand information conveyed and assimilate it to understand how it affects your role and your function. Then summarize and share it with your team so they understand how their daily work contributes to the overall success of your business.

> *Understand the difference between leading a team and running a business: a people leader focuses on results at the functional, or micro, level; a business leader, on results at the enterprise, or macro, level.*

One simple but often overlooked tip for leaders is to learn the language of your executive team. Executives have phrases, buzzwords, or slogans they like to use. Keep an eye and an ear out for them in their written communication or when they speak at town halls and other events. Incorporate that lingo into your vocabulary. The specialized, detailed information we deal with in regulatory can be overwhelming to those who are not trained in the function. If you can translate a tech-heavy message into the language executives speak, they are more likely to receive your message favorably, and you are more likely to achieve the desired outcome of your communication. This holds true whether you interface directly with your executive team or not, because if you do not translate it, a more senior leader will have to do it. By doing it yourself, you save them time and demonstrate that you recognize the value in doing so.

This next point is not specific to regulatory affairs, because leaders of all functions should be doing this: demonstrate cross-functional value within your organization. Know what your cross-functional peers want and need, and work with them to get it. In the meantime, you will gain a valuable new perspective on the business and, most likely, earn an ally to boot. Most leaders will reciprocate because they, like you, understand the value of relationships in getting things done.

For example, I am on a product rationalization team within my operating unit. The purpose of the team is to regularly review our portfolio from a cross-functional perspective and ensure that our product mix remains optimally balanced. When I am in those meetings, I provide regulatory input when needed, but my role is as a business partner first and a regulatory affairs leader second. This is an example of how, as a leader, you will have to rise out of the microcosm of regulatory and take a more generalized view. Yes, you are still a regulatory affairs expert, but you no longer have the luxury of one area of focus. You are now a strategist, not a specialist. You rely on your team for the details. Do not try to know every answer. But do know where to find every answer.

Attribute 4: Executive presence

Valentine has described executive presence as one's "ability to inspire confidence" among your subordinates, peers, and senior leaders[3] so that subordinates "will want to follow you," peers will see you as capable and dependable, and leaders will recognize your potential.

Many shades of executive presence

There is no single approach to executive presence, and everyone can develop it. However, a key attribute of ex-

ecutive presence is the ability to convey confidence and to draw focus and hold it. For extroverted leaders, this might not be a challenge, because they do not mind the spotlight. However, introverted leaders might struggle with this. The cost of extroversion for introverts can be high. Extended periods of extroversion can be exhausting, but it is also something you can learn to manage. And it is important to do so because the higher you go the more critical executive presence becomes and the more present you need to be for your team and for your company. This is especially true if you want to accelerate your career path in a mid- to large-size company.

As a senior leader in a large company, days of meetings and conferences and weeks of travel are part of my job. However, these events can also physically and mentally exhaust me as an introvert. As I have advanced in my career, I have learned ways to take time for myself so that I can show up every day focused, refreshed, and recharged.

> *The cost of extroversion for introverts can be high. Extended periods of extroversion can be exhausting, but it is also something you can learn to manage.*

Developing an executive presence

Many of us are our own worst critics, and few external forces can stand in the way of your success as resolutely as you can. The first step to developing your own brand of executive presence is to believe that you deserve to be where you are. Only then can you present yourself well and perform with confidence. With that in mind, it might be helpful to briefly discuss imposter syndrome, which can be an issue for people moving into and through leadership roles. Imposter syndrome is the condition of feeling anxious about your competence and not being able to internalize your success, despite being objectively high performing in your role. This condition often results in people feeling like a fraud or a phony and doubting their abilities. Imposter syndrome is common and can impede the development of the confidence and charisma that is essential to executive presence.[4]

- Whether you suffer from imposter syndrome or not, here are a few practical suggestions for building up your executive presence:
- Research the topic. There are many articles, TED talks, and leadership development sites that talk about how to develop and strengthen this leadership muscle.
- Watch other leaders to find two or three people that strike you as having executive presence. What traits do they have that you might emulate?
- Ask your manager for feedback on your level of executive presence. Do they believe you possess it? How can you improve it?

Get a coach. There are coaches who specialize in helping people develop into executive material. If you are in a large company, chances are there are leadership development and/or coaching programs available to all levels of leaders.

For years, my preferred method for honing my executive presence has been imitation of a senior leader I admire, someone I can see myself being on my best day. Generally, I do not personally know the people I use as my ideals, but if you personally know yours, do not be shy about going up to them and complimenting their style. Consider asking for 30 minutes of their time if you have specific questions about how you can adapt your style to be similar to theirs. Remember: imitation can be the sincerest form of flattery, and if you do not ask, the answer is always no.

The bottom line is that executive presence can be learned and perfected. However you achieve it, find a style that feels right for you.

Attribute 5: Make corporate politics work for you

Corporate politics are often talked about with disdain

or distaste, and sometimes the topic is associated with negativity and one-upmanship in the office. The truth is more nuanced than that. Ultimately, corporate politics are neither good nor bad; they just are. In the end, we are all human. All companies are composed of complex relationships, and this naturally leads to a diversity of opinions and, often, to competing agendas.

Use your network

Start with your network. A strong network is critical to getting what you want or need for yourself or your team, so networking matters, and it matters a lot. I will not focus on the how and why of building a strong network in this article but instead on one of the less frequently discussed benefits of successful networking: political capital.

> *Political capital is the accumulation of resources and power built through relationships, trust, goodwill, and influence – a type of credit or a resource that can be spent or misspent, invested, or lost.*

Many people think of a network as being primarily for their own benefit – for career growth or to have connections to people who can help you in some way. But I believe one of the most important things a solid network can offer is political capital, and political capital is invaluable to leaders. Political capital is the accumulation of resources and power built through relationships, trust, goodwill, and influence. It is often described as a type of credit, or a resource that can be spent or misspent, invested, or lost.

Some time ago, I wanted to assign a high-potential but junior-level regulatory specialist to the core team of a business-critical project. Usually, high-visibility projects are assigned to senior members of the regulatory affairs team, but I felt this person was a good fit, had the right skill set and attitude, and would benefit from this development opportunity. However, one of my cross-functional peers was skeptical of allowing such a junior member of the team to work on the project. He had several valid concerns, but after discussing his concerns and sharing the reasoning behind my request, he agreed it could be beneficial to bring this person onto the team.

In this situation, I was successful because my colleague and I had already established a rapport; he knew my reputation and trusted my judgment. I had earned political capital with him that I was now spending to achieve my goal of placing the best person on the project. If that person failed to deliver, I would lose political capital with my peer. If that person succeeded, I would earn back all the capital I spent, and then some. When considered in that light, almost any interaction where a level of persuasiveness or trust is needed by either party could be considered an exchange of political capital. Political capital takes time to build, however, and is not earned with every interaction. Be selective about where you spend it and on whom.

Two other topics that fall under the umbrella of corporate politics are mentorship and sponsorship. Everyone talks about how critical both are to success, but many people either do not know the difference or do not understand what each does.

You could think of mentorship as the Obi Wan Factor and sponsorship as the Invisible Hand. In the first *Star Wars* trilogy, Obi Wan (the mentor) guided Luke Skywalker (the mentee) through challenges and helped him find the answers he needed to continue his growth and development as a Jedi. Mentors are people you seek out for advice and guidance; you usually meet with them regularly for a period of time about specific issues you want to address in your career. Generally, you will have multiple mentors throughout your career.

Sponsors are "the Invisible Hand" because they are your advocates and champions when you are not in the room; they speak up on your behalf in meetings you may never even know take place. You may or may not know you

have a sponsor – often, a sponsor will be a senior leader who knows of you, is impressed by something you have accomplished, or takes an interest in your career for some other reason. Some people will tell you they are sponsoring you, but this does not always happen. In some cases, you may not have even met the person who decides to sponsor your career. Some people have mentors who are also sponsors, which is a great position to be in, but not mandatory for your success.

> *Mentors are people you seek out for advice and guidance, and sponsors are your advocates when you are not in the room; they may speak up on your behalf in meetings you may never know take place.*

It is expected that you will seek out people to mentor you, but traditionally it was frowned upon to ask someone to be your sponsor. The idea was that your work and reputation would speak for you so powerfully that sponsors would "find" you. However, as business norms shift and change with the generations, some people are starting to actively seek out sponsors.

The final piece of the corporate politics puzzle is communication. The popular advice is to communicate up, down, and across an organization. Skilled leaders can do all three with ease, but it takes time and practice to perfect. Here are a few tips for communication with each group:

- **Up (senior leadership).** You know how little spare time you have; leaders senior to you have even less, so make your interactions count. When you have the opportunity to meet with senior leaders, be as prepared as possible, even if you're only presenting a slide for three minutes out of a 90-minute meeting. If you bump into an executive in the cafeteria, take the opportunity to introduce yourself: name, title, business unit, and whom you report to, so they can place you in the context of their world. If time permits, you could make a brief comment on an enterprise-wide project or mention something you heard them say in a recent appearance (this is why it is critical to attend town halls and earnings calls). Thank them for their time and let them get on with their day. Their time is valuable and so is yours, so be precise, respectful, and memorable.
- **Across (peers).** You can accomplish a lot with a strong peer alliance (cross-functionally or within your function), but this is also the trickiest group to manage. Peers can be overused, becoming a clique or an echo chamber for your own agenda; underused, if you view them as competition; or misused, as in when you treat them like a gossip group. The ideal peer relationship is balanced, reciprocal, and mutually beneficial. It should be regularly nurtured and developed; do not contact your peers only when you need something from them. Keep the lines of communication open by putting regular quarterly meetings with key individuals in your peer group on your calendar.
- **Down (junior-level managers, individual contributors).** This is the part of the "up, down, across" saying that bothers me. Communicating "down" implies that you are communicating to people beneath you, or lesser than you. It does not matter what your title is – we are all human, so no one should be "beneath" you. I prefer to refer to this as communicating "through," as in through the organization at the level of junior colleagues or individual contributors. This group is very important – these are the people doing the work, maintaining the daily business, innovating, and delivering results. Even so, communication to individual contributors is often overlooked by leaders, especially senior leaders. I have been guilty of this myself and, while it was not intentional on my part, it was felt very personally by my team. As a leader, it is your duty to share as much information as you reasonably can with your team. Always try to help them understand

the rationale behind decisions made at your level. You may not be able to give them all the information you have, but what you do share should be as detailed and informative as possible.

Attribute 6: Use passion to drive vision

Some teams have a vision statement, some do not. Often, leaders will use the company mission instead. But some companies are so large that smaller business units within can feel detached from the larger organization. In those cases, it is useful to develop a team vision, one grounded in the larger corporate mission but unique to the team's function and its individuals.

> *It can be useful for smaller business units to develop a team vision, one grounded in the larger corporate mission but unique to the team's function and its individuals.*

Passion drives engagement and momentum, and this is something a leader brings to the team. Your passion engages others in building a shared vision, but passion looks different for different people. Some people think of passion as performative, like a motivational speaker onstage, and for some people, outward expression of their passion comes naturally. However, passion can also be driven by a quietly powerful conviction, a strong dedication to a team, project, or ideal. No matter how you express it, be authentic in sharing your passion.

If you and your team choose to develop a team vision, it should not be long and full of exclamation points. It may or may not be tied to a larger goal or long-term objective for your team. What it should be is concise, direct, and memorable.

Attribute 7: Be a lifelong learner

If you're not learning, personally or professionally, you're obsoleting yourself. But as a leader, you must prioritize what you learn. Staying current on regulatory knowledge is important yet becomes harder as you advance in your career. You must balance that specialized knowledge with a high level of general business acumen.

Train yourself to adapt what you learn to what you need to know at a particular stage in your career. Above all, do not stay hyperfocused on regulatory affairs. Expand your knowledge base as you grow, and remember that the more senior your position, the broader your base of knowledge must be. Put habits in place early that will allow you to rely on your team for information, to delegate tasks, and to stay informed about, but not buried in, the details. If you are looking to move up in your career with any speed, be deliberate about it, and that includes any knowledge or training you acquire on the way. Continuing to build your knowledge base is vital, but be purposeful about it.

Most importantly, gain and share knowledge in equal measure. The wisdom you gain on your career journey doesn't just make you a stronger leader. It benefits your team when you share the knowledge, and it benefits your business partners when your contributions add value beyond providing a regulatory perspective.

Conclusion

There are many roads to leadership. Some are purposeful, and some are serendipitous; some are structured, and others are organic. All can benefit from the development of the attributes discussed in this article. No matter where your personal leadership journey leads you, just strive to be the best you can be, and you will find positivity and success in your growth.

About the author

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