Medical Device Development from Ideation to Regulation and Technology Transfer in Low- and Middle-income Countries

Roxanne P. De Leon, ECE, MTM[1] and Lourdes Marie S. Tejero, PhD, MTM, MA, CGNC[2,3]

[1]*Electrical and Electronics Engineering Institute, University of the Philippines Diliman, Quezon City, Philippines*
[2]*Technology Transfer and Business Development Office, University of the Philippines Manila*
[3]*College of Nursing, University of the Philippines Manila*

ABSTRACT

Necessity motivates innovators in low- to middle-income countries (LMICs) to develop medical devices that solve unmet local health needs. At the start of each process, multidisciplinary teams incubate ideas. Design planning and validation require funding, infrastructure, procurement, and testing. Ultimately, the regulatory and technology transfer processes usher the technology to market. These stages are standard procedures in developed nations; in an LMIC, these present a new set of hurdles to overcome. To assist innovators, this paper describes the hurdles from ideation to regulation and technology transfer and delineates mechanisms to address them.

Keywords: medical device, innovation, health technology, technology transfer, ASEAN

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Corresponding author: Roxanne P. De Leon, ECE, MTM
Electrical and Electronics Engineering Institute
University of the Philippines Diliman
Velasquez St., Quezon City 1101, Philippines
Email: rpdeleon2@up.edu.ph
ORCiD: https://orcid.org/0000-0001-9581-1719

BACKGROUND

Necessity propels innovation; innovation, in turn, fulfills the mind.[1] Medical device innovation stimulates scientists, especially in low- to middle-income countries (LMICs), to save lives, alleviate suffering, and protect communities from disease.

Challenges abound, from the lack of material resources (training, funding, and infrastructure) to environmental, ethical,[2] and social concerns, and the dearth of skilled personnel – often lost to the "brain drain." Scientists struggle to divide their time between research, clinical load, and administrative responsibilities. Even when medical devices are completed, they go largely unused, lacking needs assessment, relevance, infrastructure, and trained personnel.[3] These issues point to the lack of a "medical device management system."

The innovator must navigate these challenges in the medical device development (MDD) process. We outline the steps (Figure 1); enumerate needs and hurdles from ideation to regulation and technology transfer; and delineate mechanisms to address these needs (Table 1), specifically in the Association of Southeast Asian Nations (ASEAN) region.

INCUBATING AND BOLSTERING INNOVATIVE IDEAS

The synergy of interdisciplinary teams – medicine and engineering; science and the arts – has proven fruitful.[4] Collaborators are found in unconventional places: cross-border collaborations and public engagement[5] (safeguarding

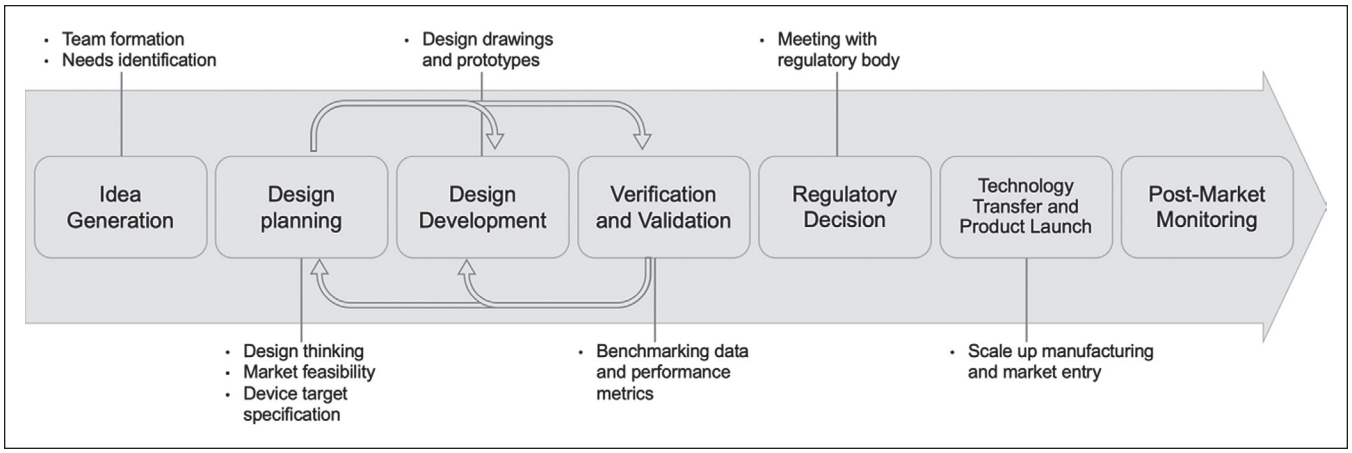

Figure 1. Medical device development process.

Table 1. Summary of the challenges in medical device development in LMICs and mechanisms to address them

MDD Stage	Need	Challenges	Solutions
Idea generation	Incubate and bolster innovative ideas	• Limited human, material, and environmental resources • Social concerns • A dearth of skilled personnel lost through 'brain drain' to high-income countries	• Develop technologies that maximize the value of health care with limited resources • Form interdisciplinary teams to ensure all aspects (clinical, engineering, business) of device development are addressed • Expand cross-border collaborations of interdisciplinary teams • Utilize different modes of communication (online, in-person) to reduce geographic and social barriers
Design planning	Ensure that the device meets the health technology requirements (user, clinical, economic, organizational)	• Mismatch of device design with stakeholders' needs	• Practice the design thinking approach to ensure that needs genuinely drive the specifications to be developed.[8]
Design development verification and validation	Develop and refine the device to meet usability, functionality, safety, and effectiveness Design for manufacturability, risk analysis, and management to ensure a seamless regulatory approval for commercial distribution	• Lack of funding needed to advance device development to the next stage[3] • Lack of facilities and resources that cause a delay in the design process • Ethical concerns in human trials as a result of poverty, lack of education, missing policies, and the like • Robust requirements for regulatory standards compliance	• Diversify funding options and strategies by exploring different funding options, including those beyond the local landscape • Consider different types of grants (i.e., research, program vs. project, education, and others) and funding sources (i.e., prizes, crowdsourcing, venture capital investment, corporate sponsorship, donations, services in kind, and others)[8] • Explore financing models such as the Development Impact Bond (DIB) • Conduct an environmental scan to identify possible leads to source the needed resources • Reach out to individuals and institutions abroad through referrals, emails, or cold calls to explore possible forms of collaboration • Employ a more rigid process for securing protocol approval from a duly constituted ethics review committee • Institutionalize nationwide regulation of clinical trials • Keep a design document containing all the device iterations for version control
Regulatory compliance	Prepare regulatory requirements for commercial distribution	• Determine the device risk classification needed for regulatory approval • Costs associated with seeking regulatory approval • The lengthy approval process that impedes immediate market adaption	• Create a target product profile (TPP) as soon as the design planning stage • Identify the target market of the device, as regulatory requirements vary per territory • Utilize online platforms to initially check if a device is considered a medical device.[35] (i.e., Singapore HSA interactive webpage: https://www.hsa.gov.sg/medical-devices/registration/is-it-a-medical-device) • Explore funding options mentioned above • For teams working in a university setting, consider building partnerships with industries with existing regulatory permits to skip several steps of the process

against data breaches) help bridge the personnel gap left by the "brain drain." A case in point: working on a physical protective device needed for COVID-19, our team comprises doctors, engineers, and experts from Fine Arts. This ensures that the product is clinically effective in preventing the transmission of disease and is aesthetically acceptable to the wearers.

Diversity comes with its unique problem: the "differentiating-integrating paradox,[6]" which must be managed through paradoxical leadership and its five characteristics: 1) being self-centered and at the same time other-centered; 2) keeping both distance and closeness with followers; 3) dealing with others uniformly while fostering individualization; 4) regulating work behaviors while allowing flexibility; 5) keeping decision controls while allowing autonomy among subordinates. This takes the perspective of each member and generates new ideas.

FROM DESIGN PLANNING TO VALIDATION TESTING

In design planning, the team evaluates the stakeholders' needs, market feasibility, and target specifications[7] to develop design drawings and prototypes. They then test these prototypes to ensure their safety, efficacy, and validity. In contrast with high-income countries, in LMICs, these stages are often an obstacle course marred by inadequate funding of bureaucracy.

Design Planning and Development

Design thinking is an iterative process of problem-solving that accommodates the user's needs.[8] It involves empathizing to understand the root cause of the problem – then reframing them into opportunities for innovation.

The design team meets with potential users (including patients, physicians, nurses)[7] to learn the user needs, inputs, and requirements unique to their context.[3] For example, a portable cloud-based health monitoring system might be unusable in a rural setting without internet connectivity. Similarly, it is not economical for a low-resource municipality to acquire ten units of a device that costs several thousand dollars each. Through customer interviews and meetings,[9,10] these issues are brought to light and enhance the device's value.[11] These should result in a well-defined set of device specifications. The product design is refined through continuous feedback from engineers – for manufacturability and risk analysis – and end users – for usability and functionality.

Funding

Many innovators fall into the "valley of death" due to the lack of funding to advance device development to the next stage.[3] Except for Singapore, funding across the ASEAN member states is consistently low,[12] the majority of which comes from the government. Scientists must learn to diversify their funding sources.

Funding can come in various forms; grants (research, program, project, education) competition prizes, crowd-sourcing, venture capital investment, corporate sponsorship, donations, services in kind, and others.[8] International organizations finance projects worldwide, especially in LMICs; these are accessible online through institutional databases. It is important to note that funders have specific eligibility criteria for their grants, frequently heavily influencing the project design.

Funding mechanisms have also been marked by innovation. For example, the Development Impact Bond (DIB) model coordinates four players – 1) investors who provide the capital, 2) service providers who execute the intervention, 3) outcome funders who repay the investors once the intervention reaches a milestone, and 4) an independent third party that verifies the results of the intervention.[13] Some researches use Core Funding: donors contribute to an unearmarked pool, then receive a Monitoring and Evaluation Framework report. This mechanism helps build capacity and maintain the autonomy of research institutes.[14]

Infrastructure and Procurement

Even with good design, prototyping that takes a few days in a developed nation may take a few weeks to a few months or even a year in an LMIC. Infrastructure is inadequate, and item procurement is often delayed or inaccessible. Scientists must scout both local and international sources and substitute where necessary.

Verification and Validation

Prototypes undergo verification and validation (V&V) testing of their parameters, specifications, and safety for public use.[7,15,16] Verification tests include benchtop, analytical, preliminary performance, biocompatibility, durability/longevity tests, usability tests, and feasibility studies. Validation tests check that the device meets the users' needs and requirements which may include clinical testing in human subjects.[7] V&V tests are based on international standards and are used to comply with regulatory requirements.[17]

Scientists may see regulations as a deterrent rather than a stimulant to innovation.[3] Many verification tests are still done abroad due to limited ISO-13845 testing facilities locally.[18–24] For example, a medical-grade face mask for healthcare workers must demonstrate good breathability, have identified internal and external faces, and exhibit 98% droplet filtration, preferably fluid resistance (performance standards set by EN 14683 Type IIR, ASTM F2100 Level 1, 2 or 3, and YY 0469, with at least 98% bacterial droplet filtration).[25] In countries such as the Philippines, there are very few facilities that can conduct such tests; local innovators collaborated with private industry on a smaller scale to test these performance standards.

Some medical devices must undergo clinical evaluation; high-risk devices require in vivo testing on human beings for their safety and effectiveness, similar to the four phases

of clinical trials for medications.[26] These come with ethical concerns unique to LMICs. For instance, patients may remain uninformed about the experimentation and are unaware that they can opt out of a clinical trial, thinking this will be taken against them. An ethics review committee (ERC) must approve and oversee all protocols to ensure the ethical testing of medical devices.

NAVIGATING THROUGH THE REGULATORY HURDLES

Regulatory Pathways to Market

Once the device reaches an acceptable risk level, the team finalizes the design and prepares the regulatory requirements for commercial distribution.[7] The team compiles all the information about the device, including the V&V tests, in a technical document called a dossier;[27–29] the depth of information depends on the device's risk classification.

The submission and approval process depends on country-specific policies and legislation, sociocultural behavior towards disease and medication, language differences, and religious norms and traditions.[30] The US Food and Drug Administration's Center for Devices and Radiological Health regulates the US market; Health Sciences Authority regulates for Singapore; the Philippine Food and Drug Administration regulates for the Philippines; each country in the European Union regulates for themselves.

Problems that impede technology transfer from the researchers to the include: identifying and verifying the risk classification of the medical device; the regulatory cost[3]; the duration of the approval process; and partnering with industry.

Is it a Medical Device?

The first question is this: whether the product is a medical device. The World Health Organization defines a medical device as "any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) … and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means."[31] This definition varies between territories and must be verified by innovators who want to launch the product in a specific location.[26,29,32–34] The World Health Organization's definition of a medical device applies to all member states of the ASEAN region, comprising Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Viet Nam, through the ASEAN Medical Device Directive;[26] this may be checked through Singapore's Health Sciences Authority's interactive webpage.[35]

What risk classification does it belong to?

Once the product is determined to be a medical device, device developers assign its risk classification. The system implemented by regulatory authorities is based on the level of control necessary to assure the safety and effectiveness of the device.[29,36,37] In the ASEAN region, medical devices are classified as Class A (low-risk), Class B (low-moderate risk), Class C (moderate-high risk), or Class D (high-risk)[26] where the potential hazard and harm that a device might cause in case of a malfunction is directly proportional to its risk classification.[38,39] Simple medical devices such as tongue depressors, walking aids, wheelchairs, and oxygen masks are Class A medical devices, while hypodermic needles, suction equipment, and condoms are Class B medical devices. Class C devices include lung ventilators and orthopedic implants, while Class D or high-risk devices include pacemakers, stents, and neurological catheters.[35,40,41]

The final decision about device classification lies on the authority covering the target territory; this is more complex as no one size fits all. For instance, regular gauze is a Class A device, a gauze with an internal sponge is class B, but a gauze with medicine or biologic is a Class D device. They all seem to fall under the gauze category, but the varying mechanisms of action and the indications for use result in differences in device classifications. Similarly, non-sterile examination gloves are Class A devices, but surgical, sterile gloves are Class B devices.[41] A higher risk classification translates to more tests needed to establish safety and a longer approval process. Scientists need to consider the anticipated risk classification of their device as early as the funding application and planning stage of their development process.

The target product profile (TPP) – initially used in drug development[42] – may be used as a starting point for classification; it is a concise summary that identifies risks and frames the device development to comply with the regulatory standards for safety and effectiveness.[43–45] At the minimum, the initial profile contains the device description, its intended use, and indications for use, answering the 5 W's: what it is, how it works, who it is for, why, when, and where to use it. A well-defined TPP dictates the appropriate tests and maximizes funding.

Is it ready for regulatory submission?

The regulatory approval of medical devices is a lengthy and costly process. Once submitted, it may take over 235 working days and cost more than 56,000 US Dollars (depending on the risk classification, completeness of the documents submitted, and the jurisdiction).[46] Scientists must consult regulatory authorities,[47–51] for guidance on the regulatory pathway, the timing of submission, and the best way to minimize the back-and-forth after submission.

The ASEAN region's medical device directive (AMDD) unifies the classification system, conformity requirements, and technical documentation requirements. Once a medical device is approved for market authorization in one ASEAN

country, the same documents can be filed in another country in the region. Manufacturers and distributors can quickly enter the region collectively, while local LMICs can develop their own medical devices while looking to a larger target market.[52–54] Each ASEAN country's medical device authority implements the guidelines based on the AMDD.[55–60]

SCALING UP AND PARTNERSHIPS: FROM IDEATION TO TECHNOLOGY TRANSFER

Medical device development is complete once the product reaches the public through product launch and post-launch assessment.[7,15,16,38,61] From prototyping to public use, partnerships and collaborations are critical. University technology transfer offices help innovators build partnerships and commercialize their technologies;[62] it evaluates patentability and commercialization potential.

The technology is scaled up either through direct industry licensing or through starting up a new company.[63] Partnering with established manufacturers can improve success in regulatory approval, industry adoption, and commercialization; however, they are few and are focused on profitable basic devices (such as surgical gloves and bandages), limiting the opportunity for advanced medical device innovation.[64–69] The technology-readiness level of the device must be optimized by engaging industry partners as funders, early adopters, or co-developers.[70] Innovators can leverage their intellectual property (patent, trademark, copyright work, trade secrets, or know-how) as an asset in the commercialization of their device.[71–73]

CONCLUSION

The medical device innovator's journey from ideation to regulation and technology transfer is replete with hurdles that must be overcome. Challenges abound but are surmountable. Innovators must take stock of one's resources and capabilities, as well as those of the institution and locality. From there, they build on these existing resources and reach out to others for a collaborative partnership.

Often, inventors are experts in their science but may falter in bringing their invention to its ultimate destination: the user. The keys to successfully achieving these milestones are a resolute will and the proper know-how.

List of Abbreviations

LMICs: Low- to Middle-Income Countries
MDD: Medical Device Development
ASEAN: Association of Southeast Asian Nations
COVID-19: Coronavirus Disease
DIB: Development Impact Bond
V&V: Verification and validation
ERC: Ethics Review Committees
TPP: Target Product Profile
TRL: Technology Readiness Level

Statement of Authorship

Both authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising and approved the final version submitted.

Author Disclosure

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