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RECENT ADVANCEMENT IN PEDIATRIC MEDICAL DEVICE DEVELOPMENT AND APPROVAL OF USFDA

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ABSTRACT

The challenge in pediatric medical device development known as FDA barriers can be elaborated by the impacts of the characteristics and regulatory, ethical, and financial barriers in view that physiological and developmental aspects of children and adults vary. Although babies and children are some of the most frequently monitored patients, there are not many devices on the market, which are child-specific in terms of design, testing, and approval. This review discusses recent progress in the area, e.g., 3D printing of individualized devices; the existence of pediatric-specific biomarkers that allow early diagnosis of the diseases; innovations of critical care and near-infrared spectroscopy, and the development of smart ventilators. It also outlines the major regulatory pathways that have been used by the U.S. Food and drug administration (FDA) to approve pediatric devices, and such include the 510(k) premarket notification, Premarket approval (PMA), De novo designation, and humanitarian device exemption (HDE). These actions are part of a continuous progress towards the reduction of the innovation gap in pediatric care and more effective medical devices used with children.

INTRODUCTION

The expression children are not little adults is common in the field of pediatrics used to emphasize the specific differences in physiology, neurodevelopment, manifestation of diseases, methods of diagnosis, and treatment of diseases between children and adults. Regrettably, the same fundamental differences can be applied even to the differences in the funding and support of the healthcare system and medical innovation to cover the pediatric population. (JuanC.Espinoza, MD June 22, 2021) .Few medical devices are developed and authorized to be used with children. More usually, appliances initially developed for adults are changed to suit children frequently in manner not originally intended. This innovation gap that exists between the adult and pediatric medical technologies is influenced by a combination of factors which are regulatory, financial and developmental in nature.

Diseases in children are diagnosed and treated with the help of medical devices. Although they are crucial to the field, these devices are not given much focus in the design, formulation, or processes of regulations training or education that healthcare providers need to understand, thereby creating a knowledge gap in the field. This problem is also worsened in the field of pediatrics by the availability of limited devices that are specially designed, tested, and adopted by children. Consequently, most pediatric applications are based either on the permission referred to as off-label use or physician-based modifications of the grown up devices. This is especially evident with a small example where the successful use of adult biliary stents to treat stenotic cardiac vessels in infants, whereby a technology developed in adults was appropriately re-purposed to treat children demonstrates the necessity to re-use adult technology to address the needs of children.

This review was developed through a comprehensive evaluation of published literature, analysis of relevant regulatory guidance documents, and consultations with subject matter experts. Its primary objective is to provide an overview of recent advancements in the development and regulatory approval processes of pediatric medical devices.(Juan Espinoza etal.,2022).

2.MEDICAL DEVICE :

Medical devices encompass a wide spectrum of products, ranging from basic tools like tongue depressors and bedpans to highly advanced technologies such as programmable pacemakers and closed-loop artificial pancreas systems. The category also includes

in vitro diagnostic (IVD) tools such as reagents, diagnostic kits, and blood glucose monitors. Moreover, certain radiation-emitting electronic products used for medical purposes or associated with medical claims—like x-ray machines, diagnostic ultrasound systems, and medical lasers—are classified as medical devices.

According to Section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act, a medical device is defined as any instrument, apparatus, implement, machine, implant, in vitro reagent, or related item, including accessories and component parts, that meets one or more of the followingcriteria:
(A) is listed in the official National Formulary or United States Pharmacopeia (or their supplements);
(B) is intended for diagnosis, treatment, cure, mitigation, or prevention of disease in humans oranimals;
(C) is intended to affect the structure or function of the human or animal body, without achieving its primary effect through chemical action or metabolism.
Notably, certain software functions excluded under Section 520 are not considered devices under this definition.(USFDA,2022).

2.1 CLASSIFICATION OF MEDICAL DEVICE :

The U.S. Food and Drug Administration (FDA) divides medical devices into three classes (Classes I, II, and III) depending on (1) the purpose of use; and (2) the risk it causes to patients.

.Class I: Low risk and have the less regulatory control. These mostly comprise the simple, not-invasive equipment like the adhesive bandage and a hand-held stethoscope

.Class II devices have moderate-risks and they need greater oversight by the regulatory bodies usually via the 510(k) premarket notification process. Some examples are powered wheelchairs and infusion pumps.

.Class III devices are medical devices that are of high risk but either life sustaining, life supporting or implanted. Since they play such an important role they become subject to Premarket Approval (PMA) to prove their safety and effectiveness. Such products include implantable defibrillators and pacemakers (USFDA,2022).

3.PEDIATRIC MEDICAL DEVICE :

pediatric medical devices are meant to diagnose or treat diseases and conditions in persons between birth and age 21.The Federal Food, Drug, and Cosmetic Act (FD&C Act) describes a pediatric patient as an individual that is only 21 years old or younger at diagnosis or treatment.

Under this wide group, further classification of patients is done into certain subpopulations of pediatric patients according to their stages of development (USFDA,2020).

Some of the medical devices have been designed specifically to serve children, whereas other devices are derived or adapted to meet general application off adult oriented devices. Making devices used by children is a different problem: the patients are generally smaller and more mobile than adults, their anatomies and physiologies change as they age, and they might have a sustained need of these devices. This also brings up other issues pertaining to the durability of the device, its biocompatibility and long-term impact of implanted materials in the growing life time span (USFDA,2024).

.The production of medical devices dealing with children has its specific problems. The products, even though some are specifically designed and targeted at children, are evolved or adapted form adult devices, or general purpose devices**.**

.The difference between pediatric patients and adults is huge; they need special attention to all the differences including size, activity, and continuous changes in anatomy, and physiology during the development..

.Moreover, the risk of use of the device in children during prolonged periods brings up critical issues on durability, safety of the materials, and the consequences associated with many years of exposure to the implanted components during growth and development (USFDA,2020).

4.RECENT TECHNOLOGICAL ADVANCEMENT IN PEDIATIC CRITICAL CARE MEDICINE :

4.1 ARTIFICIAL INTELLIGENCE:

Artificial Intelligence (AI) refers to a variety in the methodology, which allows computers to demonstrate human behavior and mental functioning. AI has found its way more profoundly in the context of medical studies and practice with time(Morley J et al.,2020). Artificial intelligence is discovered in 1956 by a Massachusetts Institute of Technology scientist known as John McCarthy. Since that time, AI has developed exponentially and in the XXI century, it has been playing a revolutionary role in many spheres of the economy, including medical one. In the field of medicine, AI has brought a lot of changes that include providing solutions to large-scale, exhaustive health records, including electronic health records (EHRs) and medical big data analytics, and intelligent health information systems(Shu LQ et al., 2019) .

Such AI-powered clinical tools have the potential to supplement conventional decision-making with clinical expertise in pediatrics; however, they must be used in the context of supervision, because they can make pediatrics more accurate with diagnosis, increasingly consistent, and evidence-based in interventions(Shu LQ et al., 2019(Sloane EB et al., 2020).

ChatGPT is one of the most well-known AI applications that has revealed a natural language processing (NLP) model that draws on an unsupervised machine learning algorithm that can interpret unstructured and unlabeled data. It has the use in diverse areas of medical practice, such as literature review, data analysis, summarization of complex information, manuscript writing, and assistance in clinical research projects(Corsello A et al., 2023)(Xiao D et al., 2023). But as its adoption is on the rise there are rising questions of whether its use is correct and ethical or not.On the whole, the application of AI in clinical medicine has turned out to be ubiquitous as almost every sphere of care delivery and research is affected by its use.

4.1.1 Research Artificial Intelligence (AI) is emerging to be an effective device in medical researching especially in secondary research and evidence synthesis. Literature review tools like Rayyan QCRI and Nested Knowledge are becoming more popular to enhance research workflow by automating processes such as literature screening, data tagging and text compilation and synthesis of results (Adusumilli G et al., 2021) .There is a great potential of AI in neonatal and pediatric care in primary research work. It assists in diagnostic interpretations, clinical diagnosis assistance, and assessment of complex conditions, including childhood airway abnormality. Furthermore, AI may also help predict significant clinical outcomes, i.e., mortality, morbidity, inotrope requirements, hospital stay and other long-term prognoses, and thus strengthen clinical decision-making and tailorized patient care (Adegboro CO et al., 2022) (Chioma R et al.,2023).

4.1.2 AI driven virtual assistance :Virtual assistants are AI-backed assistants that prove more and more useful as an aid in the wellness and mental health of children and adolescents. They are customizable around a child, their age, history, and symptoms and just by using these tools, parents and caregivers are able to get credible health information and make even better decisions(Lee D et al.,2021). Specifically, in children with neurodevelopmental disorders, AI-based interactive robots have had potential in aiding daily activities, as well as the provision of therapy to children with neurodevelopmental conditions like autism. All these technologies and especially those that are used in the chemical bandwidth are excellent add-ons to conventional care because many autism children take to them with greater ease than traditional interventions involving human interaction.

4.1.3 Operational management :This involves predicting the shortage and surplus of patients, managing the medical provisions, and bed occupancy rate, transfer of patients to and fro different facilities, progression of attention of a patient, and the discharge of a patient. With its use, hospitals will be able to plan their resource allocations, maximize patient flow, and minimize administrative overheads, so that clinicians can focus more on providing quality patients care(Dogru AK et al.,2020).

4.1.4 Predictive modelling :The tools can also be used to predict major clinical outcomes, which include mortality, hospital stay, and chances of survival in patients who need critical inpatient care. Their usefulness was particularly clear during the COVID-19 pandemic, where predictive models were central to such aspects as spreading the risk of infection and areas of high risk of containment, as well as mortality rates(Payedimarri AB et al., 2021)(Santosh KC et al.,2020).

4.1.5 Intelligent health data analytics :Healthcare data analytics is intended to achieve the best use of the existing

resources and improve the quality of care and clinical performance. Such methods become more frequently considered in precision medicine, disease prediction, outcome-projection, point-of-care (POC) diagnostic devices, and AI-based clinical decision support(Abidi SSR et al.,2023). Moreover, artificial intelligence would relieve healthcare professionals by automating menial administrative duties, e.g., data entry and booking of appointments, giving them more time and concentration to personal attention of patients.

4.2 3D PRINTING FOR PEDIATRIC MEDICAL DEVICE:

Additive manufacturing Three-dimensional printing (3DP) Additive manufacturing refers to processes used to synthesize three-dimensional objects in such a way that materials are deposited successively and in layers. The technology has allowed the manufacturing of unique medical equipment based on patient requirements. There are myriad of uses with 3DP applied in surgeons, dentistry, drug delivery, orthotics, prosthetics, tissue engineering, respiratory support, and even in robotic interface in the field of pediatric care. Among the most obvious benefits of medical 3D printing in pediatrics is the fact that it can be used to create devices that are made to fit an individual. It is more important, they are made to fit the changes in anatomy as a patient grows. Moreover, 3DP may provide considerable advantages to more traditional manufacturing processes: it no longer requires a lot of time and money, does not waste materials and does not imply a variety of subsequent operations of moulds making, machining, manual smoothing, etc.,(Willox, M et al.,2020)

Three-dimensional printing (3DP) presents a cost-effective, time-saving, and more precise alternative to traditional manufacturing methods for producing custom-designed medical devices. It significantly lowers expenses by eliminating the need for molds and reducing material waste typically generated through subtractive techniques like chip removal. Moreover, processes such as milling, forging, and surface finishing become unnecessary, resulting in reduced manual labor and minimizing the likelihood of human error.(Redaelli, D.F et al.,2020)(Redaelli, D.F et al.,2018)One of the earliest applications of three-dimensional printing (3DP) in medicine was the creation of patient-specific anatomical models generated from medical imaging data, such as CT scans and MRI. These models have been valuable tools in surgical planning, allowing for enhanced visualization of complex anatomy. Additionally, they have proven useful for improving communication with patients and their families about surgical procedures, as well as serving as effective resources for medical education and training(Sukanya et al.,2021) Additional applications of 3D printing (3DP) in the healthcare of children and young people (CYP) include dentistry, drug development, and drug delivery. These innovations offer new opportunities to enhance the safety, effectiveness, and accessibility of medications. Moreover, 3DP facilitates the design and production of assistive devices tailored to individuals with limited mobility, further supporting personalized care. (Norman,J et al.,2017)(Xu,X Degerli et al.,2021)(Degerli et al.,2020).

Figure 1: Facial mapping enables the creation of a 3D model for a custom-fitted, non-invasive ventilation mask (left), which can then be 3D printed for personalized pediatric use (right).

4.3 BIOMARKERS

The field of critical care among children has been highly advanced in regard to the invention of intelligent and more advanced ICU ventilators, monitoring, and medical equipment which is specifically made to fit the needs of the children that are highly complicated. During recent years, there was a significant development of the biomarker research in the context of the health sciences. Biomarkers are an essential part of the diagnosis process, as well as the disease progression or regression, as well as treatment efficiency analysis.

This improvement in the diagnostic efficiency and reduction in laboratory waiting times through the evolving point-of-care (POC) devices with a variety of novel biomarkers helps in the reduction of clinical decision times. Nevertheless, no equitable replication of biomarkers that are valid in adults in children exists, as there exist developmental variations in children that change how physiological processes occur in children. It is on the basis of this appreciation that specific pediatric biomarkers, e.g., neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1), have been discovered, which have been demonstrated in various studies to be able to detect acute kidney injury in neonates and children.(Koyner JL et al.,2020)(MediH B et al.,2016)

Sepsis is one of the leading causes of death of sick children in an intensive care unit hence its importance as a target of biomarker research. Among the most promising developments stands out the Pediatric Sepsis Biomarker Risk Model (PERSEVERE), that studied the panel of serum biomarkers to support early diagnosis of sepsis and prognosticate the risk of death. Using a combination of bioinformatics and machine learning, the study discovered a list of potential genes related to a 28-day mortality that in the future may become an effective risk stratification tool and guide individualised management of pediatric sepsis.(Jacobs L et al.,2019)

Figure 2 : Digital biomarker

4.4 The field of critical care among children has been highly advanced in regard to the invention of intelligent and more advanced ICU ventilators, monitoring, and medical equipment which is specifically made to fit the needs of the children that are highly complicated.

The important developments in the same sphere are presented in the following sections.

4.4.1 Near-Infrared Spectroscopy (NIRS):

Non-pulsatile oximetry Near-infrared spectroscopy (NIRS) is a maturing technology that estimates tissue oxygenation in a regional tissue. (Mittnacht AJ et al.,2010) .One such device with non-invasive sensor is the Oxyprem device developed in Switzerland consisting of a reusable, non-invasive sensor placed in a headgear to monitor the cerebral oxygenation in premature neonates at its best. This is a technology that is already being

explored in regard to its clinical usefulness in pediatric acute kidney injury (AKI), and neurocritical care. (Kleiser S et al.,2017)

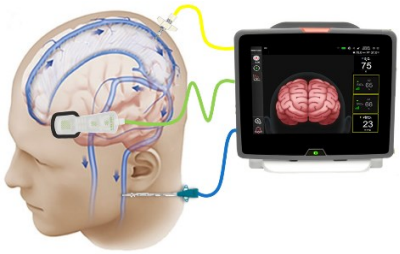

Figure 3 :Near infrared spectroscopy device

4.4.2: Point-Of-Care(poc) Diagnostic device :
The tools are used to diagnose respectively with high speed, are either non-invasive or minimally invasive, as well as help in real-time dynamic management of multiple critical conditions.(Drain PK et al.,2014)Examples of representative test devices of the point-of-care industry are hemoglobinometers, lactate and ammonia meters, blood gas analysers, troponin test cards.

Figure 4 :Point of care diagnostic device

4.4.3 Intelligent and Adaptive Ventilators:
The number of more sophisticated ventilation modes that have been implemented including neurally adjusted ventilatory assist (NAVA), closed-loop inspired oxygen control (CLIO), adaptive support ventilation, high-frequency oscillatory ventilation (HFOV), and several hybrid strategies- has improved patient-ventilator interface and made it possible to manage on a breath-by-breath basic(Miller AG et al.,2021).

Figure 5 :Medical ventilator

4.4.4 Prone Ventilation Beds:
After COVID-19 pandemic, prone ventilation has been identified as one of the measuring options of success in the management of Acute Respiratory Distress Syndrome(ADRS) (Petrone P et al.,2021).In order to go in line with this strategy, kinetic beds have been designed specialized to help in the safe positioning of paralyzed ARDS patients that need high levels of ventilator support.

Figure 6 :Prone ventilation beds

5.Major Barriers to Pediatric Medical Device Development:
The development of pediatric devices encompasses various unique issues of clinical, technical, regulatory and financial nature. Some of these obstacles were greatly analyzed in government and academic articles and a summary follows below and in the table on the adjacent page.

Category	Challenges and Examples
Clinical Considerations	-Physiological features of children differ significantly when compared with adults and keep on varying throughout their development process -Adult specific diseases do not use the same diagnostic tests or treatments on the pediatric patients though they have the same medical condition. - Any type of medical device must be set to respect the child in terms of neurodevelopmental and cognitive level - Children are active and prone to strange behavior which may impact the reliability of the medical equipment used with them
Technical Challenges	-The smaller anatomical dimensions of children and their ever-changing physical shape challenge the engineering of the devices to be used. - Extensive usage of gadgets in children poses serious questions about biocompatibility of the material, possible degradation or safety of long-term usage
Regulatory & Ethical Issues	-It is difficult enough to recruit proper participants because pediatric populations are small and more heterogeneous in nature -The application of clinical trials to the critically ill children has serious ethicalonfinements. -The issue of consent and assent to participation in the trials of children is a complex procedure where acceptance is made by the guardians and the institution - The consent and assent procedure involved in pediatric clinical trials are not simple, as they should include both parental or guardian consent and institutional oversight. -The use of sham procedure or blinded control in studies conducted on children may be considered a form of ethical misconduct or impossible. -No compulsory labelling-related requirements exist in regard to Pediatric labelling requirements to the medical devices -This efficiency of FDA reviewers related to pediatric medical device may somewhat be different.
Financial & Market Barriers	-A small size of pediatric patient base usually eliminates the business incentive in making specific medical equipment.

	-Activities that are involved in developing and validating pediatric devices are faced with substantial costs which in addition to uncertain rates of returns, serves as a barrier -Pediatric innovation is also stunted due to the lack of financial assistance, as well as a reduced level of reimbursements and more complex payment models -Lack of financial backing is a setback to pediatric innovation, coupled with the reduced reimbursements and an increased complexity in price structures.

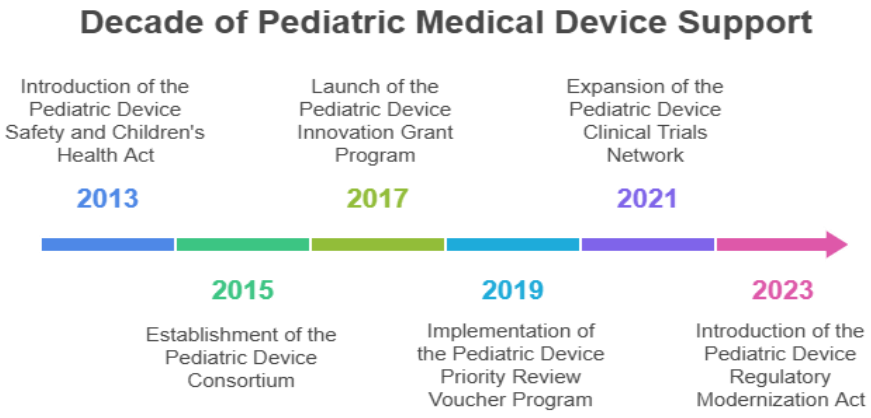

Figure 7: Timeline of recent regulatory and legislative initiatives to support pediatric medical devices. Key legislative and regulatory initiatives relating to medical devices over the past 15 years.

6.APPROVAL PROCESS FOR PEDRIATIC MEDICAL DEVICES :

Pathway Name	Purpose	FDA Review Timeline
Premarket Notification 510(k)	The object is to demonstrate that the new device is equal (similar to) with regard to safety and effectiveness and the intended use similar to an already legally marketed device (predicate device).	90 days
Premarket Approval (PMA)	This route involves the conclusion of scientific measures normally found in clinical trials in order to show that the high-risk (Class III) medical equipment is safe and effective.	180 days
De Novo Classification	This pathway (intended by the FDA to be used with innovative, low- to moderate-risk devices over which a suitable predicate does not exist) installs a new device classification and regulatory framework.	150 days
Humanitarian Device Exemption (HDE)	This is a device specific pathway intended to address rare diseases that present with 8,000 or less patients per year in the U.S where traditional clinical trials fail to be feasible.	75 days

6.1 PREMARKET APPROVAL PROCESS :

The most comprehensive regulatory- scientific scrutiny procedure that applies to the medical devices is Premarket Approval (PMA) and it is similar to New Drug Application (NDA) process through which novel pharmaceuticals undergo (Van Norman GA et al.,2016).

Class III pathway is mandatory to devices that falls in Class III and are classified as high-risk devices. Therefore, accreditation requires solid clinical data based on well designed clinical trials to demonstrate safety and efficacy of the device. PMA studies are frequently done through learning centers since they are multifaceted in planning, conducting, and monitoring. Such tests may prove to be costly and time-consuming, although, in a few instances, the FDA takes the clinical records obtained in studies that are carried out elsewhere in the world.

One of them is Medtronic MiniMed 770G System, which is a hybrid closed-loop system that measures glucose levels consistently, and automatically changes the level of basal insulin. This system was approved by PMA July 2020 as pediatric device in individuals aged 2-years and older (USFDA,2020).

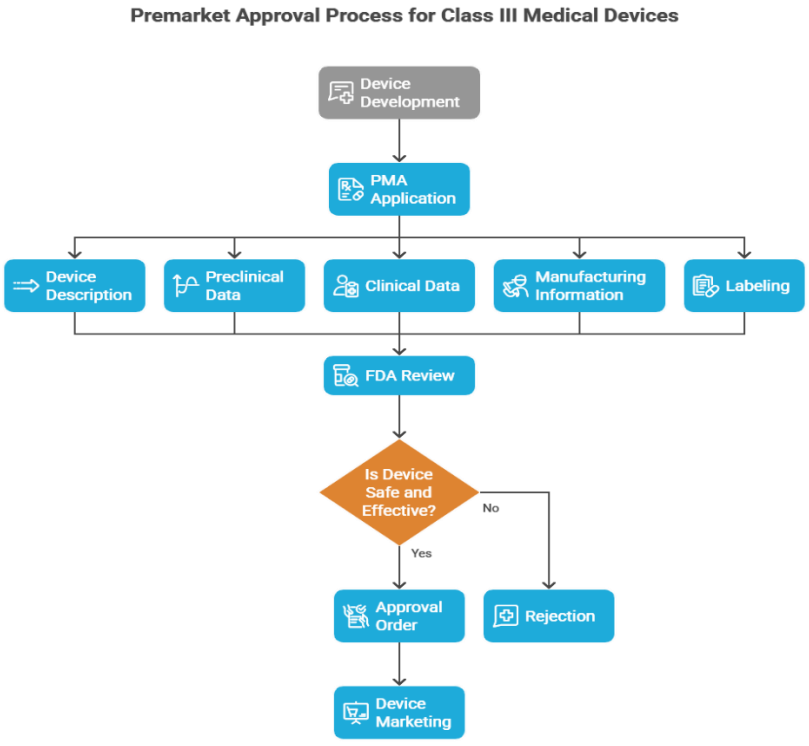

Figure 8 : Premarket approval process(PMA)

6.2 510 (K) PREMARKET NOTIFICATION PATHWAY:-

The process that is most commonly exercised to support Class II medical devices is the Premarket Notification 510(k). With such a pathway, manufacturers have to show that their device is substantially equivalent to an existing, lawfully marketed device, called a predicate device. The concept of substantial equivalence denotes that a new device is liable to the same intended use and has comparable safety and efficacy, and is manufactured using either identical or modified technology, or otherwise has a different technology that is not associated with novel security or efficacy challenges. Notably, the equipment is not supposed to be the same as the predicate.

As an example, the Abbott FreeStyle Libre 2 continuous glucose monitor (CGM) was accorded 510(k) clearance in June 2020, with the predicate being the Dexcom G6 CGM. Although there are several dissimilarities between the two devices, both will be aimed at diabetes management and make use of analogous underlying technology (amperometric glucose sensing in interstitial fluid). Abbott has proved the safety and performance of its device on laboratory as well as clinical demonstrations.The U.S. Food and Drug Administration (USFDA,2020).

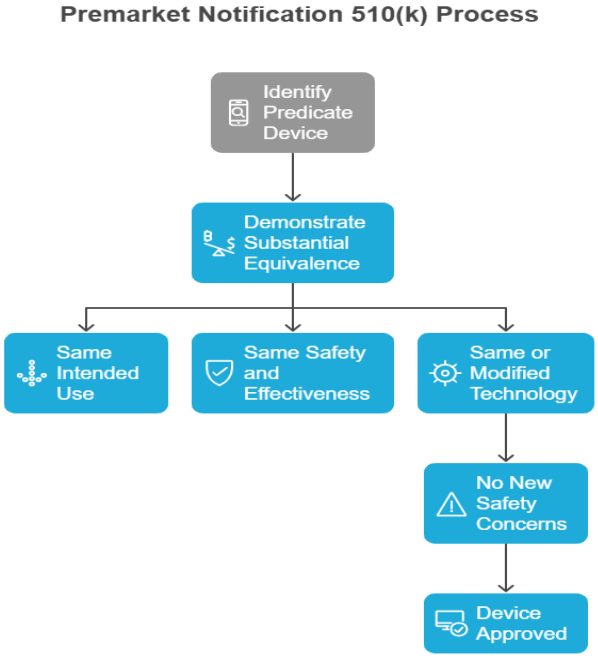

Figure 9: Premarket notification pathway510(k)

6.3 DE NOVO CLASSIFICATION PATHWAY:

The De Novo Classification pathway is intended to be used by the low- to moderate-risk medical devices that are similar to the Class I or II devices but do not have the predicate that is legally marketed. New technologies may be associated with these devices, they may perform new or combinations of functions, or they may target another group of patients. Given that there is no predicate, such devices cannot receive the 510(k) process. Rather than this, there is the De Novo pathway, which provides a way to be approved initially, and such as the PMA process is. When the authorization of a device is via this pathway, this constitutes a new category of device and thereafter may be used as the predicate to other future filings under 510(k). The example of the Dexcom G6 continuous glucose monitor that was subsequently the predicate to Abbott FreeStyle Libre 2 was originally approved by the De Novo process in 2018 (USFDA,2018).

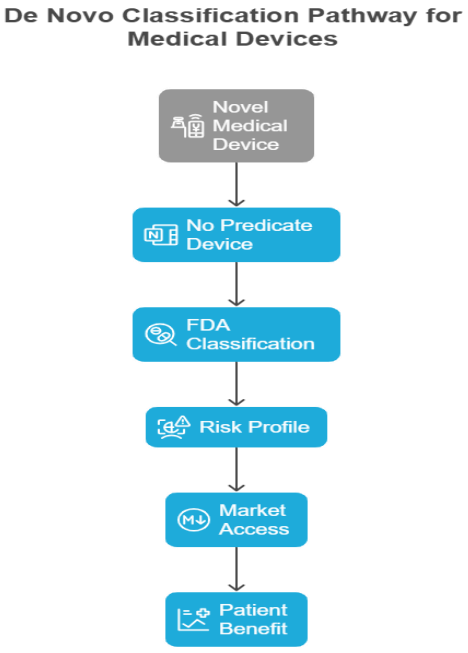

Figure 10 :Devoclassification pathway

6.4 HUMANITARIAN DEVICE EXEMPTION(HDE):

Humanitarian Device Exemption (HDE) route is an option to devices that have been granted Humanitarian Use Device (HUD) status. These devices have moderate or high risks (Class II or III) and are meant to be used in rare conditions or diseases, when it is not practical, ethical or feasible to conduct large-scale clinical trials. Conversely, unlike other regulatory pathways, approval through HDE entails the demonstration that likely benefits in relation to the possible risk should be carried out on the basis of the present treatments .HDE- and PMA-approved devices differ in two major ways. To start with, there should be the use of HDE in those institutions that are under the supervision of the Institutional Review Board (IRB), but not the provision of the informed consent. Second, these devices have restrictions on their commercial trade. With indications on adult uses, the producers will not make profits other than the development and research costs. Pediatric HDE devices, however, will be exempted to this profit restriction on the condition that particular circumstances are met. Nonetheless, they are restricted in their distribution by an Annual Distribution Number (ADN) focusing on anticipating the application of the devices per patient and multiplying it through 8,000.The exemption will not apply to sales exceeding this amount. An outstanding case is that of the Berlin Heart EXCOR Pediatric Ventricular Assist Device that was approved based on the HDE pathway to grant temporary mechanical circulatory support in children awaiting transplantation of new hearts (EXCOR et al.,2011).

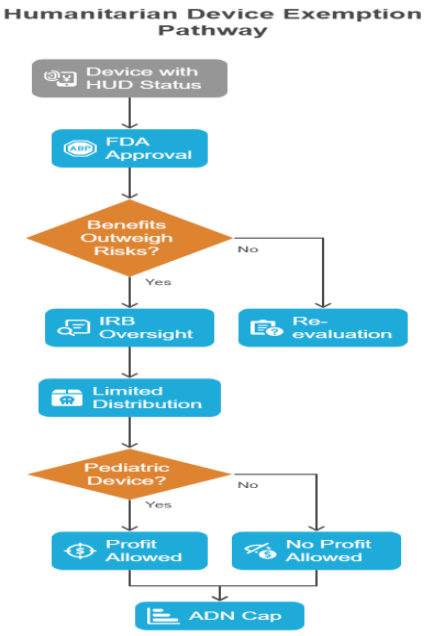

Figure 11 :Humanitarian device exemption(HDE)

CONCLUSION

Indeed, pediatric medical devices have traditionally remained behind adult technologies not only because of different physiological issues, but also due to lack of market pressure to develop the devices in question and various ethical complications surrounding pediatric trials. Nevertheless, the latest technological developments like 3D printing, smart ventilators, and biomarker-based diagnostics are changing the practice of pediatrics. Combing with the changing FDA regulation and better understanding of children needs, these developments are leading to the production of safer, more personalized and effective, pediatric devices. Further action is needed so that this momentum is maintained by clinicians, regulators, researchers and other stakeholders in the industry.

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