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THE COMMERCIAL ASPECTS OF REGULATORY APPROVALS

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Abstract:
Objective *To investigate the regulatory approval of new medical devices.*
Design *Cross sectional study of new medical devices reported in the biomedical literature.*
Data sources *PubMed was searched between 1 January 2000 and 31 December 2004 to identify clinical studies of new medical devices. The search was carried out during this period to allow time for regulatory approval.*
Eligibility criteria for study selection *Articles were included if they reported a clinical study of a new medical device and there was no evidence of a previous clinical study in the literature. We defined a medical device according to the US Food and Drug Administration as an "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article."*
Main outcome measures *Type of device, target specialty, and involvement of academia or of industry for each clinical study. The FDA medical databases were then searched for clearance or approval relevant to the device.*
Results *5574 titles and abstracts were screened, 493 full text articles assessed for eligibility, and 218 clinical studies of new medical devices included. In all, 99/218 (45%) of the devices described in clinical studies ultimately received regulatory clearance or approval. These included 510(k) clearance for devices determined to be "substantially equivalent" to another legally marketed device (78/99; 79%), premarket approval for high risk devices (17/99; 17%), and others (4/99; 4%). Of these, 43 devices (43/99; 43%) were actually cleared or approved before a clinical study was published.*
Conclusions *We identified a multitude of new medical devices in clinical studies, almost half of which received regulatory clearance or approval. The 510(k) pathway was most commonly used, and clearance often preceded the first published clinical study.*

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INTRODUCTION;

Randomized controlled trials (RCTs) have been considered the gold standard to demonstrate efficacy since the 1960s.[1,2] While current routes to market for investigational drugs typically require at least two pivotal RCTs, these are time-consuming, costly, and produce evi- dence that can have limited applicability in real-world clinical practice. There is, therefore, a move towards investigating innovative ways to improve the efficiency of clinical research.[3,4]

The controlled nature of an RCT offers advantages in evidence generation as there are standard methods to reduce bias (like random- ization and blinding), and they have comprehensive measurement of outcomes to demonstrate efficacy against both active and placebo controls.[5] However, RCTs do not accurately reflect real-world circumstances under which patients are treated; thus, there is often a need for observational studies to support additional evidence generation, particularly around questions of safety.

Real-world data (RWD) forms the basis for real-world evidence (RWE) and can be extracted from a broad range of sources such as patient registries, health care databases, claims databases, patient net-works, social media, and patient-generated data from wearables.[6-9] The definitions of RWD and RWE are relatively consistent between key regulatory agencies (see Table 1).[7,8,10] While RWE from observa- tional studies is well accepted for post-approval safety monitoring and to answer pharmacoeconomic questions[3,11,12] its contribution to regulatory decisions around effectiveness has been more limited. Indeed, evidence quality can be compromised by confounding by indi- cation or a general lack of rigorous collection standards.[5] There is, therefore, a need for the development of novel trial methodologies that can take the best parts of traditional RCT and observational study designs to produce RWE that provides adequate scientific evidence for regulatory decision-making. It has already been recognised by health authorities that there is a wide spectrum of potential uses of RWD/RWE in clinical studies, some of which preserve key features such as randomization.[13]

1 REGULATORS ARE WILLING TO EMBRACE NEW APPROACHES TO RWE

While acceptance of the role RWE could play in regulatory decision-making is not universal, opinions within regulatory agencies are evolving, and there is a growing acknowledgement that the current drug approval process no longer fully meets current health care needs.[14] For example, Dr Janet Woodcock, Director of the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research, has acknowledged that the current drug approval system is “broken” and expressed the agency's commitment to find new ways to collect and utilize patient data to improve the process.[14] Dr Woodcock has said, “FDA will work with its stakeholders to understand how RWE can best be used to increase the efficiency of clinical research and answer questions that may not have been answered in the trials that led to the drug approval, for example how a drug works in populations that weren't studied prior to approval.”[14] The use of RWE to support effectiveness decisions has been used in rare diseases, as highlighted by the examples of BAVENCIO and BLINCYTO (Case study boxes 1 and 2), both of which received accelerated approval using data from external, historical controls.[15,16] The case of BLINCYTO is of particular interest, as it was subsequently approved as a treatment for minimal residual disease in patients with acute lymphoblastic leukemia.[17] This approval was based on the results of a single-arm trial supported by RWE providing benchmarking information and was the first example of the FDA approving a drug for minimal residual disease.[18] A randomized clinical trial incorporating pragmatic design elements was also recently used to support a label extension for a drug treating a more common condition, schizophrenia, as demonstrated by the example of INVEGA/SUSTENNA (Case study box 3).[19-21] This demonstrates the willingness of regulatory authorities to consider RWE for regulatory decision-making when there is an unmet medical need.[22]

AIM AND OBJECTIVE

AIM

A review of successful regulatory approvals and the sequences between them was completed for companies that achieved US Food and Drug Administration (FDA) premarket approval or new drug approvals (NDAs) or device clearances in the fields of fluorescent imaging agents, open surgery imaging devices, and their approved medical indications.

DISCUSSION

To have a significant impact in clinical use and the subsequent patient outcomes, fluorescence- guided surgery (FGS) requires US Food and Drug Administration (FDA) approved commercial drugs and devices for each specific medical indication. The lessons learned from approval of one imaging agent or imaging system, can inform the regulatory pathway for a completely different surgical specialty or indication. Dissemination of these imaging agents and devices has been ubiquitous in the field of FGS and it is this diffusion of ideas that has helped the field progress. A study of the FDA approvals and clearance processes in the past can help us to see trends and key milestones that are shaping what is possible clinically. Company investment in imaging agents and devices drives the field forward, and result in the regulatory applications and approvals found on the FDA website. While many regulatory review papers are forward-looking perspectives, few have examined the history of approvals with an eye to learning from past lessons. In this article, we complete a historical review of key milestones and pathways for approved devices/agents with a focus on: (i) fluorescent imaging agents; (ii) fluorescent imaging devices for surgery; and (iii) charting the sequence of indications where they were approved for use, and the linear connections between them.

The main driver in the field of FGS is the fluorescent imaging agents used, and so analysis of the field should start with these. New imaging agent "new drug approvals" (NDAs) are approved by the FDA, and surprisingly all agents used for fluorescence imaging today were originally approved not as fluorophores, but for their other features. The earliest approval was indocyanine green (ICG) in 1959 as a green pigmented dye for use as a visible imaging agent. Fluorescein followed this in 1972, similarly as a visible-light absorbing imaging agent used in conjunction with a densitometer to measure hepatic function and cardiac output testing. Figure 1 shows four major optical agents and their financial impact in the field. While ICG has only become highly successfully used in fluorescence imaging within in the last 15 years, the growth in the use of fluorescein has been steady in retinal imaging for decades. These two vascular flow agents dominant the FGS market. A related footnote is the research ongoing with fluorescence from methylene blue (MB) and isosulfan blue;[7–]although they are not approved as fluorescent agents, they are indicated for use as blue dyes for visible contrast to guide breast surgery and MB as a treatment for methemoglobinemia. The most advanced tissue-specific fluoro- phore has been forms of aminolevulinic acid (ALA), which is metabolically converted to fluo- rescent protoporphyrin IX (PpIX) in the mitochondria of active cells and was originally approved as a topical photodynamic therapy agent for skin lesions in 1999 as Levulan®.ALA is gen- erally a cellular metabolism-specific agent because PpIX is produced by the heme synthesis pathway, instead of vascular or perfusion specific, and so it has unique imaging characteristics that affect the imaging system design, mostly in terms of sensitivity and wavelength band. ALA in various forms has seen approvals in bladder cancer detection and neurosurgical glioma image guidance. Strategies for approval of investigational agents are closely held industry

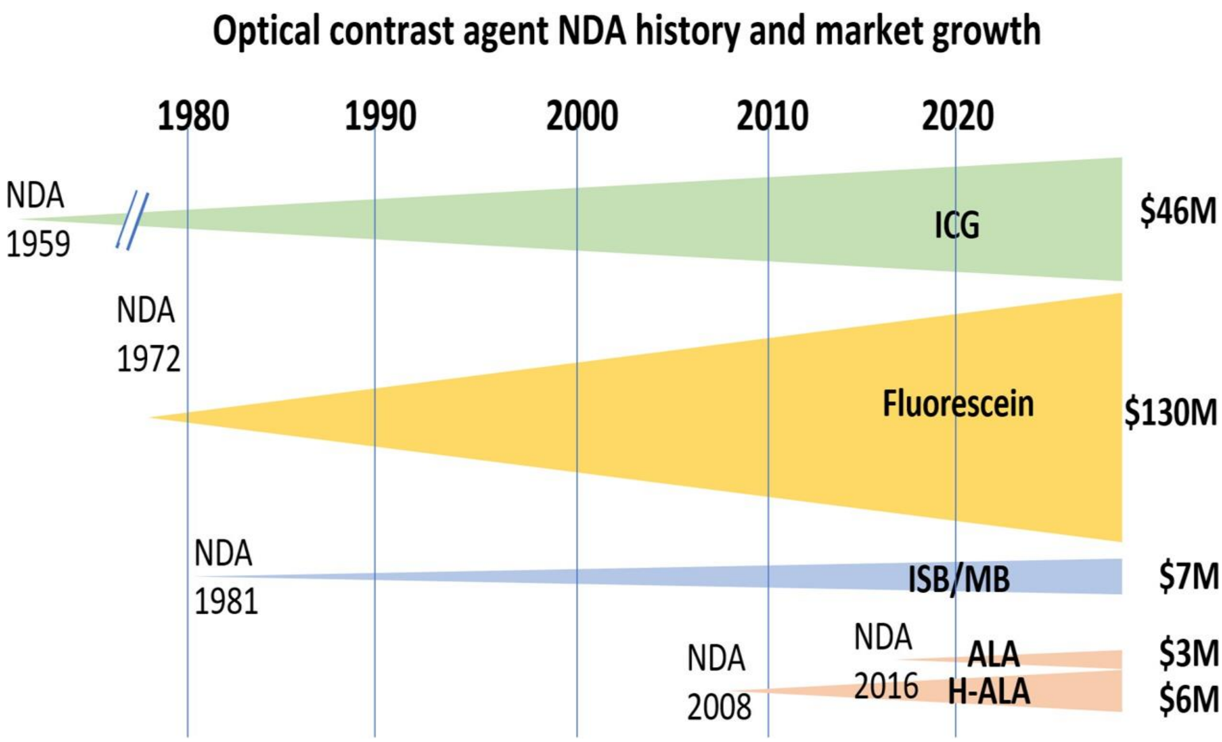


Fig. 1 Optical imaging agent development has its origins dating back to the early to middle of last century, with ICG, fluorescein, and MB each having been used in multiple human studies prior to their NDA dates, and each originally approved for other applications, such as an absorbing agent in the cases of ICG and fluorescein and as a therapeutic in the cases of MB and ALA. The modern use of ALA as a pre-cursor to fluorescence from heme metabolism started after its use in the 1990s as a photodynamic agent, and subsequent realization of its fluorescence imaging potential in the early 2000s.

trade secrets. However, a careful review of the publicly available documents for approved agents may help us understand the history of approaches to approval for new agents in medical indications.

Although fluorescent agents are key to generating sufficient signal to background, the device platform is critical for successful in situ imaging. Commitment to an imaging device for identifying anatomy or for oncological clinical trials must consider aspects of the tissue type, surgical approach, cost, and the fluorophore properties. The pivotal step in pre-marketing clear- ance for such an indication is through filing an application with the FDA. While it might be commonly thought that these devices are approved with the use of an existing NDA imaging agent, it is interesting to recognize that market approval/clearance of systems as an imaging agent-device combination was initially more common, but that this is decreasing in relative num- bers as the field broadens. The “combination product” route at the FDA is complex because of the need to have staff review both the new imaging agent and the new device. Recent changes in regulatory statutes and policy in the FDA Reauthorization Act of 2017, have also led to fewer combination product designations by the Office of Combination Products. Additionally, from the industry perspective, the complexity of good manufacturing practices for both the imaging agent and the device is high, and quite different in nature, so the staff involved both at the company and the FDA increases and the bar for approval of both is necessarily high. So, more commonly now companies are seeking to approve or clear either an imaging agent or a device, one at a time. This reduces financial risk and makes FDA decision-making simpler and perhaps more trans- parent, but also allows the company to focus its products in one core area instead of two.

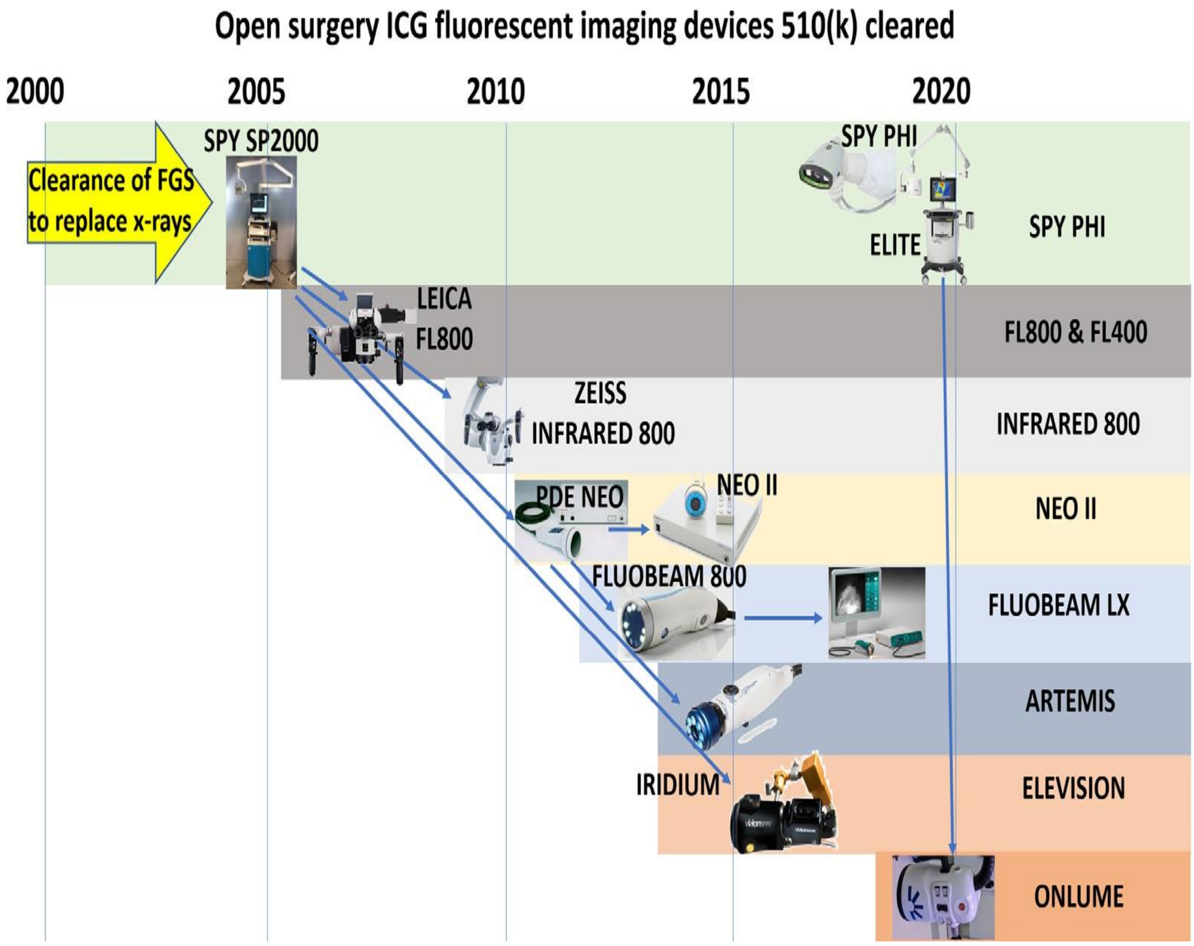
The relative risk of the device and intended use results in the device categorization of Class I, II, or III. Most devices are designated Class II, and so clearances are achieved through the 510(K) pathway, where a new device is proven by the company to be safe and effective by being sub- stantially equivalent to an existing cleared device. This approach, considered the path of least resistance, and cost, become an argument in justification and logic in the application to try to show that two devices are substantially similar in their intended use, even if they have very significant differences in other ways. For Class III devices, a Premarket Approval (PMA) appli- cation is required for devices that “. . . support or sustain human life, are of substantial impor- tance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.” However, there are few of these applications in the FGS field, mostly because the indications being sought are as a visualization tool in surgery. Most manufacturers developing devices for indications such as tissue perfusion have been successful in gaining clear- ance for their devices as Class II technology.

Historically, FDA has required device manufacturers to submit PMAs for indications that involve claims of cancer detection. In the assessment of these devices, it is critical to remember how the imaging information will be used during the procedure by the surgeon, and that this forms just one piece of information, whereas the surgeon will consider all the information avail- able to them at the time including visual and tactile information, aided also by frozen section pathology. As with other aspects of optical imaging technology regulation, the FDA may be further refining its position on this classification of FGS systems. One example of such regu- latory evolution is the De Novo application. Prior to the De Novo option, a device with a Class II risk was automatically re-designated as a Class III device requiring an PMA submission, if no substantially equivalent predicate device exists and the 510(k) application fails.[27] The De Novo path offers another route by which a new device can demonstrate its indication safely and appro- priately without the burden of a Class III designation. In all these premarket filings with the FDA, the device can be cleared for sale if the application is deemed successful, but the strategy of which pathway to choose occurs early on and can be extremely expensive if chosen incorrectly, or highly cost saving if an easier path is found. These costs directly contribute to the success or failure of the field, and so a study of these regulatory issues is synergistic with the development and testing of device technology.
An examination of trends in clearances for the same indication can be illuminating. Alternatively, additions of indications to an existing approved device are a well-established path- way to broaden its intended use and subsequent market. Specifically, there are important lessons in the synergy across different surgical sub-specialties. The device clearances that have occurred across technologies have been critically important to advance FGS, for example where an indication in vascular flow in retinal imaging can be used to justify an indication in tissue flap surgery to assess vascular perfusion. There have not been that many explicit examples of cross- ing sub-specialty, as often companies focus within a subspecialty and work on a range of tech- nologies within that field; however, these cross-specialty indications are key to expanded use of FGS.

Recently, several 510(k) clearance applications from different companies have clustered around a set of indications in open surgery, where devices are cleared by a single predicate. This pathway in a proven medical indication leads to the fastest commercial success, although it can be limiting for the field if there is insufficient penetration to yield success from multiple devices. In the end, comparisons of clearance pathways that have been successful in translation will be important, given that this interdisciplinary cross communication is often driven both by the companies and between surgeons and specialties. This review takes a historical view of the pathways and describes the commercial successes in that context.

History of New Imaging Agent Approvals as Fluorescent Agents

The history of retinal angiography is longer than any other use of exogenous fluorescence in medicine with experimental use dating back to 1961, and FDA NDA occurring in 1972. Fluorescence angiography of the eye evolved early and is dominated by fluorescein because of its value in surface imaging angiography with the Heidelberg retinal angiograph. However, imaging of deeper choroidal circulation was not possible with this, and so ICG was used as an imaging agent for this lower layer of the eye. The absorption mode was used initially, and later fluorescence was exploited. Still despite the differences in use, the market for fluo- rescein in fundus imaging appears stronger than ICG (see Fig. 1), indicating that the value of surface imaging appears stronger than subsurface, in this indication.
The translation of ICG fluorescence to other indications occurred through many investigator- led studies through the late 20th century, leading up to the first regulatory clearance application for use in surgical guidance by Novadaq with their 2005 clearance for the SPY SP2000 (see Fig. 2). The importance of this milestone is that this indication was approved with a new device, being based partially upon equivalence to x-ray vascular imaging of tissue, and partially upon fluorescence fundus imaging (see Fig. 3). This led to expanded use of ICG in a range of indication



Karl Storz D-Light C Photodynamic Diagnostic system for blue-light cystoscopy. The next NDA for ALA was through the 2017 Gleolan NDA for neurosurgical resection guidance of glioma. This latter NDAwas a milestone in that two imaging systems existed at the time of this NDA, and the approval was not tied to use of either of them.

The transition from ICG and fluorescein to ALA-based agents marks the transition from vascular/perfusion imaging to tissue-based metabolic probes. This brings with it a signal that is 100× lower than ICG and likely 1000× lower than Fluorescein. The need to have better back- ground rejection is much higher, and the motivation to quantify the signal is higher, because it is not being used as a binary indication of flow, as ICG often is. Rather it is used as a probe of metabolism, which has large variations in production.

MB has never been approved as an FGS agent due to a range of reasons, including toxicity and low fluorescence yield. It is not clear that it will reach approval despite the large numbers of investigator-initiated human studies with it. Perhaps most importantly, MB is a generic imaging agent and used for a diagnostic purpose, as such most industry will be unlikely to accept the costs associated with advanced phase trials and so further development with it as an FGS agent is in question. It will likely remain an absorption-based agent for lymph node mapping, and the low emission yield may limit its use as it would have features such as ICG, but within the edge of the visible spectrum, which is less desirable technically because of room light contamination. However, its spectrum of absorption and emission can match that of ALA-PpIX, and so there may be synergy in the use of FGS systems designed for the latter, being applied to MB applications.

Pathways

The origins of surgical guidance with fluorescence are intimately tied into the NDAs and device clearances, but the approval of a new indication can be accompanied by a new device, or the new indication can be approved for an existing device. Perhaps most interestingly, the existence of several cleared devices in laparoscopic and open surgery has led to growth in new indications with the same devices in recent years. In this section, indications are reviewed, which are some- times tied into new devices, or sometimes just cleared based upon existing devices. These regu- latory milestones

Open Surgery FGS Indications

The original clearance for the SPY SP2000 was for "intra-operative visual assessment of the coronary vasculature and bypass grafts during CABG surgery" (K042961, 2005). It was cleared as a combination product, whose primary mode of action was mediated by the device. This judgement by FDA allowed the SPY SP2000 to be cleared by 510(k) with the provision that the ICG be over labeled to include indications for use in angiography that specified dosage, route of administration, and period of imaging. The same device later became cleared for the more widely used indication of "visual assessment of blood flow as an adjunctive method for the evaluation of tissue perfusion, and related tissue transfer circulation in tissue and free flaps used in plastic, micro- and reconstructive surgical procedures." (K063345, 2007). It was later cleared for surgeons to "visually assess blood flow and related tissue perfusion during organ transplant procedures" (K073130, 2008), and then for "visual assessment of arterial and venous blood flow and related tissue perfusion during GI surgical procedures" (K100371, 2010). With the develop- ment of the endoscopic systems, the Spy Scope (Pinpoint) was cleared (K091515, 2009), and its use was broadened (K150956, 2016) to a much wider indication band allowing "surgeons to perform minimally invasive surgery using standard endoscope visible light and visual assess- ment of vessels, blood flow and related tissue perfusion, and at least one of the major extra- hepatic bile ducts (cystic duct, common bile duct, or common hepatic duct), using near-infrared imaging." Additionally, "fluorescence imaging of biliary ducts . . . with standard of care white light." These broader indications allow a much wider range of use and facilitated larger growth in surgical use. In more recent clearances, it has been approved for interstitial administration of ICG and "intraoperative fluorescence imaging and visualization of the lymphatic system, including lymphatic vessels and lymph nodes" (K200737, 2020). This new route of administration for ICG required Novadaq to pursue a new NDA for its own ICG via the 505 (b) (2) pathway, for a brand of ICG that is specific to device clearances for lymphatic applications.[34] There are other clear- ances for new systems and new packaged forms of ICG, but these clearances that broadened the use cases of ICG imaging have brought in other surgical specialties into the use of both the handheld open surgical systems and the endoscopic systems. More discussion of systems appro- vals is in the later section on New Device Clearances.

Neurosurgery FGS Indications

Neurosurgery FGS research existed as early as 1948 with fluorescein,[35] although this was never approved for human use until 2017. The use of ICG for angiographic imaging was first approved in 2006 (K061871) by the Leica FL800, and later in 2010 (K100468) by Karl Zeiss INFRARED 800 and FLOW 800. While these were successful, the ability to see the surface vascular clarity of fluorescein was cleared in 2017 (K162991) in the Zeiss Yellow 560.

Interestingly the predi- cate for this latter indication was the SPY SP2000 system, showing the lasting power of older established device predicates, even though not in the same indication.

Arguably the largest change in FGS occurred in 2017 with the NDA approval of Gleolan by NX Development Corporation as a metabolic indicator of tissue malignancy. What is most inter- esting about this NDA is that it was not linked to a device, although there were two devices used in early studies. The Zeiss BLUE 400 fluorescence system was able to be marketed directly as a Class I product, given that all surgical microscopes are viewed as Class I products. This was perhaps a final milestone in fluorescence guidance systems as low-risk devices. Part of the rationale for neurosurgical imaging devices being class I is that they are supplementary to the neurosurgeon directly viewing the fluorescence by their eye through the binoculars, and indeed all early imaging of ALA-PPIX in glioma neurosurgery was done by surgeon vision. Thus, the risk of the imaging system itself was viewed as low, given that it was considered supplementary to the neurosurgical procedure. However, by 2018, the Leica FL400 system was required to be cleared as a De Novo application (DEN180024), categorized as a class II device. This change in the regulatory pathway appears to have been related to the use of optical filters changing the information stream, and so the Leica FL400 system used the SPY SP2000 as an established predicate for vascular imaging with filtered fluorescent light imaging. These two devices, the Zeiss BLUE 400 and the Leica FL400, illustrate how complex and mixed the process to approve these devices can be, especially when they are approached as attachments or add on to existing systems, as is typically done in neurosurgery.

Endoscopic FGS Indications

The origins of endoscopic use with FGS has a longer history based around endogenous visible emission imaging. The first of these were approved in 1996 by Xillix in the Life-Lung broncho- scope as a PMA (P950042 S001),[36–38] and later approved as the Onco-Life Endoscopic system (P950042 S003) in 2005,[39–41] and subsequently re-branded (P950042 S003) by Novadaq in 2007.[42] Modern use of exogenous agents with endoscopic systems started with the approval of the SPY Scope in 2009 (K091515) and rapidly expanded with robotic surgery use in 2010 with the Intuitive Surgical da Vinci Fluorescence Imaging Surgical System (K101077), and eventually the Firefly system in 2014 (K141077).[43–47] Several other systems have been cleared as well, but the linkage to open surgery is less apparent, and so a detailed analysis of this surgical subspecialty is not the focus of this review. The market use for ICG has grown with these devices and will likely continue as procedures and adoption grows.

Bladder Indication

Cystoscopy with fluorescence has only one set of approvals that included both an NDA and a PMA for using hexaminolevulate HCl (CysView®) (NDA 022555) contrast that is instilled in the bladder, and visualization with the Karl Storz D-Light C system (P050027 S010). The develop- ment of this in Europe preceded the NDA approvals by the FDA in 2010 and the adoption of this methodology has been slow, due to the complexity of instillation and incubation time. Today though this indication appears promising, although issues around instillation into the bladder and integration into current practice is a topic of interest.

New Device Clearances in Open Surgery—Predicates and New Pathways

Perhaps no other single clearance has been as important to open surgery as 2005 510(k) of the SPY Intraoperative Imaging System SP2000 to be used with ICG, developed by Novadaq Technologies Inc. (K042961). What makes this clearance most notable is that it had two predi- cate devices designated that were distinctly different than the applicant device, including the Philips Integra Series 2 Angiographic x-ray system (K984545) which was for diagnostic quality images during cardiac, vascular, neurovascular, and interventional applications. There was a second predicate device, the Heidelberg Retinal Angiographic System (K944261) which was for imaging the posterior segment of the eye and could be used with ICG. The applicants suc- cessfully argued that the SPY system could match combined functionality of the combination of these two predicates when imaging vascular perfusion. This kind of split predicate is less common in more recent device clearances. After this clearance, most 510(k) applications used this SPY device or equivalent devices to it, as their predicate (see Fig. 3). This pathway relies on the more obvious argument that the subsequent devices perform the same function of imaging tissue perfusion by fluorescence following intravenous administration of ICG. To achieve clear- ance, the SPY system had to show it complied with all IEC and UL requirements, and complete animal and human testing. Taken together this is an expensive and time-consuming series of studies. However, the lesson of this single clearance is that it is possible to make the argument that fluorescence imaging is substantially equivalent to x-ray imaging for the purposes of assessing vascular function.

Subsequent devices are shown in Fig. 3, where the cascade of clearances around the range of open surgery indications is clearly targeted. The five major companies that have advanced systems to the pre-market approval [Hamamatsu, Fluoptics, Quest Medical, Visionsense (now Medtronic), and OnLume], have each benefitted from the predicates available to them from the SPY Novadaq systems (now Stryker). These clearances are not surprising, and are rather an indication of a growing market that can likely support more than one system on the market.

Discussion of the differences or critical considerations for these devices is outside the scope of this paper but was recently reviewed, however, it is worth commenting that light control (in/ out/filtering/intensities) and software ergonomics are probably the key elements that will drive the success or failure of device.

NDAs for fluorescence imaging agents have historically been driven by imaging agents that were not originally approved for use as fluorescence technology. ICG and fluorescein were originally approved as absorbing dyes. Similarly, MB and different forms of ALA were approved for their therapeutic value, not their fluorescence. It is fascinating to see how the lateral translation of these dyes into diagnostic use was facilitated by NDAs that were driven by different company efforts. In instances when imaging agent NDAs were approved and the imaging agent was avail- able for immediate use with multiple devices (e.g., such as Gleolan with Zeiss and Leica micro- scopes), this was only possible because the devices used were historically classified as a surgical aid and Risk Class 1. More commonly, the barriers to approving a new imaging agent-device combination for surgical visualization are high, and this will likely continue to temper the rate of new market entries with the most successful entrants targeting only the most profitable procedures.

For FGS devices, PMA approvals are generally less common than 510(k) clearances, simply because of the investment required and the business risks involved in establishing a fundamentally new device and indication. The 510(k) pathway represents a lower regulatory burden and con- sequently also a lower risk proposition. Of course, the drawback of the 510(k) pathway is that the indications for use may be less compelling (as they are not life sustaining) and there is likely more competition in the market. The growth of newly cleared Risk Class II devices around the same set of indications has been what is occurring in open-field FGS systems, as shown in Fig. 3. The field is expanding and the indications for use with these devices are expanding, and so several com- panies are offering devices to serve the needs of specialty surgeons and their techniques.

One of the most striking approvals was the 510(k) clearance of the SPY SP2000, mostly because it was for an indication based upon predicate devices that were arguably quite different devices. The use of such a split predicate is less common in recent clearances, however, the SP2000 history demonstrates that when argued carefully, this approach has been strategically successful in gaining a market clearance which might otherwise have required a De Novo clear- ance or PMA approval. Both latter pathways are more complex in argument and carry a higher risk in approval. Perhaps most interestingly, although the SP2000 is no longer being manufac- tured, it remains the traceable root predicate in clearance of several subsequent devices from multiple companies. Clearly, this single approval is one of the major events in the history of FGS in open surgery.

As the field of FGS grows, these open surgery tools are now gaining a widespread adoption, and as surgeons recognize the capabilities of these tools, there is a lateral spread of the tech- nology into other indications and/or other surgical specialties. These new indications for existing cleared FGS devices and imaging agents broaden the use driving FGS toward a standard of care and creating an environment that encourages further investment in the development and com- mercialization of this promising technology.

The value of the global pharmaceutical market is expected to grow 5-7 percent in 2011, to USD 880 billion according to IMS Health. The pharmaceutical industry is one of the highly regulated industries, to protect the health and well being of the masses. The structures of drug regulation that exist today i.e. drug laws, drug regulatory agencies, drug evaluation boards, quality control laboratories, drug information centers, etc., have evolved over time in response both to the increasingly sophisticated pharmaceutical sector, and to the apparent needs of society. In some countries, the passing of comprehensive drug laws was a result of crisis-led change, when public demand led to the adoption of more restrictive legislations to provide stronger safeguards for the public.

While drug laws provide the basis for drug regulation, regulatory tools such as standards and guidelines equip drug regulatory authorities with the practical means of implementing those laws. Though the world pharmaceutical regulations are in continuous process of harmonization, they can be divided into four major categories based on the region, development strategy, regulations and marketing interest.

- ♣ North America (US, Canada)
- ♣ Europe (Europe Union, Eastern Europe)
- ♣ Rest of the World (Asia Paciic minus Japan, ANZ, GCC, LATAM, CEE, CIS)
- ♣ Japan

(LATAM: Latin America; CEE – Central East Europe; CIS – Commonwealth Independent States; ANZ – Australia, New Zealand; ROW – Rest of World)

Based on the economy and regulatory control of the countries, these are grouped into Regulated markets (US, EU, Japan, ANZ) or Emerging Markets (ROW excluding ANZ). They not only differ by their region, but also in various other aspects like: how they regulate the pharmaceuticals, the different guidelines for registering the drugs, requirements to maintain the registrations, registration fee, patent regulations and so on. In this article, we will briely touch upon the different regulatory perspectives of these regions mainly emphasizing on US and EU and its effect on the pharmaceutical manufacturers.
Both USA and Canada are the major markets in the pharma industry. The US enjoys the largest player tag in terms of value in the pharma sector. It is valued approximately at USD 300 bn in 2009. The US has evolved from no regulation in the 18th century to one of the highly admired, favorite regulatory authority in the world. The Food and Drug Administration (FDA) within the U.S. Department of Health and Human Services, regulates the drug approval system in United States with the help of six product centers including Center for Drug Evaluation and Research (CDER) and Center for Biologicals Evaluation and Research (CBER).
The drug registration procedure in US is majorly categorized into three parts, New Drug Applications (NDA), Abbreviated

New Drug Applications (ANDA) and the mix of both which is widely called as 505 (b)(2) Applications. Fig. 1 illustrates the different kinds of routes available to get the registration of pharmaceuticals in US under the Section 505 of the 'Federal Food Drug and Cosmetic Act'.
Till 1980s, mostly innovators dominated the US pharma market. The introduction of "Drug Price Competition and Patent Term Restoration Act of 1984" i.e. HatchWaxman Act can be termed as birth of generic industry in US which helped generic companies to lourish in US.

505(b)(1) or New Drug Application (NDA):
This route is mainly used to get the approval for New Chemical Entities (NCE) which contains full reports of investigations of safety and effectiveness (Pre-clinical, Phase I to Phase IV study reports). NDA is preceded by the Investigational New Drug Application (IND).
505(b)(2) Application:

This application is same as full NDA, except that this NDA is based on "investigations … relied on by the applicant for approval of the application …and for which the applicant has not obtained a right of reference or use. The applicant majorly relies on published literature, FDA's Federal Register. This route is often used for changes to an approved drug (Change in dosage form, strength, indication etc.)
505(j) or ANDA or Generic Drug Application:

This section is used for obtaining marketing authorization of exact or close copies of already approved drugs. The application is submitted under any of the below subsections of 505(j) of Federal Act In Canada, the manufacturer may seek authorization to sell the product in Canada by iling a New Drug Submission with Health Products and Food Branch (HPFB). A New Drug Submission (NDS), typically contains scientiic information about the product's safety, eficacy and quality. It includes the results of both the pre-clinical and clinical studies. An Abbreviated NDS (ANDS) is used for a generic product. The generic product must be shown to be as safe and eficacious as the reference product usually established with bioequivalence studies.

A Supplemental NDS (SNDS) must be iled by the manufacturer if certain changes are made to already-authorized products. Such changes might include the dosage form or strength of the drug product, the formulation, method of manufacture, labeling or recommended route of administration. An SNDS must also be submitted to HPFB if the manufacturer wants to expand the indications (claims or conditions of use) for the drug product.

Other factors for consideration:
Patents Scenario
All developed nations (US, EU, Japan, ANZ) have established a product patent which runs for 20 years from the date of patent iling. In US, Japan, Australia the original patent term can be extended by a maximum of ive years, if undue delays take place during the regulatory approval.

In case of Para IV application in US, it is mandatory for the manufacturer to notify the original patent holder, who can take up to 45 days to bring an infringement suit against the manufacturer, if he feels his patents are being violated. However, if no such action is taken within the stipulated period, certiication of the ANDA applicant will be accepted by the FDA. If an infringement action is brought in time, FDA suspends approval of the ANDA until the date of court's decision or up to 30 months. If the court's decision goes in favor of the patent owner, FDA suspends the approval till expiry of the patent.
In EU member states, an extension of the patent term is obtained by seeking a supplementary protection certiicate (SPC). The SPC regime came into force in the European Community on 1 January 1993 but has not been uniformly implemented by all European countries. The SPC takes effect for a maximum of 5

years after the expiry of the original patent term; however, the exact length of the extension granted under the Regulation is determined by national law. Applications for the SPC must be iled on a country-by-country basis. There is no unitary European SPC. In developing regions, countries like Brazil, Argentina, Canada, China, India, Malaysia, Russia, Taiwan, and South Africa have 20 years of patent term. The term can be extended up to 5 years in some of these countries.

Exclusivities

Data exclusivity is a period granted to the innovator companies in which no other company can ile any type of application for that particular molecule. There are other exclusivities available to promote the company which engages in the innovation or incremental innovations. Table(3) summarizes the various exclusivities available in three major regions.

It is very critical to understand the data exclusivities in various regions in order to estimate the iling timelines of applications as well as to determine the marketing strategies.

Components of regulatory iling and Data Requirements

The US, EU and Japan are a part of International Conference on Harmonization (ICH), hence the technical requirements for registration of Pharmaceuticals follow the ICH recommendations. These countries require data as per the requirements of Common Technical Document (CTD). The CTD is organized into ive modules. Module 1 is region speciic and Modules 2, 3, 4 and 5 are intended to be common for all regions. Rest of the region / countries insist on following ICH region for some data like stability, clinical trials though it follows majorly its own regulations. For instance, the ASEAN countries require data as per ASEAN CTD (ACTD) which is same as ICH CTD for data requirements organized in Parts. The brief contents of CTD and major requirements for various regions.

Indian Regulations

India being the leading supplier of API and generic drugs to the world, it is important to understand the Indian requirements and regulations associated with pharmaceuticals. When the applicant intends to develop and export the pharmaceuticals, it is necessary to comply with regulations set forth in the Drugs and Cosmetics Act 1940 and Rules 1945. There are some necessary licenses to be obtained as mentioned for developing and exporting the drug products.

An increase in the development by non-global companies could have an important impact on the issue of global regulatory approvals. Because most therapeutic agents for hematologic malignancies were first approved in the US, it is important for each country to make these agents available at the earliest through the review and approval process. At this point, nonglobal companies typically do not have offices worldwide, and pivotal trials for the US approval conducted by non-global companies may be performed in limited regions. Previous reports have suggested that drug approval delay is still a crucial problem in countries outside the US, and enrollment of patients from various countries in global clinical trials is one promising approach to shorten approval delays. Since clinical trials conducted by non-global companies may fail to include participants from various countries, approval of novel drugs from non-global companies could be particularly delayed in countries outside the US. Actually, there is a major concern in Japan known as “drug loss,” which means that drugs mainly for rare diseases from non-global companies are not introduced in Japan for long periods of time after the US approval. However, detailed analyses focusing on the clinical trials of drugs from non-global companies and their impact on the EU have not been fully evaluated.

CONCLUSION:

The optimal framework for the regulatory approval of medical innovations remains unclear. This study suggests that many new devices do receive regulatory approval but often lack clinical trial data supporting their safety and effectiveness. The IDEAL model makes several proposals for the staged introduction of innovations in surgery (and other disciplines that offer complex interventions), including randomised controlled trials to assess safety and effectiveness. At present, few relevant randomised controlled trials are published, and fewer still meet current quality standards for optimal reporting. Changes in the regulatory approval of devices that would require trials for proof of safety and effectiveness might promote adherence to the IDEAL model.

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