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Review Article

Compliance Challenges in Medical Affairs

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ABSTRACT

The role of Medical Affairs has dramatically evolved over the last couple of years to the point it can be considered as the new "Center of Gravity" of many pharmaceutical companies. Not long ago, the role of Medical Affairs professionals was limited to addressing questions asked by prescribers to sales representatives. Then, mail was the preferred channel of communication, when today health care professionals and patients are computer savvy and access internet several times a day. Today, these Medical Affairs departments have a much larger role, including publication management, KOLs identification and management, Medical Science Liaison management, interaction with patients' organizations, just to name a few. Indeed, in 2020 most stakeholders are no longer satisfied with demonstration of efficacy and safety; what needs to be demonstrated is the value and value increase provided by new treatments. But at the same time, the hurdles to demonstrate value are higher.

This evolution did not go without new challenges, particularly in terms of compliance, that are currently only addressed to a limited extend. Indeed, Customer-facing and proactive informational efforts can look commercial in nature. As medical affairs teams align more with the commercial sectors, they can be considered as potentially compromising the benefit of medical affairs' independent perspective and judgment.

Different approaches have been implemented to address these compliance challenges, keeping in mind that very significant penalties have been imposed in case of compliance infringements. There will always be a certain ambiguity in this medical affairs role; however, a corporate culture of compliance, the absolute priority to building trust with Health Care professionals, the embedment of compliance professionals in the Medical Affairs departments are some of the emerging solutions, in a context where the limits between compliance and non-compliance are often blurry.

At the end of the day the most valuable asset is "trust" by all stakeholders, and this is not to be compromised by short-term business objectives.

INTRODUCTION

In the 80's, the role of medical affairs was limited to training of sales representatives, reporting of adverse events and addressing questions from HC providers, forwarded by pharma sales representatives, either by phone or regular mail. In other words, this was at best a support function to commercial, often seen as a "sales prevention department" by marketing and sales executives. Mail and phone were then the main communication channels, as MINITEL (an internet ancestor) was not even available. Obviously, the landscape has dramatically changed.

Medical affairs departments now play an increasingly vital role for pharmaceutical companies [1]. Their role is multifaceted and include KOL management, MSL training and management, publication management, Health Economics and Outcome Research, interaction with patients' organizations.

Indeed, the role of patients will also fundamentally change with the rise of consumerism in healthcare, the fact that patients go very often online to get up-to-date information on their diseases and possible emerging therapies. Another important evolution is represented by the fact that Physicians role is reduced in drug decision is much more limited; this evolution has been seen for already couple of years with the adoption of generics and is now seen with biosimilars, for which new stakeholders (payers, pharmacists) play a larger role. Indeed, even if for biosimilars, non-medical switching is not universally accepted, there is little doubt that, with the current economic crisis, switching reference compounds by biosimilars is very likely to become the norm and not the exception.

Another important evolution is that pharmacos have backed off the traditional sales rep model and Medical Affairs emerged in their wake with a major expansion in the number and role of field based Medical Science Liaisons (MSLs). Not long-ago representatives visited prescribers up to 3 times a week to deliver marginally different messages; it's clear today that access to HCP by traditional sales reps has been drastically limited, for prescribers have no time to waste and also for credibility of these commercial messages was more and more limited. As the government has heightened its scrutiny of drug promotion, companies have backed off the traditional sales rep model. Medical affairs emerged in their wake.

Medical Affairs personnel have both scientific and clinical experience; their role mainly consists in delivering to health care professionals accurate, fair and balanced, high value medical information. One of their challenges is that they also are a "bridge" between R&D and commercial departments and at the same tine a "firewall" between these 2 functions.

Medical affairs personnel have a variety of functions:

- management of key thought-leader relationships, including KOLs Advisory Boards
- interaction with patients' organizations
- developing educational information programs,
- medical writing,
- internal training,
- answering off-label questions from healthcare providers,
- managing Investigators Initiated Studies (ISS),
- publication management,
- Health Economics and Outcome Research,
- in some organizations, pharmacovigilance is also part of the medical affairs function,

Hence, as highlighted in the diagram below, Medical affairs have multiple interactions with different departments, such as drug safety, business development, clinical research, market research, competitive intelligence, public relations, marketing, public relations.

COMPLIANCE CHALLENGES, THE GREY AREAS [1-4]

"Neurosis is the inability to tolerate ambiguity." S. Freud

Off-label promotion, not disclosing negative trial results while touting positive results, inadequate CME programs, are not only damaging pharmaceutical company's reputation, they can lead to expensive settlements. Below are mentioned some of the Medical Affairs department activities in which some level of ambiguity may be difficult to avoid:

Investigator initiated studies (IIS)

Are clinical studies initiated and managed by a non-pharmaceutical company researcher, like individual investigators, institutions, collaborative study groups or cooperative groups. They can help by generating data on effectiveness and safety of a drug in the real-world

environment and attempt to address questions that clinicians face in their day-to-day practice. Literature abounds in several IISs that have changed the way medicine is practiced. In principle, pharmaceutical companies have no say in the objectives, design, endpoints of these studies; they are supposed to approve and fund them uniquely based on their scientific merits. Unfortunately, experience shows that these IIS can be "inspired" by Medical Affairs, which is not in line with the official purpose of these studies. Even, if Medical Affairs does not interfere with the study design and objectives, they naturally tend to approve and fund those that at a minimum will not hurt the product image.

Publication management

Most pharmacos are officially committed to publish all meaningful data they generate; however, the trials that will be published depends to a large extend on what the company wishes to publish, in support of the product communication. Officially, the principal investigator of a trial is supposed to be free to design the trial and publish the data as he feels appropriate; however, he/she is entirely dependent on the sponsor providing him the data, the statistical analysis, and experience shows that investigators not always have the resources, the expertise to adequately evaluate the data submitted by the sponsor. Usually the sponsor keeps the right to review trial data and discuss the publication draft with the investigator, which can delay the publication. The trial report is nearly always drafted by a CRO appointed by the sponsor and quite often, the sponsor's medical writing team is providing the investigator with a publication draft, that the principal investigator is supposed to review and validate.

KOL management [5,6]

The term itself of KOL management shows the way KOLs think and publicly provide guidance on treatments can be influenced by the Pharmacos Medical Affairs departments; first, KOLs do get compensated for their participation to Clinical Experts Advisory Boards, participating to such Boards is usually as a sign of acknowledgment of their expertise, a chance to provide input in the development of new therapies. Selection of participants of such Ad Boards is a challenging exercise, trying to find the right balance between expertise/credibility of these groups of experts and ensuring they will provide adequate support in line with companies' objectives. One of the additional challenges is that these top-KOLs are often advisors of several competing companies and confidentiality may represent an additional challenge.

Medical information programs

Prescribers are supposed to get their medical information on new therapies from perusing literature, participating to relevant congresses. In practise, many of them are overwhelmed and get their continuous medical education from their interaction with Medical Affairs Liaisons and Medical Education Programs sponsored by Pharmaceutical companies. These programs are usually "accredited", are of good quality and present a fair and balanced perspective on the topic to be presented. It remains that the selection of topic presented is often biased, based on the topics a company wants to illustrate, in support to their communication strategy.

Interaction with patients' organizations

The development of new medicines is undertaken to improve the health and outcomes of patients. However, until recently, patient involvement in biopharmaceutical development has often been infrequent, episodic and restricted to the periphery apart from direct participation in clinical trials and post-approval activities such as disease education. More recently the concept of 'patient centricity' [4] and the opportunity to include patient-centred activities in drug development has been a key topic of interest. Most pharmaceutical company officially state they are "patient-centric" and many have created specific departments, often part of Medical Affairs to ensure patients' input into drug development is considered. Regulators also want to ensure the development program that are submitted for approval are not ignoring patients' perspectives, e.g. clinical trial feasibility, relevance for patients of study objectives and endpoints.

Obviously, this patient centric approach has obvious merits but expose to the risk of presenting biased information to an audience of non-specialists and influencing them in a way that is not entirely appropriate [7].

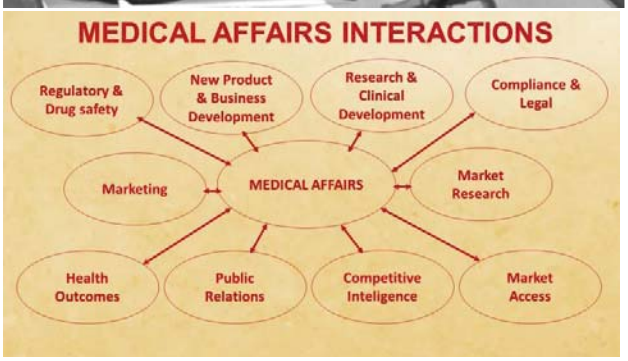
One more potential compliance challenge is represented by the fact that many Patient Advocacy Groups (PAGs) rely on pharmaceutical funding, either as unrestricted medical grants or project funding provided for a specific activity, which must be declared by the pharmaceutical company.

Withdrawal of funding can present a PAG with a funding crisis. This is where early transparency, and a clearly defined, detailed, agreed contract, can minimise the risk of reputational damage.

HEOR and value demonstration

As a scientific discipline that quantifies the economic and clinical outcomes of medical technology, HEOR helps manufacturers of pharmaceuticals and devices communicate the value of their innovations to stakeholders.

As local payers come under more pressure to constrain costs, the value of Health Economics and Outcomes Research (HEOR) is increasing. Hence, HEOR, once considered a mere support function, is now playing a central part in the internal decision-making process.



Source AGNODIKI medical consulting.

Indeed, HEOR can't simply be bolted on at the end of the process. An important part of this is making sure that phase 3 registration trials have both economic as well as clinical endpoints, so that the data is available to market access teams later. HEOR can provide data to help healthcare payers determine if treatments work in the populations they serve, and how much of the drug or treatment cost should be reimbursed by the healthcare system. Companies often must show decision-makers that the drug's price is worth the expense because the product will cost-effective in the long run–perhaps by leading to less hospital admissions.

Compliance issues can obviously emerge in interactions between commercial payers and HEOR personnel. Couple of potential compliance questions should be discussed between Medical Affairs and Compliance executives. These questions go around which studies are funded and not, which studies (positive and negative) will be used in the interaction with payers. HEOR discussions with managed markets are indeed one of most contentious issues and the toughest to fully plan for.

Key performance indicators?

One of the additional challenges is the wish to measure the impact of Medical Affairs; it is an old saying that one cannot manage what you can't measure. it is indeed very challenging to measure the true impact, the value that scientific and medical information has on patient care. Different Key Performance Indicators (KPIs) have been suggested and to some extend implemented: number of "meaningful" contacts with opinion leaders, the number of new research projects, the number of publications in peer-reviewed journals, number of Clinical Advisory Boards have all be used to assess the impact, if not performance of MSLs and more generally medical affairs. They have the merits of strictly measuring scientific topics, but not without obvious limitations, e.g. the time between availability of clinical data and their publication can easily take up to 2 years. One example is of is represented by check-point inhibitor immunotherapies, whose the first journal papers did not appear until 2016.

FDA guidance [8-10]

The recent (2018) FDA guidance on "Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers- Guidance for Industry" does provide useful information for firms about how FDA evaluates firms' medical product. The purpose of this guidance is "to provide clarity regarding FDA's thinking when examining the consistency of a firm's product communications with that product's own FDA-required labelling". FDA uses three factors to determine whether the representations or suggestions in a product communication are consistent with the product's FDA-required labelling, acknowledging these different factors can overlap. As stated in this guidance," simply analyzing whether there is a conflict between the information in the communication and the FDA-required labelling is not always sufficient to determine whether a communication is consistent with the FDA-required labelling". All these elements show the complexity of complying the FDA regulations on this matter. The distinction between "solicited" and unsolicited" request is addressed in another FDA guidance. This is so complex that the FDA drafted several pages, illustrated by multiple examples to clarify the differences between these 2 types of requests.

EMERGING SOLUTIONS

Based on the above, one could conclude that this area of Medical Affairs represents from a compliance perspective a mine field. Clearly, there are significant challenges but also emerging solutions that can help companies be truly compliant.

SOPs

The FDA considers requests for off-label information that are "prompted in any way" by a manufacturer or its representatives to be solicited requests.

FDA is mainly concerned that a company intended the drug be used outside of what was specifically approved or cleared by FDA.

Here again the border between solicited and unsolicited request is not clear-cut, as the discussion can be oriented in such a way that prescribers officially, formally request "off-label information".

Hence, detailed SOPs are clearly needed to help Medical Affairs staff, particularly MSLs who need clear guidance on what they can and cannot say. These SOPs must impose a thorough documentation of communications; these SOPs do not have to be only written; In real life, a complex lengthy set of written SOPs are unlikely to be fully implemented; videos, Apps can help achieve the compliance objectives. Of note, it is useful to ask Medical Affairs to draft their own SOPs, under Compliance specialist guidance; this is the safest way to ensure these SOPs are relevant; SOPs drafted by compliance departments and given "over the wall" to Medical Affairs are unlikely to be truly adopted and complied with.

However, one should keep in mind that SOPs may be tough to write for "grey-area" issues and provide limited support if a strong corporate culture of compliance is not communicated to all employees by company executives.

Compliance audits and Inspections

Many pharmacos do audit their medical affairs departments to ensure the MSLs fully comply with company SOPs. This model has its limits and continuous readiness models may be more efficient than traditional audits and inspection models.

A corporate culture of transparency

Large pharmacos that have a long-term perspective and vision see the value of compliance in all areas, including Medical Affairs. This policy can have short-term challenges, in the promotion of on compound or the other, in one geography or the other. However, the value of "trust" by relevant stakeholders, including prescribers is more critical than short-term sales objectives. This vision needs to be clearly communicated as often as needed by senior management. This will help address the following topic, namely talent retention.

In Europe, the transparency of this collaboration between pharmaceutical industry and medical doctors has been made possible by the Compliance and Disclosure Policy published by the European Federation of Pharmaceutical Industries and Associations (EFPIA), which represents the major pharmaceutical companies operating in Europe, and includes as members some but not all companies active in infertility and women's health. Under the EFPIA Disclosure Code of conduct, companies need to disclose transfers of value including amounts, activity type and the names of the recipient Health Care Professionals and Organizations. EFPIA member companies have also implemented very strict internal quality control processes and

procedures in the design, statistical analysis, reporting, publication and communication of clinical research, according to Good Clinical Practice and other regulations, and are regularly inspected by competent authorities such as the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) for all trials used in marketing authorization applications

Patients truly at the center of all pharmaceutical companies endeavors

As consumers become increasingly more engaged in their own healthcare decision-making, healthcare stakeholders must evolve their strategies to address the needs of patients as consumers. They already seek solutions, tools, and information that help them focus on costs, quality, and convenience. In the very near future, consumers will be taking much more control over their healthcare. In other words, Patients are no longer recipients of healthcare, they are active participants. Hence, pharmaceutical companies must find a way to stay relevant in a world where patients are likely to pay more and more. Research shows that companies should not only embrace this enterprise-wide approach of embedding patient-centricity efforts but prepare to participate in an emerging ecosystem where disease foundations, patient advocacy groups, health plans, health systems and physicians, regulators, competitors, and technology and wellness companies are all better connected so that the patient is truly at the center. One should also take advantage of existing and upcoming digital and data analytics opportunities to engage the patient and collect data on patient outcomes as well as their unmet needs. In other words, claiming a company is "patient-centric" as they all do in 2020 is not sufficient, a true internal revolution has to occur,

Human resources

The above-mentioned myriad challenges can only be met by upgrading human-resource capabilities and developing a deeper talent pipeline that extends into the upper echelons of the company. There was a time during which the least talented people were relegated to "medical information"; today to address the extend of knowledge and experience needed to fulfil the Medical Affairs function, companies need to hire and develop very talented people with both scientific background and are "commercially sensitive".

Measuring medical affairs impact in a compliant way

There is no magic bullet here; however solutions are available: Medmeme is leveraging the largest set of published science in the world so medical affairs teams can validate their activities, via a concept known as Share of Scientific Voice (SoSV). SoSV is the collective number of times a manufacturer's drug or molecule is noted in the scientific literature and it can be a critical factor of success in the years leading up to the launch of a new product. With its counterpart, Share of Scientific ImpactSM- a quality score that measures the impact of any given piece of scientific dissemination

Embedding compliance into medical affairs departments

In most pharmacos, there is a drug development department and a separate audit department; similarly, there is a Medical Affairs department and a Compliance department. These kinds of structure open the door to lack of collaboration, even distrust between these different entities. Indeed, clinical developers tend to consider the auditors as policemen, and Medical Affairs want to ensure they will not being caught by the "Compliance Police Department".

An alternative model, probably more challenging to implement but likely meeting better the overall objective of compliance is to embed compliance specialists within the Medical Affairs department; this has several benefits: Compliance managers will understand better what is happening in real life and possibly adjust their requirements and SOPs. A relationship of trust can develop if people are co-located in the same floor, leading Medical Affairs to consult compliance folks on a regular basis. This way compliance will be seen as a partner, not a policeman.

"At the end of the day, it's all about trust"

CONCLUSION

Compliance in the field of Medical Affairs is a challenging topic, especially considering the myriad of functions under the "Medical Affairs" umbrella.

These challenges can only be met by upgrading human-resource capabilities and developing a deeper talent pipeline that extends into the upper echelons of the company. Compliance audits and inspections can provide useful additional support. SOPs do need to be developed but nothing will not replace the need for developing a clearly company culture of compliance, regularly communicated throughout the organization by the most senior executives. A company culture of Patient-centricity, clearly stating that integrity is the norm, bringing under the same roof Medical Affairs and compliance specialists provides at the minimum the opportunity to improve the dialog and communication between the 2 entities. These are likely the most efficient ways to address the current mistrust of most stakeholders vis-à-vis the pharmaceutical industry.

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