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HCFI Expert Round Table on Off-label Use of Drugs, Disposables and Devices

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Off-label use means that the particular drug is used for an indication that is not otherwise approved by the regulatory authority, which is the Drug Controller General of India (DCGI) in India, and is not included in the package insert or label carrying instructions about indications, contraindications and dosing and other instructions. Off-label use of drugs is common in clinical practice all over the world.

The US Food and Drug Administration (FDA) allows the promotion of off-label use of drugs when there is strong supporting evidence on the safety and efficacy of such use. But, the benefits and risks of such use for an individual patient must be balanced before the drug is prescribed for an off-label use and the onus of responsibility lies with the doctor. Despite the widely prevalent practice, there is no clear guideline on the off-label use of drugs in India.

Hence, there is a need for a policy, which allows the off-label use of drugs for which there exists high quality scientific evidence.

Towards this end, an Expert Round Table on Off-label Use of Drugs, Disposables and Devices was organized by Heart Care Foundation of India (HCFI) to build a consensus around this issue and send recommendations to the regulatory authorities to formulate a guideline on off-label use of drugs in the country.

HCFI EXPERT ROUND TABLE SUTRA

"In absence of any unethical considerations or a safety issue AND in presence of strong international or national scientific evidence; off-label use in other country; guideline or consensus statement; prevalent use in the clinical practice ***WITH no reported side effects*** *under PvPI and the drug is not under RISK MAP category,* ***THEN*** *the use of the available DCGI approved drug (including medical devices and disposables) is justified for off-label indications under implied consent.* ***In all other situations, one needs to take an informed consent."***

DEFINITION OF OFF-LABEL USE OF DRUGS, DISPOSABLES AND DEVICES

Off-label use of drugs is the use of pharmaceutical drugs (drug, device, disposable) for an unapproved indication or in an unapproved age group, dosage or route of administration.

Marketing of pharmaceuticals for off-label use is usually prohibited. But, both prescription drugs and over-the-counter (OTC) drugs can be used in off-label ways, although most studies of off-label use focus on prescription drugs.

Off-label use is generally considered legal across the world unless it violates ethical guidelines or safety regulations.

More than 50% of all drugs are prescribed off-label based on available scientific and safety evidence and amongst psychiatrists and children, the number is even higher.

NEED FOR THE POLICY

In the matter of **Balram Prasad vs. Kunal Saha & Ors** on 24 October, 2013, the Apex Court said *"73. …….. In fact punitive damages are routinely awarded in medical negligence cases in western countries for reckless and reprehensible act by the doctors or hospitals in order to send a deterrent message to other members of the medical community. In a similar case, the Court of Appeals in South Carolina in Welch Vs. Epstein [31] held that* ***a neurosurgeon is guilty for reckless therapy after he used a drug in*** *clear disregard to the warning given by the drug manufacturer causing the death of a patient. This Court has categorically held that the injection Depomedrol used at the rate of 80 mg twice daily by Dr Sukumar Mukherjee was in clear violation of the manufacturer's warning and recommendation and admittedly, the instruction regarding direction for use of the medicine had not been followed in the instant case. This Court has also made it clear that the excessive use of the medicine by the doctor was out of sheer ignorance of basic hazards relating*

to the use of steroids as also lack of judgment. ***No doctor has the right to use the drug beyond the maximum recommended dose.***"

EXISTENT GOVERNMENT POLICY

As per the reply received by HCFI to a Right to Information (RTI) filed HCFI/March/2019/042 dated 18th March 2019, the Central Drugs Standard Control Organization (CDSCO) vide reply Z-28020/233/2019-DC dated 3rd May 2019 replied as under "Medical devices notified under Drugs and Cosmetics Act, 1940 are regulated as per the provisions of Medical Devices Rules, 2017. As per rule 44 (k) of Medical Devices Rules, 2017, if the device is intended for single use, it should be labeled appropriately. Further there is mention in Medical Devices Rules to label the device appropriately if the device is intended for single use.

Penalty in case of violation of any provisions of Drugs and Cosmetics Act, 1940 and Medical Devices Rules, 2017 will be prescribed as per the said Act and Rules.

Refurbishing of medical devices and disposables does not come under the purview of CDSCO. However, refurbishing of medical equipment comes under the Ministry of Environment, Forest and Climate change.

HAS DCGI ALLOWED OFF-LABEL USE OF DRUGS?

The government can ban off-label use of any drug as it did in the case of bevacizumab. On January 21, 2016, the DCGI took the bold step of prohibiting the use of intraocular bevacizumab as off-label treatment for various retinal diseases. Unfortunately, this decision put a large percentage of the population at risk of inaccessibility to treatment for common blinding retinal diseases. But, after 2 months, the DCGI agreed to withdraw the alert notice, enabling retinal surgeons to again use bevacizumab.

This decision may be a landmark judgment for India and other countries around the world to look at evidence-based off-label use of drugs.

Clearly, there is a need for an off-label policy.

The pharmaceuticals cannot be promoted or advertised legally. The onus therefore falls on the medical profession to "certify" the off-label use of drugs.

Time has come to formulate guidelines. We need to build a baseline document and draft suggestions to be sent to medical specialty societies cum associations and/or all medical stakeholders before sending it to the regulatory authorities.

LEGAL IMPLICATIONS WHEN THERE IS NO POLICY

In the present scenario, we need to protect ourselves from the legal risks. Even if there is scientific evidence showing the beneficial action of the off-label use of a drug, the first step should be to find an answer to counter the judgment to safeguard ourselves. All Supreme Court judgments are guidelines, till they are made into law. Once they become a law, they cannot be challenged.

- **Source of Law:** The main sources of law in India are the Constitution, statutes (legislation), customary law and case law. Statutes are enacted by Parliament, State legislatures and Union Territory legislatures. Besides, there is a vast body of laws known as subordinate legislation in the form of rules, regulations as well as byelaws made by Central/State governments and local authorities like municipal corporations, municipalities, gram panchayats and other local bodies. This subordinate legislation is made under the authority conferred or delegated either by Parliament or State or Union Territory legislatures concerned. Judicial decisions of superior courts like Supreme Court and High Courts are important sources of law. Decisions of Supreme Court are binding on all courts within the territory of India. Local customs and conventions which are not against statute, morality, etc., are also recognized and taken into account by courts while administering justice in certain spheres (https://archive.india.gov.in/citizen/lawnorder.php?id=6).
- When there is a law, rule or any policy, then any violation of the said law, rule or policy is unethical and illegal.
- When there is no government policy, the Court often relies on reliable authentic literature; authentic peer group consensus; published literature, guidelines and consensus statements.
- The admissibility of evidence in Courts in India is dependent on its relevancy as per the provisions of Indian Evidence Act. Illegality or impropriety in obtaining the evidence will not affect its admissibility, if it is otherwise relevant. Test of admissibility of evidence lies in its relevancy and not on how it was obtained. In Kuruma v The Queen [1955] AC 197, the Privy Council laid down that if the evidence is admissible, the Court is not concerned how it was obtained. The Privy Council observed: *"...the test to be applied in considering whether evidence is admissible is whether it is relevant to the matters in issue. If it is, it is admissible, and*

the Court is not concerned with how the evidence was obtained." These observations of the Privy Council were quoted with approval by the Supreme Court in P**ooran Mal v Director of Inspection AIR 1974 SC 348.** After quoting the above observations of the Privy Council, the Supreme Court observed as follows: "*It would be thus seen that in India, as in English, where the test of admissibility of evidence lies in its relevancy, unless there is an express or necessarily implied prohibition in the Constitution or other law, evidence obtained as a result of illegal search or seizure is not liable to be shut out*."

CAN A DOCTOR BE HELD LIABLE FOR MERE DEVIATION FROM NORMAL PRACTICE?

- The Hon'ble Supreme Court of India in the matter titled as **"Jacob Mathew versus State of Punjab & Anr** on 5 August, 2005" has held that:

  "*A mere deviation from normal professional practice is not necessary evidence of negligence. Let it also be noted that a mere accident is not evidence of negligence. So also, an error of judgment on the part of a professional is not negligence per se. Higher the acuteness in emergency and higher the complication, more are the chances of error of judgment*."

  …..The degree of skill and care required by a medical practitioner is so stated in Halsbury's Laws of England (Fourth Edition, Vol 30 Para 35): "…… and a person is not liable in negligence because someone else of greater skill and knowledge would have prescribed different treatment or operated in a different way; nor is he guilty of negligence if he has acted in accordance with a practice accepted as proper by a responsible body of medical men skilled in that particular art, even though a body of adverse opinion also existed among medical men."

- In the matter titled as "**Achutrao Haribhau Khodwa vs. State of Maharashtra**, 1996 SCC (2) 634", the Hon'ble Supreme Court has held that:

  "*The skill of medical practitioners differs from doctor to doctor. The very nature of the profession is such that there may be more than one course of treatment which may be advisable for treating a patient. Courts would indeed be slow in attributing negligence on the part of a doctor if he has performed his duties to the best of his ability and with due care and caution. Medical opinion may differ with regard to the course of action to be taken by a doctor treating a patient, but as long as a doctor acts in a manner which is acceptable to the medical profession, and the Court finds that he has attended on the patient with due care, skill and diligence and if the patient still does not survive or suffers a permanent ailment, it would be difficult to hold the doctor to be guilty of negligence*."

- The opinion has to be by an authentic body. In the matter titled as **"Vinitha Ashok versus Lakshmi Hospital**, AIR 2001 SC 3914", the Hon'ble Supreme Court has held that:

  "*[28] Thus in large majority of cases, it has been demonstrated that a doctor will be liable for negligence in respect of diagnosis and treatment in spite of a body of professional opinion approving his conduct where it has not been established to the court's satisfaction that such opinion relied on is reasonable or responsible. If it can be demonstrated that the professional opinion is not capable of withstanding the logical analysis, the court would be entitled to hold that the body of opinion is not reasonable or responsible*."

- In the matter titled as "**Kusum Sharma & Others versus Batra Hospital & Medical Research Centre**, 2010 (3) SCC 480", the Hon'ble Supreme Court of India has held that:

  "*In the realm of diagnosis and treatment there is scope for genuine difference of opinion and one professional doctor is clearly not negligent merely because his conclusion differs from that of other professional doctor*."

  "*The medical professionals are entitled to get protection so long as they perform their duties with reasonable skill and competence and in the interest of the patients. The interest and welfare of the patients have to be paramount for the medical professionals*."

- **Indian Penal Code Section 92 - Act done in good faith for benefit of a person without consent:** "*Nothing is an offence by reason of any harm which it may causes to a person for whose benefit it is done in good faith, even without that person's consent, if the circumstances are such that it is impossible for that person to signify consent, or if that person is incapable of giving consent, and has no guardian or other person in lawful charge of him from whom it is possible to obtain consent in time for the thing to be done with benefit*."

- **IPC Section 88 - Act not intended to cause death, done by consent in good faith for person's benefit**: "*Nothing, which is not intended to cause death, is an offence by reason of any harm which it may cause, or be intended by the doer to cause, or be known by the doer to be likely to cause, to any person for whose benefit it is done in good faith, and who has given a consent, whether express or implied to suffer that harm, or to take the risk of that harm*."

LAW ON OFF-LABEL USE OF DRUGS IN THE US AND UK

- **In the United States**, the law permits a physician or other health care practitioner to prescribe an approved medication for indications other than their specific FDA-approved indications. Pharmaceutical companies are not allowed to promote a drug for any other purpose without formal FDA approval. However, once a drug has been approved for sale for one purpose, physicians are free to prescribe it for any other purpose that in their professional judgment is both safe and effective, and are not limited to official, FDA-approved indications.

  This off-label prescribing is most commonly done with older, generic medications that have found new uses but have not had the formal (and often costly) applications and studies required by the FDA to formally approve the drug for these new indications. However, there is often extensive medical literature to support the off-label use.
- **Regulation in the United Kingdom:** Physicians in the United Kingdom (UK) can prescribe medications off-label. According to General Medical Council guidance, the physician must be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate safety and efficacy. Prescribing may be necessary when no suitably licensed medicine is available to meet the patient's need (or when the prescribing is part of approved research).

ROUND TABLE CONSENSUS ON OFF-LABEL USE OF DRUGS

Few Examples of Off-label Use

- Metformin in India is used off-label for polycystic ovarian disease (PCOD), which is used by gynecologists across the country; Federation of Obstetrics & Gynaecological Societies of India (FOGSI), Indian Menopausal Society, Endocrine Society of India recommend this use in their guidelines. No consent needs to be taken if used for this indication; but, it is not DCGI-approved for this indication. Use of metformin-myoinositol combination in PCOD is also an off-label use.
- Amlodipine is approved for use only for mild and moderate hypertension, but it is also being used for severe hypertension, which is an off-label use.
- Use of aspirin in acute myocardial infarction is not a DCGI-approved indication.
- Using injection methotrexate for sarcoidosis, one may need to take an informed consent.

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"Anticipate and prepare ourselves"

- To begin with, sensitize the medical profession on this issue. Most doctors are unaware of off-label use.
- Identify situations in which drug/s can be used off-label; supported by strong scientific evidence; being used for the said indication for years and PvPI has not recorded any adverse effect with the drug.
- Seek recommendations from professional associations and societies as they understand safety issues and scientific evidences.
- Sensitize the ethics committees of institutions regarding this issue.
- National workshops: Invite specialists with scientific data; organize round tables in different zones of the country. Points to be discussed in these workshops:
  - Safety and ethics of off-label use
  - Is the drug used anywhere else in the world or in India for the off-label indication?
  - Is the drug approved for off-label indication/s in other countries?
  - Are there enough international/national studies on the off-label use?
- Invite government participation
- Include off-label use as part of informed consent; hospitals must have their individual "Ethics Committee guidelines" on this till a national policy is available.
- Phase 4 post-marketing trials should be regulated. Adverse events should be reported. This will strengthen PvPI.
- Robust data including level of evidence is needed along with risk-benefit analysis.

- Commercial bias and conflict of interest needs to be taken care of.
- Expert evidence by peer group is accepted by the Courts as "prevalent practice", "peer group recommendations" or "society recommendations" unless there is a national existing policy. Till a law is formulated, this can be followed.
- Submit the draft to DCGI with copy to Health Ministry and other regulatory bodies; follow-up with RTIs; file PIL if no satisfactory reply.

Guidance on Reuse of Cardiovascular Catheters and Devices in India

- Each medical establishment should have its own off-label, list of devices which can be reprocessed; number of times a device can be reused; Reprocess, Reuse, Re-Sterilize Committee consisting of doctors, infection control officers, microbiologists, nurses, and administrators to oversee central sterilization, re-processing, infection control, biomedical engineering and cost accounting.
- The above committee should have approval of the Institutional Ethics Committee.
- The in-house committee should take responsibility for the protocol linked to safety issues.
- The medical establishment should provide adequate space for reprocessing, trained personnel and other consumables that are required.
- Standard and validated written protocols should be followed for reprocessing for each type of single use device.
- Establishment should ensure a mechanism for tracking of such devices.
- There should be a periodic review and audit.
- Cardiology and other specialties reusing catheters should formulate common guidelines and standard operating procedures for reuse. These guidelines should include the list of items that can be reused, the number of recommended reuses, the procedure for reuse and validating effectiveness of reprocessing procedures, to ensure sterility and intact functionality of these devices and ensure quality control.
- An adverse event record should be maintained for all reused devices and there should be a periodic review and audit.
- Third party reprocessing units should be encouraged and need to be stringently regulated and accountable for quality control.
- The reused catheters/devices should not be billed on the new item rate to the patient as the reuse policy is primarily done to reduce the cost.
- The cost of sterilization process should be accounted for in the catheterization laboratory charges and/or should not exceed 10% of the original cost of the catheters.
- Reused cardiac implantable electronic devices (CIEDs) should not be charged.
- Made or make in India concept for these single use devices (SUDs) should be encouraged and facilitated to offset the cost, issues related to reuse and improve penetration of therapy.
- Engagement with the health regulatory authorities and price control for all imported medical devices should be addressed. Sealing the maximum retail price (MRP) based on the landing price with a well-defined formula for different SUDs should be established.
- ICMED: There is a basic policy on reprocessing of single use devices; it needs to be expanded. This assumes significance given the waste generated causing environmental hazard, an important public health problem today. Three important issues to be taken care of with regard to SUDs: Identify which SUDs can be reused safely, consent and that the benefit of cost has been passed over to the consumer.

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No Repeat Imaging for Most Adrenal Tumors, Call to Change Guidelines

Adrenal tumors found incidentally on imaging tests that are either nonfunctioning or have mild cortisol excess are highly unlikely to grow significantly or to develop into cancer or Cushing syndrome, US and UK researchers have found.

The results of this new meta-analysis therefore suggest that guidelines on the management of these tumors need to be updated to reflect the clinical reality - that is, patients do not need repeated imaging or testing over years of follow-up, say the authors. The study was published online June 25 in *Annals of Internal Medicine.*