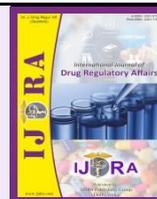


Available online on 15 Mar, 2021 at <https://ijdra.com/index.php/journal>**International Journal of Drug Regulatory Affairs**Published by Diva Enterprises Pvt. Ltd., New Delhi
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Review Article

A Proposal for new Quality attributes for Schedule R of the Indian Drugs and Cosmetics Act, 1940

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Abstract

Original sin is not life but it is a part of life. It establishes psychological, mental and physical health. Statistics reveal several deaths of pregnant mothers, ectopic pregnancy, child deaths or original sin related diseases, apart from lethal consequences which is out of the scope of this article. Use of contraceptive methods may be beneficial in several circumstances avoiding unwanted pregnancies. A few television channels were scrolling the various contraceptive methods and educating the citizens for a good health perspective. The objective of this review is not only to enlighten the various contraceptive methods but also in knowing their failure level methods and some unique evaluation methods that can be included in Schedule R of the Drugs and Cosmetics Act, 1940 so as to append the quality attributes with in-vitro and in-vivo original sin correlated models. The review illustrates role of researchers/pharmacist/medical professionals in problem solving skills and is also expected to answer the general questions experienced and witnessed by the author relating to original sin including gender sensitization. In India, several national level bodies also insist for academic accreditations the contributions relating to gender sensitization and the article meets criteria as well. If the author as a common man sends a sample for current products for assessing abstract attributes, does Central Drugs Laboratory can?, a thought in this direction is needed which in turn indicates role of questionnaires/instruments in the Drugs and Cosmetics Act, 1940 and Rules 1945. Does a need of a statutory warning for original sin products is necessary, a question is raised and a review by persons skilled in art is proposed. The article illustrates either side to the context. The article also helps to overcome barriers from society, professional point of view relating to original sin related research either at the pre-clinical or at the clinical levels.

Keywords: Contraception, failure indices, methods, evaluation, gender sensitization, health related quality of life, HRQOL, instruments**Article Info:** Received 15 Dec. 2020; Review Completed 17 Feb. 2021; Accepted 27 Feb. 2021**Cite this article as:**Subba Rao B. A Proposal for new Quality attributes for Schedule R of the Indian Drugs and Cosmetics Act, 1940. Int J Drug Reg Affairs [Internet]. 2021 Mar 15 [cited 2021 Mar 15]; 9(1):10-14. Available from: <http://ijdra.com/index.php/journal/article/view/449>

DOI: 10.22270/ijdra.v9i1.449

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1. Introduction

One side of contraception is family planning but the other side is to minimize pregnancy related deaths of the mother, ectopic pregnancy, unexpected abortions, child deaths and prevent from sexually transmitted diseases. Even though several methods are available, a few are quite commonly well known, especially in India. The current article is to enlighten the various methods, indices how failure is calculated.

2. Indices of Contraception Failure (1)

It was reported that it is difficult to measure failure rate because the method and user characteristics contribute to failure. However, four methods (1) were reported i.e., theoretical or method failure rates; actual or use failure rates; the Pearl index and the Life-table rate.

Theoretical or method failure rates

It is the percentage of women who would experience accidental pregnancy in the first year of use given perfect (correct and consistent) use. The rates are calculated by counting only those pregnancies that can be attributed to failure of the method itself. Any pregnancies that occur as a result of user error are eliminated from the calculation.

Actual or Use failure

It is the percentage of women experiencing an accidental pregnancy in the first year of use and is calculated by counting all pregnancies that occur while a couple is using a contraceptive method. The method has subjective element which is dependent upon the user's statement of whether or not contraception was in fact being used when the pregnancy occurred.

The Pearl Index

It is the number of accidental pregnancies per 100 women-years of exposure. The ratio can be deceptive to

those not familiar with the index because it is based on a scale ranging from zero (if there are no failures) to 1200 (if all women studied became pregnant in the first month of the study).

$$\text{Pearl Index} = \frac{\text{Unintended pregnancies}}{\text{Total woman - months of exposure}} \times 1200$$

Life-table

It is expressed as the number of women who accidentally become pregnant in one year out of 100 women who started the method and continued to use it unless they became pregnant. The rate measures the proportion of contraceptive failure within a year and control for duration of use by calculating a separate failure rate for each month. Life table rates control for duration of use and is the most reliable and consistent means of measuring failure.

3. Contraception Methods-In Detail (1)

Voluntary Sterilization (1)

Sterilization technique is the most widely used technique for family planning in the World and is one of the most effective. It is economical, permanent, highly effective and relatively safe. Among the male and female sterilization, commonly called as vasectomy and tubectomy, it is the former that is simpler, safer and less expensive. Even though both the methods are reversible, the success rate is the minimal and if the individuals have such plans of reversal, certainly the method is not preferable. In either the cases, a kind of cut or blockade procedures are available.

Intra-Uterine Devices (IUD) and Vaginal rings (1, 2)

Intrauterine devices are small metal or plastic devices placed in the uterus through the cervical canal. It is believed that IUDs interfere with sperm motility and ovum transport with a mode of action in prevention of fertilization. Postcoitally, IUDs are believed to play a role of abortifacients.

Intrauterine devices (IUDs) are of two types i.e., medicated and non-medicated. Figure 1, illustrates the lead models of development of intrauterine devices and among those, the widely compatible models are the ‘T’, ‘7’, ‘Lippes loop’ designs minimizing expulsion.

Among the medicated, the models are either copper wound or with polymer based controlled release steroidal hormones. The available non-medicated are the stainless steel ring or the Lippes loop.

In 1974, the ‘7’ shaped CU-7 IUD, containing 89 mg of copper wire wound around the vertical limb of a 7-shaped polypropylene plastic device to give an effective surface area of approximately 200 mm² was initially approved by USFDA for 2 years and at a later stage for 3 years. As time passed, T-shaped IUD was used to release natural progesterone for local contraceptive activity. Some of the commercial models are Copper T 380 A, Copper T 200, Copper T 220 C, Multiload 375, Multiload 250, Nova T; Lippes loop D, double stainless steel ring. Intrauterine devices are one of the highly effective, safe and reversible means of preventing

pregnancy. Among the IUDs, copper containing have the lowest risk of ectopic pregnancy.

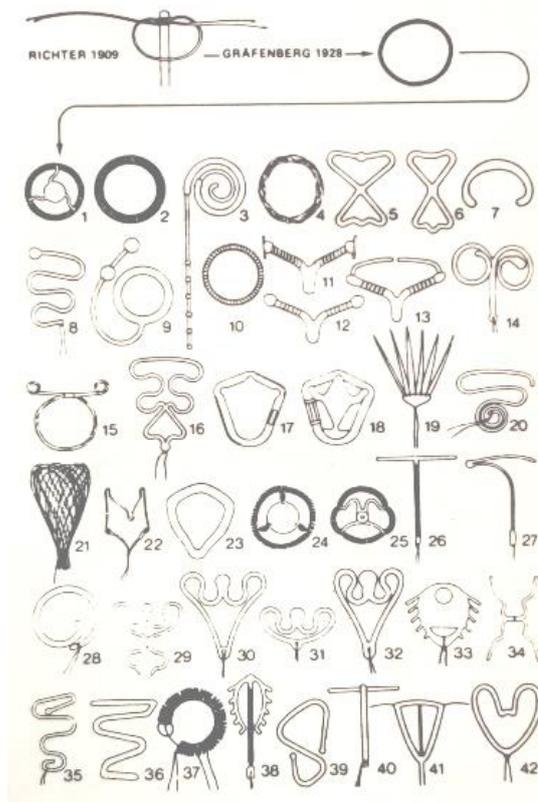


Figure 1. Historically developed IUDs

As a latest technology, IUD implant model ‘Gyne Fix’ (3) is found promising for its fixed, frameless and flexible model, Figure 2. The design is found to be easy in insertion with optimal anchoring possessing with low expulsion, high efficacy and high acceptability. The device consists of a non-biodegradable suture thread made of surgical 00 monofilament polypropylene, on which six copper sleeves (each 5 mm in length and 2.2 mm in diameter) are threaded, providing a total surface area of 330 mm² exposed copper. The upper and lower sleeves are crimped onto the thread, keeping the sleeves in place. To insert the device, like other models such as ‘T’, ‘7’ designs; the current design uses an applicator of 4-mm wide uterine sound with a movable flange. The role of applicator is to pre-determine the penetration depth.



Figure 2. Gyne Fix Implant (3)

The principle of insertion of IUD involves firstly, folding the IUD and pulling into a plastic tube called introducer, secondly the introducer is then inserted into the uterus, thirdly the IUD is forced out of the introducer by a rod, and fourthly the IUD takes up its position in the uterus, Figure 3.

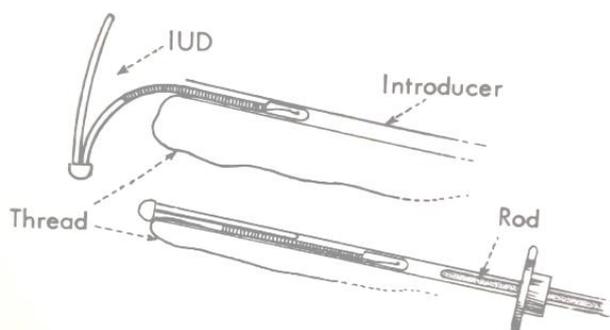


Figure 3. Intrauterine Device

Vaginal rings (2) made of silicone elastomer, thermo plastic polymers are currently available in market, Figure 4, where in comprises of a reservoir or a matrix release system. Drugs like 17 β -estradiol, etonogestrel, ethinyl estradiol, progesterone, dapivarine, maraviroc, tenofovir, MK-2048, ulipristal acetate were used. Several of these rings are either in market, or in clinical trials.

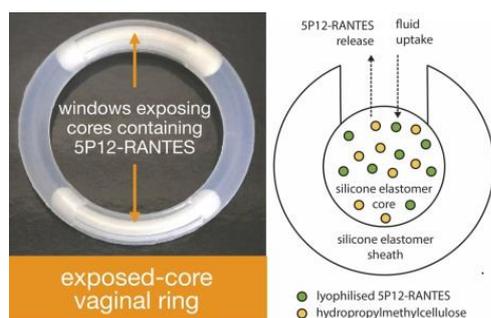


Figure 4. Vaginal rings (2)

Oral Contraceptives (1)

Currently, oral contraceptives can be categorized into two types i.e., hormonal or non-hormonal (non-steroidal). In case of the former, a combination of estrogen and progestogen are used to prevent pregnancy. When taken daily, the hormones inhibit ovulation, alter endometrial lining and impair sperm passage into the uterus by thickening the cervical mucus. Postcoitally, when administered the hormones prevent implantation of fertilized egg. In case of the latter, Indian origin, Centchroman (Ormeloxifene), a safe and effective non-steroidal contraceptive is available in the market with the trade name "Saheli".

In case of starting of hormonal combination pill, the subject should start the first cycle of pills within the first five days of her menstrual period. If a woman wishes to start on a particular day of the week, and that day is beyond the fifth day of her menstrual cycle, she should be advised to use additional protection against pregnancy for seven days after she starts the pill.

Management of missed pills is advised as follows:

- i. If one pill is missed, the pill should be taken as soon as the woman remembers.
- ii. If two pills are missed in the first two weeks, the woman should take two pills on two consecutive days and then continue with the rest of the pack as usual.
- iii. If two pills are missed in the third week, or if more than two are missed consecutively at any time in the cycle, the woman should discard the pack and start a new one immediately.

In case of Centchroman, it is administered twice per week for first twelve weeks of use and from thirteenth it is advised once per week.

It is always advised whenever pills are missed; another contraceptive method (barrier or abstinence) should be used for a minimum of one week to secure additional protection.

Progestogen-only method is found to eliminate risks associated with estrogen and protects from pregnancy by thickening cervical mucus, changing the endometrium (making it inhospitable to implantation), and often inhibiting ovulation.

Sub-dermal implant (1)

Norplant (4) consists of six silicone rubber capsules (each containing 36 mg of levonorgestrel) that are inserted under the skin of the woman's arm. The method provides contraceptive protection for five years. The pregnancy rate in Norplant users is 0.2 per 100 women in the first year of use, with a cumulative pregnancy rate of 3.9 per 100 women by the fifth year. The capsules can be removed at any time. It was observed that, 86 percent of women were able to conceive within one year after discontinuation.

Nestorone (5) contains a progestin in the form of 19-norprogesterone inhibits fertility at low doses when delivered through a single silastic implant. The implant is a promising candidate for contraception in lactating women because the infant would be free of the influence of the hormone excreted in the milk.

Injectables (1)

Depot-medroxyprogesterone acetate (DMPA) and norethisteroneenanthate (NET-EN) were found to be convenient and not coitus-dependent. The failure rate of DMPA (three monthly injectable) is less than 1 per 100 woman-years, for NET-EN (two-monthly injectable) less than 2 per 100 woman-years. DMPA injections should not be given less than 11 weeks or more than 14 weeks after the previous injection. Studies indicate that 60-78 percent of women conceive within one year of the last injection.

With respect to once-a-month injectable contraceptives containing both estrogen and progestogen, the combination is effective with failure rates of less than 1 percent.

Barrier methods (6)

Barrier methods include condoms, spermicides (foam, suppositories, tablets, creams, soluble films and jellies), diaphragms, cervical caps, and sponges. They either mechanically or chemically prevent sperm from entering the uterus.

Condoms are thin latex sheaths that fit over the erect penis and prevent semen from entering the vagina. Typical failure rates are approximately 12 percent in the first year of use. A combination of condom and spermicide (nonoxinol) is found effective. Condoms are free from side-effects, except those who are rubber sensitive. Currently, good quality latex condoms are found in not allowing passage of HIV. Thermoplastic elastomer (TPE) is found promising for those who are allergic to latex type condoms. Evaluation of condoms involves with respect to passive leak test and active viral challenge test. Here, the condoms were challenged with bacteriophage T7 (100 nm) and the polio virus Type 1 (PV-1, 27 nm). Here the objective of the study is with respect to size of the microorganism rather than the virulence.

In the evaluation procedure, as passive viral challenge, 10 ml of the test virus is placed in a condom, which was sealed, immersed in the specimen container, and maintained at room temperature or 37 °C for ten days. Daily samples (100 µl) were removed and assayed for virus.

In case of active viral challenge, a simulated, artificial model of intercourse is used, Figure 5. Here, a sterile, 50 ml disposable centrifuge tube (30 x 115 mm) is covered with a condom containing 4 ml of virus. This system is placed into an outer condom, containing 2 ml of virus-free medium. The apparatus is introduced into a commercially produced latex vagina. A standard procedure of 30 strokes (within 30 seconds) is used. Samples are withdrawn from the inner and outer reservoirs by sterile syringe and assayed for the presence of virus. Positive and negative controls are used where in positive controls involve condoms that are punctured six times with a 27-gauge needle and served to ensure the free passage and viability of the virus, whereas negative controls consist of condoms containing only sterile medium.

Diaphragm, caps, sponges are the other means used for sperm blockade.

Natural Planning (1)

Here calendar, rhythm, Billings', basal body temperature, symptothermal methods and the length of abstinence are used and are well known. As traditional methods, coitus interrupts includes withdrawal. The major disadvantage is its relatively high failure rate.

Postcoital methods (1)

This method is for emergency use only and is appropriate in cases of unplanned, unprotected intercourse, suspected contraceptive failure caused such as broken condom, dislodged diaphragm, missed pill etc. In such circumstances, the treatment involves administration of steroid hormones (estrogens or estrogen/progestogen combinations) within 72 hours of

unprotected intercourse. A commonly used dose Yuzpe regimen consists of 0.1 mg ethinylestradiol and 0.5 mg of levonorgestrel as soon after exposure as possible and again 12 hours later.

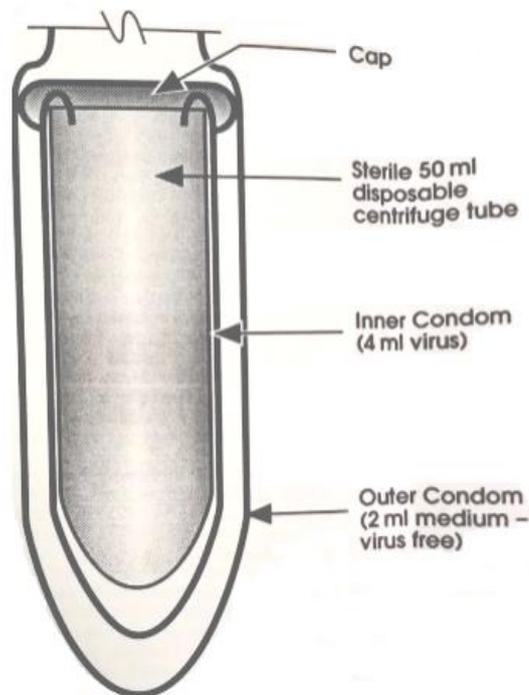


Figure 5. Artificial Intercourse model for evaluation of Condoms (6)

Breast Feeding (1)

Breast feeding has an important contraceptive effect during the early postpartum months. A breast-feeding woman who does not feed the baby foods other than breast milk, is not yet menstruating, and is less than six months postpartum has a less than 2 percent probability of becoming pregnant.

4. Conclusion

With respect to a research result telecasted on air, the top ten age busters with their corresponding ranking are laughter (10), sleep (9), nutrients (8), original sin (7), green tea (6), meditation (5), skin care (4), exercise (3), brain games (2) and water (1). Health related Quality of Life (HRQOL) involves mental and physical health of an individual. Especially in Indian work places and society, the age buster is becoming the combination of ranks of 10, 7, and 2, an assumption. It has been reported that the life span has increased by additional ten years than normal individuals living span. A review of Indian patent office database retrieves the drug coated condoms, which are not yet available in Indian market and can be expected. In addition to this, female condoms are innovative to Indian market. Researchers have overcome the issue with specific designs.

One of the television channels on air indicates for every 53 seconds one child or mother death. Even though the methods may not be responsible, keeping in view of contraception-the other side i.e., the failure indexes, the need of a statutory warning is absolutely necessary, a proposal which usually the industry sector does not object.

Orthographic projections, machine drawing and blue printing (1:1, 1:2, 1:0.5 scaling) of machines was part of curriculum during author's pharmacy academic curriculum, which is currently not included in several technical courses and should be included in pharmacy course as well so that students attain visualization, analytical skills, machine drawing additionally. When a research question was asked to patients relating to health related original sin life with the spouse, a preliminary indication is that either of the spouses is not offering either due to work stress, over load, frustrations with routine works, age factor, aches etc.

In pharmaceuticals, research involves right from etiology of the disease, including original sin research through lead molecules through cosmetics, medical devices etc. Pre-clinical anti-fertility activity for herbals or new chemical entities involves with before treatment after treatment of sperm count of rats (in males) and understanding cycle (PAP smear), count of number of implants, offspring (in females). Antisense approaches are also observed for anti-fertility activity.

To the knowledge, Schedule R of Drugs and Cosmetics Act, 1940 of the Indian speaks about quality attributes of condoms such as burst volume and pressure test and water leak test, length, width, wall thickness, quantity of lubricant, color fastness, oven conditioning (for tackiness, brittleness, other signs of deterioration) whereas for copper T and tubal ring, the Bureau of Indian Standards specifications are set to be fulfilled. Even though Central Drugs Laboratory, Chennai is involved in quality of condoms, which indicates generally the conventional male condoms, there is no emphasis on female and specially designed condoms with respect to abstract attributes. In order to establish correlation between in-vitro and in-vivo original sin, the current in-vitro simulated model of testing may be implemented for effective in-vivo correlation so that unwanted pregnancies can be avoided, since the stroke rate varies with individuals, a proposal to be ensured for feasibility. Schedule R also should include instruments/questionnaires for evaluation of abstract attributes for testing quality, a proposal. Moreover, there is a provision that a consumer may purchase and send for quality test, where the central laboratory is equipped with conventional but not for abstract attributes.

Online shopping clearly indicates condoms of the type ultra-thin, flavoured, long last, dotted, extra ribbed, excite series, extra thin, dotted and ribbed, extra dots, zig zag, female condoms, super thin, orgasmmax, extra time, contour, complete pleasure and desire series, climax delay, not out, non-toxic dotted, air, all night delay, half ribbed, half dotted, paraben-free, xtra lub, cool, power shot, tingling pleasure, dual texture, mind blowing, skinless skin, super ribbed, platinum, super dotted, wild ribbed lubricated silicone, initiated contraception lubricated protection with pleasure, 3D dotted climax, delicious flavour, re-energized dotted, xtra time dots, all night delay, silver, bonazines, mix combo, chill thrill etc.

It is necessary to remind to the policy makers that you have statutory warning for smoking and alcohol, but there is no statutory warning for original sin related products, to the knowledge even though a movie to the context was released about 35 years ago. Does a drug coated contraceptive in future can also be expected under Narcotic and Psychotropic Substances Act, a second question yet to be answered?

Acknowledgements

The author is thankful to the management, principal of College of Pharmaceutical Sciences, Manipal and the Central Library and Family Planning Department of the KMC College and Hospital, Manipal for providing the information during his study.

Financial Disclosure statement: The author received no specific funding for this work.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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