The journey of the world's first non-steroidal contraceptive from Academic venture to National family programme

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Globally, pharma companies are channelizing their investments mainly in lifestyle disorders (obesity, depression, hypertension, diabetes, respiratory disorders) and cancer for higher returns[1,2]. In recent years, though drug discovery for infectious diseases (especially viral and bacterial infections)[3,4] has received considerable public–private investments, most parasitic diseases and fertility control remains less remunerative areas for investments[1,2]. These areas pose challenges for countries with inadequate access to life-saving and health-maintaining interventions. In the Indian context, our socio-economic structure has immensely affected investments in the health sector. Our total health expenditure and government's contribution is significantly lagging behind other South-East Asian countries (Figure 1)[5]. A miniscule of this share is utilized for new drug discovery. Hence, it is unlikely that a private entity will step into financing and managing drug discovery R&D. Therefore, the government is expected to make necessary investments in new drug discoveries for affordable healthcare for the masses.

The Indian pharma industry has transformed dramatically in the last 20 years[6], but low R&D investments and rising costs of drug development have affected the pace of transformation. Further, insufficient strategic public–private partnerships and inadequate IP-framework has pushed Indian pharma investments into generics over new drug discoveries and high-risk exploratory activities. Policies are required to stimulate new drug discoveries and their commercialization at affordable price to the masses. To achieve this, an effective academia–industry alliance is essential to strike a balance between affordable healthcare and return on investments. This has been successfully demonstrated earlier for α/β arteether (anti-malarial) and centchroman (contraceptive)[7–9]. In this commentary, we describe the journey of a lead molecule from publically-funded academic research into the market through an industry partner and this molecule was eventually included into the national family planning programme as the world's first non-steroidal drug for safe contraception in women.

Discovery and development of a non-steroidal contraceptive

Post-independence, many national laboratories were established with a vision to provide better healthcare and develop a self-reliant pharma sector. India launched its first national programme for family planning in 1952. To achieve population stabilization, Government of India posed a challenge to CSIR-CDRI to initiate a programme on safe contraception for Indian women. The available oral contraceptives in those times caused many side effects such as nausea, cramps, headaches, breast tenderness, breakthrough bleeding and weight gain. In India, due to socio-cultural nurturing, anti-fertility drugs did not gain popularity. Therefore, the challenge was to develop a prototype which has anti-implantation rather than interfering in the development and maturation of the ovum itself, to increase its social acceptability. The desired molecule was required to oppose the action of female sex hormones in the uterus, but still allow these hormones to perform their biological functions in the context of blood and bone metabolism or brain and behaviour functions. Scientists at CDRI rationalized the design of a series of compounds, based on the existing knowledge about the receptor for the female sex hormone 17-beta-estradiol. Although it is known that two different forms of this receptor are expressed in different tissues, the scientists at CDRI formulated a hypothesis that it is possible to make a molecule that selectively binds to the receptor in the reproductive tissue, but not in other tissues. Scientists chemically synthesized several prototypes and evaluated their anti-contraceptive activities. Indoles and coumarins were not active, while benzofurans and napthofurans showed good anti-fertility activity, but were associated with liver toxicity. Interestingly, chromenes and chromans turned out to be promising molecules with good contraceptive potential and minimal toxicity. Lead optimization resulted in synthesis of *trans*-2,2-dimethyl-3-phenyl-4-(*p*-[β-pyrrolidinoethoxy]phenyl)-7-methoxychroman which was christened as centchroman (INN: Ormeloxifene), a chroman molecule from Central Drug Research Institute (Scheme 1)[10]. Preclinical studies demonstrated that centchroman disrupts the coordination between the rates of maturation of the developing embryo and the ripening of the uterus wall to accept it[11,12]. Pharamcokinetics studies revealed that centchroman is very well absorbed from the gut and is widely distributed in all body tissues including lungs, breasts, ovaries, uterus, etc.[13].

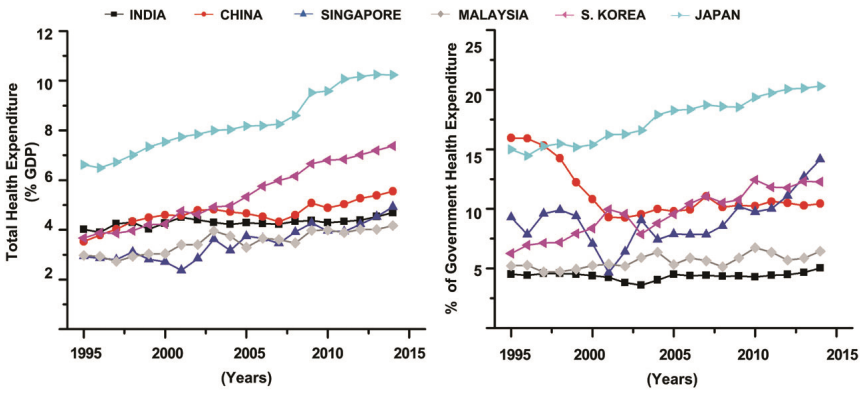


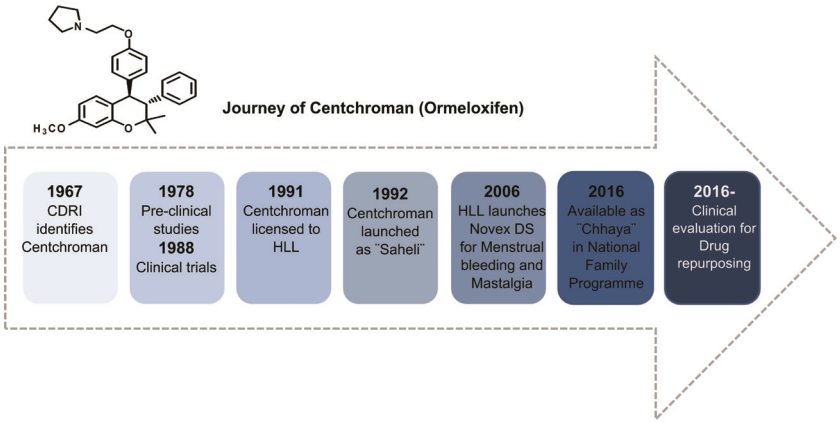
Figure 1. Total health expenditure (% GDP) and government's contribution (% health expenditure) over the last two decades across South-East Asian countries. (Courtesy: The Worldbank data).

From clinical trials to national family programme

Phase I (safety in humans) trial included single and multiple dose studies in women of reproductive age as per the drug regulatory guidelines. Centchroman has long elimination half-life and hence low dosing schedule (once a week). In phase II clinical trial, different groups of women received different doses ranging from 10 to 120 mg once a week. Phase III trials were carried out in about 2000 volunteers with an average use period of 12–18 months. The trials were conducted at 10 family welfare centres and 7 medical colleges. The dose-schedule which emerged most effective was to begin with 30 mg twice a week for 3 months, followed by 30 mg once-a-week till contraception is desired. Centchroman is non-steroidal and is devoid of side-effects reported for available steroidal contraceptives like vomiting, nausea, dizziness, weight gain, blood clots in small blood vessels, fluid retention, hypertension, breakthrough bleeding or excessive menstrual flow. Centchroman imparts anti-implantation contraceptive activity at the uterine level without disturbing the normal menstrual cycle or key elements of the brain, pituitary gland and ovaries. In clinical trials, a thorough follow-up for both nursing and non-lactating women was conducted to monitor changes in their physiology. An effective reversal to fertility upon discontinuation of centchroman was observed making centchroman suitable for spacing in child birth[14].

CSIR-CDRI licensed centchroman to HLL (Trivandrum) in 1991 which was launched as 'Saheli' in 1992 (ref. 15). Centchroman is cost-effective and currently 6 lakh women are finding a contraceptive solution in Saheli. Further, centchroman also turned out to be a drug of choice for dysfunctional uterine bleeding (DUB). HLL relaunched centchroman as novex and novex DS for DUB. Its sales have increased from 0.3 million pills in 1991–92 to 32.17 million pills in 2016–17 (Figure 2).

Any drug development venture takes 12–15 years, which includes thorough investigation in discovery/pre-clinical phase for lead identification and optimization followed by well-designed clinical trials. Centchroman followed a long journey from discovery phase to reaching the market and national family programme (Scheme 1). Currently, it is available free of cost in all primary healthcare centres across the nation as 'Chhaya'. For effective execution of this programme, ASHA workers conduct door-to-door campaigns to generate awareness about use of Chhaya, especially towards compliance of dosage. Due to prevalence of fasting practices amongst women in our country, ASHA workers advise them to start dosage regimen specifically on sundays as many do not observe fast on that day of a week. If the couple desires a (next) pregnancy, centchroman use can be discontinued and it does not interfere with growth and development of the foetus.



Scheme 1. The timelines of discovery of centchroman, its commercialization and incorporation in the National family programme.

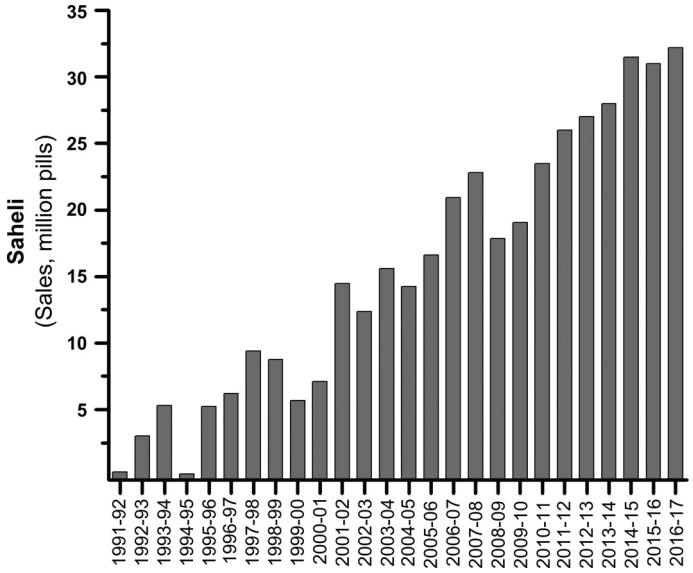
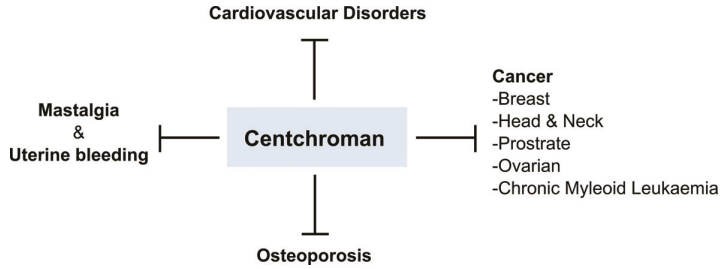


Figure 2. Sales of Saheli in the last 26 years. Major consumer states are Uttar Pradesh, Delhi, Punjab, Rajasthan, Haryana, Madhya Pradesh, Chhattisgarh, Jammu and Kashmir and West Bengal. (Courtesy: HLL, Thiruvananthapuram).

Repurposing of centchroman

CSIR-CDRI scientists also identified idiosyncratic benefits of centchroman apart from its contraceptive action (Scheme 2). Underlying mechanisms of action for anti-neoplastic, anti-oxidant, anti-osteoporotic activities of centchroman were studied[16,17]. Furthermore, use of centchroman was also shown to be associated with decrease in the incidence of pelvic inflammatory disease, ectopic pregnancy, benign breast tumours, anaemia, formation of ovarian cysts and it also boosts humoral immunity. Currently, repurposing of centchroman is under clinical evaluation. For instance, clinical



Scheme 2. Potential areas identified for drug repurposing of centchroman.

trials for breast cancer (under phase II), osteoporosis (under phase II) and mastalgia (under phase IV) are ongoing (source: HLL Lifecare Ltd.).

Fostering drug discovery and development through public–private partnerships

The journey of drug discovery is not only capital and time intensive, but also requires enormous commitment from the scientific and business development teams. In this venture, many drug-candidates are dropped due to poor efficacy, safety and profitability concerns. While the other facet is, many safe and efficacious lead molecules identified in the discovery phase, do not reach the market. The journey of centchroman from academic venture to commercialization is considered an outlier, because the licensee (HLL) being a PSU, had priorities in-line with academic partners towards public health improvement. Many public–private partnerships suffer from operational complexities in academia and lack of reciprocative response from industry partners. In the recent past, initiatives by CSIR, NRDC, DBT and DST are helping to bridge the gap between academia and industry to facilitate commercialization of products. These initiatives aim to create an ecosystem to keep drug development costs down through active collaborations of both universities and government institutes with pharma partners. In addition, the drug regulatory authorities in India have revised policies for clinical trials, but stringent regulatory mechanisms have to be implemented towards timely evaluation of safety and efficacy of drugs according to international standards to facilitate their entry into global markets.

Apart from various governmental strategies, critical steps have to be taken by both public and private partners to sustain their collaboration. First, they need to build confidence in each other's expertise and ensure that the partnership is neither over-competitive nor monopolistic and should have minimal conflict of interest. Secondly, they should support exploratory R&D activities to nurture scientific creativity and facilitate collaborations in risky endeavours. Thirdly, they need to maintain product pipelines with constant efforts in capacity building and its utilization for time-based deliveries. Fourthly, stakeholdership for product development, its use and delivery to the masses should be evaluated. It is important to understand that a drug discovery or technology development venture cannot be achieved with a myopic vision and unrealistic milestones or timelines. Hence, *manthan* of ideas and expertise between multi-organizational sectors with trust, commitment and endurance can only synergize deliverable public health needs.

Notes: Dr Suprabhat Ray and his team designed scaffolds with contraceptive activity. Dr M. M. Singh and team conducted anti-implantation related studies. Dr Anila Dwivedi and team investigated mechanism of action. Dr R. C. Gupta and team conducted pharmacokinetics and metabolism related studies. Clinical trials were supervized by Dr Swarn Nityanand. Centchroman was pursued for licensing and commercialization under the leaderships of Dr Nityanand and Dr V. P. Kamboj. This manuscript has been issued with CSIR-CDRI Communication No. 226/2017/SRK.

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