

OUTSOURCING APIs TO INDENA EXPERTISE

A common need of Pharmaceutical Companies is a feasible opportunity for Botanical Derivatives

Salvatore Gargano (Marketing Director, Indena S.p.A., Milan, Italy)

With high growth rates, profits and entry barriers, the pharmaceutical industry used to be recognized as one of the most successful business areas. However, recent years have seen the industry running up against a number of unforeseen changes in the manufacturing life cycle. These changes have inhibited the development, marketing and eventual sales of new drugs as well as increasing the potential risks and associated costs. Large Pharmaceutical Companies migrate their activities on the marketing and distribution of established products. Following the industry shake-up and a series of major mergers, multinationals are now aiming for a higher degree of specialization in specific therapeutic fields to absorb their 'drug discovery' investments, now reaching average costs of US\$ 350-500M and needing 10 years of development.

A knock-on effect of this is that large companies are pulling out of investments in the vertical industrial production of Active Pharmaceutical Ingredients (APIs), opening up new horizons for the 'Pharmaceutical Contract Manufacturing Marketplace'. Recent estimates value this "outsourcing market" in the region of 8 billion dollars.

Similar changes are extending beyond pharmaceuticals to nutraceuticals and dietary supplements which as a rule have lower entry

barriers but shorter and more unpredictable product life cycles. Once again outsourcing offers the best solution bringing agility and more rapid access times to the market.

Major companies, whose "must" is real quality products, are now forced to consider the performance of the whole Supply Chain and to give greater value to 'environmental conditions', 'traceability' and indeed the entire organizational structure of their contract manufacturer. There is a need to move from the simple client-supplier relationship to a real 'partnership' with the formalization of operations through the validation of all shared activities. Successful 'outsourcing', which starts with the reliability of the raw material producer, ends with the total satisfaction of the customer.

For over 80 years now, Indena has brought to the 'partnership' table its unique experience in managing botanical derivatives from GAP compliant medicinal plant cultivation, to the development and validation of cGMP proprietary extraction processes in line with ICH requests. Several Pharmaceutical Companies have already outsourced the production of their own strategic patented or branded products to Indena and they never had regrets. Taxol®, Endotelon®, Legalon® and MuscoRil® are just a few of these.

The Indena approach to nature is unique, balancing industrial needs and environmental respect; the company is unstinting in its endeavour to improve its cGMP standards by investment in new cutting edge machinery. 'Drug discovery' is a real challenge for a bulk producer. Indena has faced this challenge throughout the last two decades acquiring deep knowledge and management expertise in all stages in the process from development to manufacture; from the lab to the pilot project and through to industrial scale production; from IND status to final approval and marketing. There is still much we can derive from nature if we harness the knowledge we have today. This is the academic challenge Indena has pursued since its origin in 1921.



Indena's Plant in Tours, France

NEW UNITS TO STRENGTHEN SETTALA ANTI-TUMOUR DRUG PRODUCTION

The creation of two important new cytotoxic areas fully equipped with glove box containment units adds to Indena's credentials as the ideal partner for Pharmaceutical Companies developing treatments to fight cancer.

By stepping up efforts to make its anti-tumour agents available to the pharmaceutical industry, Indena, quite active in 'drug discovery', is bringing new ray of hope to countless cancer sufferers.



The new glove box units

CLINICAL EFFECTS OF SOYSELECT® ON POSTMENOPAUSAL WOMEN

Antonella Riva (Scientific Dept., Indena S.p.A., Milan, Italy)

Epidemiological and clinical data suggest soy derivatives could provide a promising treatment of menopause-related symptoms in postmenopausal women. The results available however are often conflicting. This is largely due to the high variability in composition of the different soybean products tested. To minimize this potential source of bias, a standardized soy extract (Soyselect®), prepared by Indena, was extensively investigated in several *in vitro* and *in vivo* models.

The main active ingredients of Soyselect® are isoflavonoids (such as glucosides) and saponins, both being endowed with several biological properties. The bioavailability of isoflavonoids of Soyselect® was markedly improved due to the presence of saponins.

The short-term efficacy of Soyselect® in the treatment of menopausal syndrome was assessed in two randomized, double-blind, placebo-controlled clinical studies in Europe and in the USA. In the European trial¹, 40 postmenopausal women were enrolled and 20 of them received daily 2 x 200 mg of Soyselect®

(50 mg/die of isoflavones), for six weeks.

The results showed that this product was superior to the placebo in reducing the number of hot flushes per week. Soyselect® supplementation had no estrogenic effect on the genital tract. The safety and efficacy of Soyselect® was confirmed in a second double-blind randomized placebo-controlled study². In this multicenter trial, a total of 117 postmenopausal women were randomized to receive either soy extract or a placebo. Once again, Soyselect® was effective in reducing the frequency and severity of hot flushes and did not stimulate the endometrium.

Soyselect® may be a safe and efficacious therapy for the relief of hot flushes in women who refuse or have contraindications to hormone replacement therapy. This product may indeed be considered highly innovative and Indena has in fact applied for the Italian patent and an international extension in the USA, Japan, Canada and Australia.

1. G. Scambia et al., *Clinical Effects of a Standardized Soy Extract in Postmenopausal Women: A Pilot Study*, *Menopause*, 7: 105-111, 2000
2. D. H. Upmalis et al., *Vasomotor Symptom Relief by Soy Isoflavone Extract Tablets in Postmenopausal Women: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study*, *Menopause*, 7: 236-242, 2000



Soyselect® is a highly standardized and reproducible soy extract characterized by:

- Improved isoflavonoids bioavailability due to saponins
- Good tolerability and significant efficacy in reducing the number and severity of hot flushes in postmenopausal women

THE BIOAVAILABLE FLAVONOID SILIPIDE, A NEW CHALLENGE IN ONCOLOGY

Antonella Riva (Scientific Dept., Indena S.p.A., Milan, Italy)

Recent reports have shown that silymarin has an exceptionally high anti-tumour promoting activity and affects the growth and proliferation of human breast and prostate carcinoma cells. In addition, the flavonoid silybin, the major active component in silymarin, has shown a comparable growth inhibitory effect towards human prostate, breast and cervical carcinoma cells and is equally as strong an antioxidant as

silymarin. Silybin was also found to potentiate the *in vitro* growth inhibition effect of cisplatin on human prostate, ovarian and breast cancer cells. Finally, recent *in vitro* studies suggested a potential anti-angiogenic activity of silymarin. Nevertheless, the possible therapeutic applications of this flavonoid are hampered by its very low bioavailability. IdB 1016 (Siliptide) is a complex between silybin and phosphatidylcholine and shows greater

bioavailability than either silybin or silymarin. When tested in animal models, IdB 1016 exhibited a significant antiangiogenic activity and was found to be very active in inhibiting the growth of human ovarian cancer xenografted into athymic mice. In addition, IdB 1016 was also shown to potentiate the activity of cisplatin¹. The toxicity profile of IdB 1016 has been fully investigated in rats, dogs and monkeys after administration by oral route. The compound is very well tolerated in acute, subacute, and chronic toxicity studies. The tolerability of the product was confirmed in Phase I clinical studies, following repeated administration of dosages up to 2.8 g/day to healthy volunteers².

Given the antitumor activity and the favorable toxicity profile, the use of IdB 1016 in the second-line treatment for patients with serological recurrence of ovarian cancer may be considered as a valid therapeutic strategy.

1. S. Giacomelli et al., *Silybin and its bioavailable phospholipid complex (IdB 1016) potentiate in vitro and in vivo the activity of cisplatin*, *Life Science*, 70: 1447-1459, 2002.
2. S. Malandrino and G. Pifferi, *IdB 1016 Silybin Phosphatidylcholine Complex*, *Drugs of the Future*, 15: 226-227, 1990.



UNDERSTANDING THE IMPLICATIONS OF THE EU TRADITIONAL HERBAL MEDICINE DIRECTIVE: INDENA SHOWS THE WAY IN LONDON

The Royal College of Physicians in London's Regent's Park was the prestigious setting for a one-day seminar, 'Meeting the Challenge of the Traditional Herbal Medicine Directive', organized under the auspices of The Council for Responsible Nutrition (CRN) and co-sponsored by Indena. The meeting, which took place on April 16th, was attended by over 100 people including representatives of the Medicine Control Agency (MCA) and members of major UK herbal product manufacturers.

Opening the proceedings, CRN Vice-Chairman Anthony Bush said the objective was "to raise awareness of the implications of the directive amongst UK Herbal Product marketers and particularly in registering products under the new regulations". Two Indena delegates, Scientific Director Paolo Morazzoni, together with Valerio Bombardelli, Head of Regulatory Affairs, illustrated the company position, pointing out the importance of a clear directive for the regulation and quality control of raw materials.

INDENA GIVES AN IMPORTANT CONTRIBUTION IN THE 50TH INTERNATIONAL CONGRESS OF THE SOCIETY FOR MEDICINAL PLANT RESEARCH

This year saw the 50th International Congress of the prestigious Society for Medicinal Plant Research. Indena was indeed proud to be amongst the sponsors of this important event, which took place in Barcelona. From 8th to 12th September, experts from the world over converged on the Catalan capital where they were to debate topics such as the analysis of complex mixtures of natural products. Natural anti-inflammatory treatments were high on the agenda, which also included the newer issue of clinical research on phytopharmaceuticals and opportunities to explore the less familiar areas of medicinal plants from Latin America.

Paolo Morazzoni, Indena's Scientific Director, and Ezio Bombardelli, who chairs the Scientific Board, spoke of the new perspectives in the "phytoequivalence" of botanical derivatives. Extracts could be standardized only on the basis of a combination of strict plant cultivation and harvesting conditions followed up by rigorous industrial extraction procedures. "Only by using this approach" - stated Morazzoni - "could well characterized and reproducible extracts be

prepared and submitted to the stringent pre-clinical and clinical investigations which meet the pharmaceutical guidelines". On the other hand, in non-pharmaceutical channels, the correspondence between the documentation and the composition of the products on the shelf was less tightly controlled. Dr. Bombardelli set out to underline how this aspect was crucial and damaged the consumer and producer alike. Whilst the consumer was denied any guarantee of safety and efficacy, producers of standardized and well-documented products were penalized by the lack of protection from their less scrupulous competitors. In the light of all this, "phytoequivalence" was becoming more and more a strategic issue. Nowadays, the utilization of sophisticated analytical techniques enabled the differentiation between the composition of extracts not only related to specific components but also to the unknown part. The combination of specific HPLC analysis with semiquantitative 1H- and/or 13C-NMR or NIR (Near Infra Red) Spectroscopy represents a sound approach to the question of phytoequivalence.

INDENA FINDS A NEW SETTING FOR THE JORNADA DE FITOTERAPIA

The seminar on excellence in phytotherapy meets in Mexico City

Following the success of Jornada de Fitoterapia, a one-day seminar that took place last year in Santiago, Chile, the company's Spanish affiliate, Indena S.A, organized a further meeting on February 8th, which this time was held in the Mexican capital.

As an international key player in researching and producing active principles and standardized derivatives of botanical origin, who better than Indena to illustrate the exciting opportunities offered by phytotherapy and unveil something of its own standards of excellence.

Dr. Francesco Di Piero, Indena's Senior Research Scientist, was called upon to expound on the increasing use of botanicals in the pharmaceutical, health food and cosmetics sectors. As regards the importance of botanical derivatives used as active principles, the figures speak for themselves: with over 1100 botanical extracts and around 200 pure products on the market, the business generated amounts to \$20bn.

Given the appreciation and interest shown by the audience, Indena looks forward to being able to repeat the experience in new markets where there is development potential.



Dr. Francesco Di Piero

BRINGING THE SCIENCE OF NATURE NEARER TO YOU

Mirtoselect® - New clinical studies on the Indena Bilberry Extract Mirtoselect® along with a thorough overview of all work to date in this area appear in the new product leaflet. Pharmacological studies show that Mirtoselect® is effective in increasing capillary resistance, reducing abnormal vascular permeability and performing antioxidant activity. Useful therefore in the treatment of microvascular disorders in ophthalmology and phlebology, Mirtoselect® is the only bilberry extract with clinically proven efficacy.

Greenselect® Phytosome - Tea drinking is believed to date back as far as 3000 BC in China, long before it became the tradition it is today in the English speaking world. The active constituents of tea leaves are a group of Polyphenols frequently present in green tea extracts. To overcome poor oral absorption and increase bioavailability, Indena has created a complex with soy phospholipids (Phytosome®) increasing antioxidant activity by 20%. Regular use of Greenselect® Phytosome helps protect and prevent oxidizing damage.

New launch - This year Las Vegas will see Indena launch a new botanical extract obtained through a patented extraction procedure. Unique triple standardization makes the extract an unparalleled immunostimulant as confirmed by *in vitro* and *in vivo* studies. Find out more, meet us at SupplySide West in Las Vegas!



The new Mirtoselect® leaflet is now available

A TOP QUALITY VANILLA EXTRACT FROM INDENA MADAGASCAR



Indena's Plant in Fianarantsoa

In December 1999, Indena acquired the Fianarantsoa manufacturing facility from the Madagascar government. The plant consists of two production lines, one for medicinal plant extracts, the other for alimentary plant extracts, where vanilla extraction began in 2001/2002. The process is completed in Indena's Palestro plant, in Italy (Bernett).

Traditionally, Madagascar has been a major producer of vanilla and the new production site in this African island country means that Indena can now provide top quality vanilla extracts at a very competitive price.

INDENA'S EXHIBITIONS AGENDA

- **CPhI 2002** - Paris, France
October 1-3, 2002
- **Health Ingredients Japan** - Tokyo, Japan
October 9-11, 2002
- **Supply Side West** - Las Vegas, NV, U.S.A.
December 4-6, 2002
- **Informex** - New Orleans, LA, U.S.A.
February 25 - 28, 2003
- **In-Cosmetics** - Paris, France
April 1-3, 2003
- **Supply Side East** - Secaucus, NJ, U.S.A.
May 5-7, 2003
- **Vitafoods** - Geneva, Switzerland
May 13-15, 2003
- **CPhI 2003** - Frankfurt, Germany
October 27-29, 2003



At Indena we believe that an in-depth knowledge in active ingredients derived from medicinal plants and the search for excellence at all times are crucial commitments to serving our customers in pharmaceuticals, health foods and cosmetics.

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