

# indena



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## **BOTANICAL EXTRACT STANDARDIZATION: THANKS TO INDENA THIS "CHALLENGE" GOES ON** *Francesco Di Piero and Ezio Bombardelli (Scientific Dept., Indena S.p.A., Milan, Italy)*

Over the last ten years there has been an important debate in major industrialized countries regarding the establishment of standardization criteria for botanical extracts. The debate is not over and the issue is still open.

It is generally accepted that to obtain a truly reproducible (mostly in terms of safety and efficacy) botanical derivative intended for human use, all its constituents must be stable, unchanged and consistent over time, and devoid of unpredictable toxicity and/or side effects. Currently no one is able to guarantee that these standards are being met. Instead, an extract is generally referred to as "standardized" when it is simply characterized by one or two standardized fractions. Is it actually possible to develop and produce "true" standardized extracts? And, if so, how should we go about achieving these results?

"Normal" standardization is already a hard task. The steps involved in this procedure - from the biomass (according to GAP), to the chemical isolation and characterization of the active reference compounds, from the setting up of validated analytical methods, to the final production process

(according to GMP) - give rise to a product that is reproducible only in terms of active ingredients and/or chemical markers. Obviously, obtaining a "true" standardization - that is, the reproducibility of all the components contained in the extract, including unknown ones, is a much more difficult task, but it will be absolutely essential in the future. As a matter of fact, very often two standardized products which are obtained from the same botanical species and are apparently overlapping according to their declared active ingredient content, may actually have very different profiles in terms of solubility and bioavailability. This is due mainly to the chemical and biological characteristics of the unknown fraction, which in reality should be characterized and standardized. Furthermore, two products with such different profiles cannot be considered comparable in terms of their major biological characteristics - that is, their safety and efficacy.

To truly standardize any extract the best procedure to follow, after determining a quantitative value of the active principles (by HPLC and GLC), should be first to fix a reciprocal ratio, with very strict limits, between no less than two classes of substances present in the extract (i.e. the active principles and some compounds characteristic of the extract); and second, to chemically characterize the remaining portion of the extract through spectroscopic analysis (i.e. FT-IR and <sup>13</sup>C-NMR).

As a result of these two further steps, a perfect reproducibility of the extract could be achieved and every standardized extract would then be provided with a fingerprint for its complete qualitative evaluation. Moreover, this fingerprint would enable to both verify batch-by-batch production and determine the quality of the extracts already present on the shelves. It would also allow the possibility of linking documentation (pharmacological, toxicological and clinical) to a given product, rather than the opposite. In a few words, this new approach would make the production of very highly standardized extracts possible. These products, in terms of reproducibility and stability control, would compete with pure pharmaceutical compounds and, as regards to safety and efficacy, would satisfy the requirements necessary for human use. This, for the consumer, sounds very advantageous.



Settala's plant overview

## **INDENA'S POSITION ON DIETARY SUPPLEMENTS GMPs**

The U.S. FDA has recently announced that it plans to issue new GMPs for dietary supplements (DS). At present the DSHEA (Dietary Supplement Health and Education Act - 1994) states that the manufacturing process of DS should comply with food GMPs. Indena agrees that this may be the best way to establish new regulations for DS in general (vitamins, minerals, etc.). However herbs and herbal extracts should be treated differently because of their peculiarities. A safe botanical product is first and foremost a high quality product, which means that a manufacturer must monitor the entire production process from the plantation stage, through the performance of botanical and chemical analyses on the biomasses to be employed, and finally the safety and quality control mechanisms that govern

the production process and the distribution of the final product. Regarding the issue of establishing new DS GMPs, Indena believes that the new rules should be very similar to GMPs for pharmaceuticals. Performing all the steps necessary to ensure a safe product is expensive and requires a large investment in organization as well. It is highly likely that many smaller companies (and some larger ones, as well) might not accept such a proposal because they may be unable or unwilling to make the changes necessary to comply with the new rules. Therefore, as a starting point, Indena advocates the strict application of the rules contained in the February 6<sup>th</sup>, 1997 Advanced Notice of Proposed Rulemaking (ANPR).

## DR. ED CROOM, JR. JOINS INDENA USA

Edward M. Croom, Jr., Ph.D. has joined Indena USA East as Scientific and Regulatory Affairs Manager.

"Indena continually encourages the botanical industry to raise the standard for quality, safety and consistency of all botanical products. - Indena's Managing Director Mr. Dario Bonacorsi stated - We are proud to welcome Dr. Croom to our company for his experience, his extensive knowledge of the natural products industry and his firm relationships with government agencies and congressional staff. Dr. Croom will work with scientists and regulatory authorities to assure that these high quality standards will soon be adopted – thus insuring that the millions of health-conscious consumers taking herbal supplements will be getting a legitimate product that provides the desired effect." As an expert in plant-derived therapeutic

agents and botanical medicine, Dr. Croom specializes in studying traditional medicine and applying the science of natural products to enhance human health. Prior to joining Indena, he served for 18 years as research scientist at the University of Mississippi's School of Pharmacy and as Associate Professor of Pharmacognosy. The author of many scientific articles, Dr. Croom headed the production of the plant-derived anti-malarial agent Artemisinin for the World Health Organization and worked for six years to develop a sustainable supply of the anti-cancer drug Paclitaxel from cultivated Yew needles. Furthermore, he has given presentations on botanical medicine to the National Institutes of Health (NIH) and the U.S. House of Representatives. His professional activities have included positions on the U.S. Food and Drug



Ed Croom Jr., Ph.D.

Administration's Food Advisory Committee, the NIH Center for Complementary and Alternative Medicine Ad Hoc Review Panel, the NIH Special Emphasis Grant Panel for AIDS and Cancer and the NIH Ginkgo Extract Manufacturer Advisory Committee. Dr. Croom also served on the U.S. Pharmacopeia Committee of Revision from 1995 to 2000.

## FDA APPROVES PHASE I CLINICAL TRIALS FOR POTENTIAL NEW ANTI-CANCER COMPOUND LICENSED TO BAYER BY INDENA



In October 2000, the active agent IDN 5109/BAY 59-8862 has received approval from the U.S. Food and Drug Administration to begin Phase I clinical trials. The FDA's decision to grant Investigational New Drug status (IND) to IDN 5109/BAY 59-8862 will allow researchers to evaluate the safety of this active compound. Following an agreement signed in March 2000 at Bayer's Leverkusen headquarters in Germany, Indena will supply the German multinational, on an exclusive world-wide basis, with a naturally derived anti-cancer active

substance. This could pave the way for a new generation of anti-cancer drugs. The subject of the agreement was the active principle IDN 5109, a compound patented by Indena and developed in conjunction with top Italian and US oncological centres. IDN 5109 is obtained by means of semi-synthesis

starting from 14-OH DAB (14-β-hydroxybaccatin III), a molecule extracted from leaves of the Taxus genus. 14-OH DAB is able to originate a series of derivatives, featuring cytotoxic activity, among them IDN 5109. They too are patented and have been licensed to Bayer. The IDN 5109 molecule is highly innovative in terms of effectiveness and bio-availability. Based on present scientific evidence the new active ingredient has a better anti-cancer profile than the taxanes currently available, i.e.

paclitaxel and docetaxel. The molecule in fact seems to open up the perspective of treatment of currently incurable cancers, such as those of the colon and kidneys.

Indena has now completed all the pre-clinical trials, while Bayer is carrying out the work on the new molecule by means of clinical tests and will then market its formulations. Indena has been contributing to the publication of more than 70 scientific studies concerning taxanes, of which about ten have been dedicated to the IDN 5109 molecule since 1992. Now Indena has produced substantial quantities of paclitaxel and of the intermediate principle used for its semi-synthesis employing plant biomasses for 7 years. "We have always been a key point of reference for our customers in the industrial development of patents for naturally derived substances", Mr. Bonacorsi (Indena's Managing Director) points out, "but it is the first time that Indena research has developed and patented, co-ordinating and drawing on the work of leading world research centres, a molecule of this importance. We hope to repeat the experience in the not too distant future with other original molecules that are already at an advanced stage of development."

## A PROMISING DIRECTION FOR CARDIOVASCULAR DISORDERS AND SENILE DEMENTIA/ALZHEIMER'S DISEASE

Indena has introduced a standardized *Ginkgo biloba* L. complex with a high level of bioavailability at a U.S. scientific satellite symposium organized by Indena during the annual meeting of the American Society of Pharmacognosy on July, 22<sup>nd</sup> 2000. This highly standardized complex of *Ginkgo biloba* L. should render the products containing this natural ingredient, used primarily in the treatment of cardiovascular disorders and in mild and moderate cases of senile dementia (including Alzheimer's disease), more effective.

The improved antioxidant activity of the *Ginkgo biloba* L. complex developed by Indena laboratories, patented as Ginkgoselect Phytosome<sup>®</sup>, largely results from the improved bioavailability of the principle, meaning that it is better absorbed by the body. "Complexing" *Ginkgo biloba* L. patented extract (Ginkgoselect<sup>™</sup>) with soy phospholipids has been shown to facilitate its assimilation, making it ideal for long-term treatment in cases of reduced cerebral performance.

### **GINKGOSELECT PHYTOSOME<sup>®</sup>** **A COMPLEXED GINKGO BILOBA L. EXTRACT**

Since 1986, the standardized extract of *Ginkgo biloba* L. leaves has been used to treat mild and moderate cases of senile dementia, with Alzheimer's disease making up 50-60% of these cases. Recent clinical trials have confirmed its efficacy and shown that it is well tolerated.

The standardization of medicinal plant derivatives is meant to guarantee the quality of plant-based extracts, and consequently to ensure that these extracts maintain a consistent level of efficacy. With this goal in mind, Indena devised a series of analytical tests that may be applied to *Ginkgo biloba* L. extracts in order to guarantee their efficacy and safety, and ensure that all potentially toxic substances are eliminated. During the preparation of these extracts, in fact, ginkgolic acids are removed, as they are known to have toxic and allergenic properties.

Pharmacokinetic studies conducted on healthy volunteers have demonstrated, however, that the standardized *Ginkgo biloba* L. extract has a fundamental limit due to the low level of oral bioavailability of flavonoidic components in particular, and of terpene trilactones as well. Indena's researchers have been able to improve the bioavailability of the standardized extract by using a complex prepared with soy phospholipids, known as Ginkgoselect Phytosome<sup>®</sup>.

Furthermore, this new ingredient has also shown an improved protective action against histamine-induced bronchoconstriction, through the activity of the terpene trilactones contained in the plant.

Studies conducted by Indena have led to the conclusion that Ginkgoselect Phytosome<sup>®</sup> demonstrates a superior level of pharmacological activity compared to other standardized *Ginkgo biloba* L. extracts, and is ideal for long-term treatments because of its greater efficacy at lower doses.



*Ginkgo biloba* L.



Speakers' desk

Comparative pharmacodynamic *in vivo* studies have demonstrated increased pharmacological activity of flavanol glycosides and terpene trilactones - the primary active ingredients contained in the leaves of the plant - in the complexed form of the extract. The first toxicological investigations have suggested that the complex is well tolerated in pharmacologically active doses, without inducing significant changes in bleeding time.

"This is an ingredient," explained Paolo Morazzoni, Scientific Director at Indena and member of the Committee of Experts of the United States Pharmacopoeia, "that is more effective, safer, and of higher quality, which can be used to manufacture Ginkgo-based products of an elevated qualitative standard."

The particular value of this innovation is linked in part to the ever-increasing incidence of neurological and psychiatric disorders associated with old age, such as cerebral insufficiency and senile dementia, which have become more common in recent years as the global population average age increases.

"The presence on the market of products of dubious quality, which exist because of inadequate regulation of natural dietary supplements," said Ezio Bombardelli, President of Indena's Scientific Board, "makes it imperative that companies above all promote and guarantee the quality and the efficacy of their own products, allowing consumers to demand and recognize quality, efficacy, and safety in the natural dietary supplements they purchase."

Indena applies its scientific and pharmaceutical expertise to the development and production of standardized extracts for the dietary supplement market, which are backed up by extensive research as well as pre-clinical and clinical trials.

## INDENA'S SCIENTIFIC DIRECTOR IN THE BOARD OF UNITED STATES PHARMACOPEIA

Indena's Scientific Director, Dr. Paolo Morazzoni has been nominated member of the Advisory Panel on Analytical Methods of USP (United States Pharmacopeia). USP promotes public health by establishing and disseminating officially recognized standards of quality and authoritative information for the use of medicines and other health care technologies by health professionals, patients, and consumers.



Dr. Paolo Morazzoni

## AN EVENING OF EXCELLENCE

On November 7th during the busy days of the CPhI 2000 in Milan, Indena invited its customers and international contacts to enjoy an evening in the evocative setting of a noble palazzo once owned by the Visconti, the former Ducal family of Milan. The guests experienced an unusual atmosphere, enjoyed a piano concert performed by Maestro Marco Alesi in a spectacular frescoed ballroom, and had the occasion to get to know Indena's paradigms: "Research is our Art, Excellence is our Tradition, Science is our Nature".



Marco Alesi's performance

## INDENA INAUGURATES ITS JAPANESE BRANCH

Re-asserting its strategic interest in Far Eastern markets, Indena officially opened its sales branch in Tokyo in July. Indena's straight presence on the Asian continent confirms the international character of the company, which already has several branches in Europe and in the United States. The branch will be managed by Mr. Susumu Kawada, who will be responsible for sales and marketing of pharmaceutical products, health-foods and "beauty-foods" for the Japanese market, while Nikko Chemicals Co. Ltd. will continue to distribute the company's cosmetic ingredients.



Mr. Susumu Kawada

## INDENA'S EXHIBITIONS AGENDA

- **Nutrionals 2001** - Anaheim, CA, USA (January 29- February 1, 2001)
- **The 5th Scientific Conference of the Asian Societies of Cosmetic Scientists** - Bitec, Bangkok, Thailand (March 1-3, 2001)
- **Vitafoods International 2001** - Palexpo, Geneva, Switzerland (April 24-26, 2001)
- **In-Cosmetics** - Düsseldorf Messe, Düsseldorf, Germany (April 24-26, 2001)
- **SupplySide East** - Meadowlands Exposition Center, Seacaucus, NJ, USA (May 7-9, 2001)
- **Health Ingredients Japan** - Tokyo, Japan (September 26-28, 2001)
- **SupplySide West** - The Venetian & the Sands Expo, Las Vegas, NV, U.S.A. (November 28-30, 2001)
- **CPhI** - ExCel Expocenter, Docklands, London, UK (October 8-10, 2001)

## INDENA'S SCIENTIFIC AFFILIATIONS

Indena's scientific experience is appreciated by many international organizations. Indena scientific affiliations include: United States Pharmacopoeia and American Society of Pharmacognosy (Dr. Ezio Bombardelli, President of Indena's Scientific Board and Dr. Paolo Morazzoni, Indena's Scientific Director). European Phytochemical Society and New York Academy of Sciences (Dr. Bombardelli), Society for Free Radical Research (Dr. Morazzoni) and Italian Pharmaceutical Society (Dr. Antonella Riva, Indena's Scientific Direction).



*Indena is the world's leading company dedicated to the identification, development and production of active principles derived from plants, for use in the pharmaceutical, health-food and cosmetics industries.*

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