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## INDENA WELCOMES NEW FDA RULES ON GMP STANDARDS

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The promised initiative taken by the FDA to develop GMP standards for dietary supplements is creating an opportunity for the whole industry and the FDA to refocus GMP compliance in an area which impacts millions of people. The proposed regulations, which exceed 500 pages, are to be applied to all firms that manufacture, package or hold dietary ingredients or dietary supplements. They will set down requirements for designing and constructing physical plants, establishing quality control procedures, testing manufactured dietary ingredients and dietary supplements, record keeping, and much more.

Not only industry associations, but also the main botanical manufacturers have their chance to review and comment upon the new rules. The overall aim is clearly to guarantee the quality and safety of products and ingredients, ensuring that dietary supplements are made in a consistent way, with uniform quality, regular composition, and free of potential contaminants. FDA would also have the authority to determine standards that firms should apply in production and labelling.

Indena has carefully reviewed these regulations, and submitted its own appropriate comments on them, particularly with regard to the quality and safety of botanicals:

*"Dietary ingredients suppliers should be*

*adequately qualified to assure the consistent quality and safety of the supplied product."*\*

Specifically validated or official analytical methods, which guarantee standardisation of active principles, must be implemented to ensure exact reproducibility of the products, so that the efficacy and safety may be taken for granted even in natural extracts.

It is well known that Indena has long been investing in sophisticated analytical equipment and in training skilled personnel to make its analysis department a benchmark for the industry.

Once a proper method of analysis has been correctly implemented, by monitoring the process parameters and with wide expertise in the extraction phase, Indena is also able to guarantee batch to batch consistency. This exact overlapping of a product's fingerprints is another key point in ensuring proper standardisation. Since the supply chain of a botanical extract is very backwards-integrated, it is essential that: *"methods are in place to guarantee that an adequate botanical identification of the starting plant material occurs in order to avoid any misidentification with any poisonous plant material."*\*

Indena continues to affirm the importance of unequivocal quality procedures not only with the dietary supplement, but even during the crucial phase of the extraction of botanical ingredients. Final product quality can thus be ensured when adequate care is maintained from the very early stages of plant growth. The proper recognised authorisation of ingredient manufacturers, within strict quality criteria, is in fact required to demonstrate compliance with any final GMP, and should cover the total characterisation of the extract, standardisation, consistency of batches and rigorous controls of the biomass. Indena strongly believes this new regulation is bound to improve the quality of dietary supplements in the US, and will afford greater consumer protection in what is the world's largest market for such products.

\* Extract from "Indena's Comments" sent to the FDA (August 7, 2003)

## AUTOMATION INCREASES INDENA PROCESSING-PLANT EFFICIENCY

An innovative automation system has been set up at the main Indena manufacturing site, in Settala in Italy. New dedicated software has been installed in the department where the active pharmaceutical ingredient for the oncology drug paclitaxel is purified.

This higher level of automation gives operators greater control over manufacturing operations and maintenance of valuable equipment such as reactors and chromatography columns. The new software, DeltaVBatch and AMS, could be soon extended to other plants on the site.



The new automation system

## INDENA REVEALS LATEST WORK ON IDN 5390

Two recent congresses have given Indena researchers the opportunity to highlight their work on the new experimental molecule IDN 5390, presenting no less than four pre-clinical studies on this anti-tumour agent, which like paclitaxel derives from the yew-tree. IDN 5390 is the molecule which is currently at the forefront of Indena research, given its promising profile of low toxicity, its selective activity in the inhibition of angiogenesis and the fact that it may be administered orally. The new molecule is today considered a prototype for a new class of effective and less invasive chemotherapy treatment. IDN 5390 allows metronomic chemotherapy treatment, which put simply means lower less toxic doses over a longer treatment time.

New evidence to support IDN 5390 was illustrated at this year's Freiburg international symposium on new anti-cancer agents<sup>1</sup>. *In vivo* tests on IDN 5390 involved the administration of doses of up to 4.5 g (a quantity 20 times more than the maximum dose of paclitaxel), which, during the 9 weeks of treatment, gave no evidence of toxicity. Metronomic treatment using IDN 5390 proved to be efficient against a wide range of human tumours transplanted *in vivo*,

but also for tumours resisting treatment with paclitaxel, which is still the most common taxane used in chemotherapy. Finally, the anti-tumour effects of IDN 5390 can be compared to the optimal effects of paclitaxel, but in some types of tumour such as ovarian carcinoma, resistant to both paclitaxel and cisplatin, IDN 5390 clearly has an important anti-tumour effect.

Other relevant IDN 5390 results were presented in Washington at the 94<sup>th</sup> annual meeting of the American Association of Cancer Research, AACR<sup>2</sup>, the world's most important oncology event. The data, presented as a poster, described the pharmacokinetic profile of IDN 5390, which confirms the peculiarity of this drug.

All this work is fruit of collaboration between Italian and American institutes such as *Rome's Catholic University of the Sacred Heart*, the *Istituto Nazionale dei Tumori* and the *Istituto Mario Negri* in Milan, the *Roswell Park Cancer Institute* in Buffalo and New York's *Stony Brook University*.

1. "Novel Approaches for the Discovery of Anticancer Agents" (June 18-21, 2003), organised in Freiburg (Germany) by the Central European Society for Anticancer Drug Research (CESAR) and the Freiburg University Tumour Biology Centre.

2. 94<sup>th</sup> Annual Meeting of the American Association of Cancer Research, AACR, (July 12-14, 2003), Washington D.C.

## A NEW R&D SECTION ON WWW.INDENA.COM



[www.indena.com/usrrd\\_log.asp](http://www.indena.com/usrrd_log.asp)

A new section of the Indena website entirely dedicated to new experimental molecules of botanical origin is now on line. Phytotherapy researchers, specialists and indeed anyone interested can now view the work of the Indena

Research and Development Laboratories. Access is only a click away: position the cursor on the *About Us* menu on the top left hand side of the home page and click on *Indena R&D*.

Visits to this new area are restricted, but available to all using a username and password, which will be sent by email on completion of a simple on-line registration form.

The section contains information and materials on molecules being studied by the Scientific Department.

Indena offers many promising solutions in the development of innovative drugs especially in the fields of oncology and the central nervous system. The company will grant licences for molecules identified and developed up to Clinical Phase I.

## INDENA WELCOMES VISITORS AT ITS BOOTH IN ONCOLOGY CONVENTIONS

It started in November, 2002, at the Frankfurt AACR-NCI-EORTC congress. Not only was Indena present at one of the most important oncology conventions, with its research lectures and posters, but the company also set up a welcoming booth to meet with researchers and colleagues from all over the world.

The 94<sup>th</sup> Annual Meeting of the American Association for Cancer Research (AACR) in Washington again saw Indena's active participation. Our researchers, supported by major Italian Research institutes, presented two new posters illustrating important aspects of the pre-clinical work on the novel antitumoral molecule IDN 5390 and pharmacological resistance in treatments with taxanes.

And the Indena booth is to reappear this November in Boston where the company will be able to welcome researchers, colleagues and friends to the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics.



Indena's booth

## FOOD SUPPLEMENTS CAN MAKE YOU BEAUTIFUL



Indena's new cosmetic advertisement

“Oral beauty” is a new stage in cosmeceutical development. Studies in cosmetic nutritional supplements have led to the creation of new oral products which are attracting market attention the world over. Mainly of natural origin, these supplements are enriched with active ingredients which can have beneficial effects on skin, hair, wrinkles, etc. The scientific significance of cosmetic nutritional supplements is growing as the relationship between nutrition and cutaneous physiology is investigated. Indena is deeply involved in the development of new ideas, projects and formulations based on the company's extensive know-how in applying phytotherapy to cosmetics, as demonstrated

by its close, successful cooperation with one of the major “nutricosmetics” companies, Inneov. Indena has already developed formulations with “cosmeceutical” properties, which have brought about the launch, for example, of Alextar®, a patented blend of natural antioxidants from grape seeds and the tomato plant. Indena is now working on the further development of new “oral beauty products”, for a wide range of applications.

### HERB MEDICINE SAFETY DISCUSSED IN JAPAN

Eighty seven people attended the “International Symposium on Health Supplements - Safety and Effectiveness of Herb Medicines” - held on Wednesday, October 9<sup>th</sup> at the Toranomon Pastoral Hotel in Tokyo. The event was sponsored by the Japan Health Food & Nutrition Food Association, whose General Director, Mr. Hosoya, opened the proceedings.

*“Now that the establishment of standards for ginkgo biloba extract is just around the corner,” commented Mr. Hosoya, “I feel certain that there can be no better time to hear from both Japanese and European herb medicine researchers about the quality control, safety and effectiveness of herbs as well as the status of herb supplements in the West.”* Mr. Motokichi Satake, the Executive Director of the Japan Bath Agents Industry Association delivered a lecture entitled “The Effectiveness and Safety of Curative Plants and Herbs”. He was followed by Indena's lecture on the quality and standardisation of herbs, and by Dr. Mathes from Schwabe Pharmaceuticals who examined the present and future of herb supplements in the western world. The open discussion on making herbal extracts OTC is very active in Japanese Ministry of Health, who is considering the most interesting and long used botanicals to create a new pharma category in the market.

## NEW OPPORTUNITIES FOR BOTANICALS

Ingredients not only for health foods, pharmaceuticals and cosmetics: botanicals are becoming ever more important in other markets where the value of natural products is now being appreciated.

Following this trend, animal care comes next after caring for humans: and among other initiatives whole new pet-care lines for instance are gaining popularity. Worldwide market attention is being drawn to new antidepressants for dogs and cats, immunoboosters and other kinds of supplement, as well as animal breeding enhancers. Optimising domestic animal feed is just one of the possible applications.

Another surprising area for botanicals is in the field of crop protection itself. The growing interest in organic cultivation, in fact, is promoting deeper research into interaction between plants, as well as between plants and insects or parasites, and likewise the creation of solvent-free crop pesticides is subject of new studies.

The huge chewing gum business is also about to be given a therapeutic makeover. Mint is already a well-known mouth freshener, but also other botanicals with biological activity may well be added to help prevent allergies, improve vision or sharpen mental cognition. It would be a strong temptation for today's consumers if they thought they could alleviate hay fever or learn

more easily by simply chewing gum.

More and more “functional” and “fortified” foods are finding a place in our diet. One example is the steadily growing business in food bars containing soy extracts, natural antioxidants and vitamins.

A further interesting trend in today's market is led by research into scientifically rational combinations of different botanicals. These will have complementary biological activity, but are endowed with different action mechanisms. This outcoming synergy of ingredients may often offer a higher efficacy. It is for this reason, after years of domination of “stand alone” products, combinations are now finding their real own market niches.

These diverse and exciting new applications for botanicals present new opportunities for the industry. Indena researchers are rising to the challenge.



## POLINACEA™: THE LATEST HIGHLY EFFECTIVE INGREDIENT FROM ECHINACEA

Indena has launched its totally new natural immunobooster, an innovative standardised extract derived from the roots of *Echinacea angustifolia*. The ingredient, branded Polinacea™, was presented to an invited audience of partners and professionals during the SupplySide West trade fair in Las Vegas, on December 6<sup>th</sup> 2002.

Polinacea™ alone is characterised by a unique triple standardisation that makes it different from all other Echinacea extracts. Polinacea™ is chemically defined by at least a 4% echinacoside content and 5% IDN 5405, a newly discovered polysaccharide, which contributes to immune stimulating effects. Moreover, Polinacea™ does not contain isobutylamides as they do not add any biological activity but it does contain inulin, in order to enrich the extract with a prebiotic profile.

On the basis of the results obtained from a series of *in vitro* and *in vivo* studies, Polinacea™ may well be considered an excellent immune response improver. In immunocompetent mice challenged with the parasitic infection *Leishmania major*, the extract reduced the experimentally induced leishmaniasis by 25%. In addition, Polinacea™ reduced by 30% and 40%, respectively, the *Candida albicans* induced mortality in immunocompetent and in cyclosporin A treated mice. In the same model, the best selling Echinacea product failed to produce such results. The mechanism of action consists in a direct action on T cells. In toxicological studies, Polinacea™ did not exhibit any adverse effect at doses ranging from 1g/die up to 1Kg/die. The recommended and suggested dose in health food application is 100-200 mg Polinacea/die for two weeks consumption.



*Echinacea angustifolia*

## A NEW INDENA OLIVE EXTRACT

The olive tree has long provided one of man's healthiest foods. Olive oil is a precious part of our Mediterranean diet valued for its high content of antioxidant compounds. Recently, its consumption has been associated with a decreasing incidence of cardiovascular disease. Indena has developed an olive extract, distinct from others on the market. The Indena extract is in fact obtained from the fruit of the olive, those very olives which have been pressed since time immemorial to produce our cherished oil.

Research started with careful selection of the *Olea europaea* cultivar, in order to control the quality of the raw material through the manufacturing process from the outset. Phytochemical analysis and industrial scale up led to the development of an efficient extraction procedure using the solid olive residues which

are a by-product of the virgin olive oil pressing process, with ethanol (besides water) as the only solvent.

In order to guarantee batch to batch consistency, harvesting and storage of this particular botanical matrix have been rigorously implemented. Characterised by the presence of a very high polyphenol content, the Indena olive extract offers a remarkable *in vitro* profile, and is a suitable antioxidant ingredient.



*Olea europaea*

## INDENA'S EXHIBITIONS AGENDA

- **CPhi 2003** - Messe Frankfurt, Germany  
October 27-29, 2003  
Booth G810 - Hall 8.0
- **AACR-NCI-EORTC Int. Conference:**  
"Molecular Targets and Cancer Therapeutics"  
Boston, Hynes Center, MA USA,  
November 18-21, 2003
- **INFORMEX** - Las Vegas  
The Venetian & The Sands Expo, NV, USA  
January 19-22, 2004
- **IN-COSMETICS 2004**  
Milan, Fiera di Milano, Italy  
April 27-29, 2004  
Booth L20 - Hall 20/1
- **Supply Side West** - Las Vegas  
The Venetian & The Sands Expo, NV, USA  
September 29 - October 1, 2004
- **Health Ingredients Europe**  
Amsterdam RAI, The Netherlands  
November 16-18, 2004
- **CPhi 2004** - Brussels, Belgium  
December 7-9, 2004



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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