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NEW RULES MEAN NEW CHALLENGES FOR PHYTOTHERAPY

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Something is moving in European herbals regulation: all European member States are required to implement two new directives from October 2005. Directive 2004/27/EC specifies the GMP requirements for the production of drug products and their intermediates and actives. At the same time, it implements a sort of Bolar clause, facilitating the procedure to get generics authorized. Directive 2004/24/EC includes an easier registration track for herbal medicines providing they have demonstrably been on the market for 30 years (at least 15 years inside EU) and that they have an acceptable safety profile, compatible with self-medication.

Does the implementation of these directives bring innovation possibilities for phytotherapy? On the one hand they make it easier for natural derivatives to maintain or acquire pharmaceutical status, for which formerly they did not qualify. On the other, whilst the pharmaceutical law applies very well to pure molecules, it creates insurmountable barriers to the registering of phytocomplexes. The directives also contain a series of factors which circumscribe the possibility of obtaining marketing authorization. The time limit (30 or 15+15 years for traditional products and 10 years for well-established ones) actually denies

any chance of developing innovative products. Costs and the time frame required are in fact comparable to the registration of a new drug. On the other side, natural derivatives used as ingredients in food supplements can easily represent innovative products on the market, thanks to greater flexibility permitted by the present legal framework for food. The main concern of food legislation is to safeguard consumer health by ensuring the absence of dangerous contaminants, such as pesticides, or heavy metals. Food regulations do not detail the peculiarities of natural derivatives such as the content in active principles. They only require that the product should not be harmful in the normal condition of use. This scenario could deter firms from choosing the pharmaceutical route for phytocomplexes and spur them to pursue development only in the food market. However, the following elements should be considered:

- Standardized extracts come from a complex sum of variables including botanical controls, and the monitoring of all the production steps according to GAP and GMP ensures an active principle with a constant and reproducible quality.
- These rules should be strictly applied to the production of natural derivatives, where the variation of a single parameter could bring about differences in composition, biological activity or safety profile.

Consumers need not be concerned about the total safety of their food supplements, in terms of absence of contaminants, but they also require to get products with constant quality and reproducible efficacy, through an effective content in active principles, etc.

This means that even the natural derivatives in food products should be produced in a way corresponding to their specifics, assured by the stringent drug industry rules.

Without waiting for the requirements set out in the new directives, Indena has already put in place all the necessary steps to give value to the unique potentiality offered by natural derivatives.

STATE-OF-THE-ART MANUFACTURING FOR HISTORIC PRODUCT

Innovative equipment has recently been installed to process ethanolic bilberry extract at Indena's main production site in Settala, Italy. With up to 26,000 kg of bilberry processed every day, the plant has an annual production capacity of 45 tons. A highly automated electronic control system allows the operator to monitor the entire process from a single position. The dedicated plant will process one single product and solvents used are purified within the same structure. Engineered for the production of bilberry extract, it may well be used in the future for products with a similar manufacturing process.



BILBERRY EXTRACTS: NO MORE HALF-TRUTHS

Different analytical methods used on bilberry extracts are described in specialist sources such as official pharmacopeias and scientific literature. However, most of them are inappropriate for the identification of anthocyanins, the natural pigments responsible for the biological activity of the extract itself. Indena has recently developed and validated an HPLC method that allows the identification and the direct quantification of all bilberry anthocyanins both in plant material and in extracts. This overcomes all the analytical failings of the previous methods and spots low quality or adulterated extracts.

The method is characterized by good reproducibility and high specificity, as it is able to identify unequivocally the botanical raw material used as well as evaluating the composition of the extract. This innovative procedure provides not only an effective solution to a well-known

problem in the analytical determination of the active constituents of bilberry extracts, but also an additional safeguard for Indena's bilberry extract Mirtoselect®.



ITALIAN ONCOLOGICAL RESEARCH MAKES A STEP FORWARD

Indena's Scientific Board in cooperation with the researchers of Oncological Gynaecology at Policlinico Gemelli in Rome have presented the results of two studies¹ which open up new avenues in overcoming resistance to anticancer therapies. The first study identified a new mechanism of action of Paclitaxel, one of the most common anticancer drugs derived from the leaves of *Taxus baccata*. The newly identified mechanism concerns the Bcl-2 protein, whose original function was to prevent the apoptosis or death of cancer cells. Paclitaxel has however shown the capability to convert the function of Bcl-2 protein, thus promoting cancer cell death. A second study shows the important activity of the taxane derivative IDN 5390 in the treatment of Paclitaxel resistant tumors. The results indicate that the highly bioavailable taxane IDN 5390 targets beta III tubulin, a protein that, when abundant, constitutes a mechanism of resistance to taxanes. According to Dr Ferlini of Policlinico Gemelli, "The combination of Paclitaxel and IDN 5390 may represent a new therapeutic approach as there is a high level of synergy between the two molecules".

1. Presented at 96th Congress of American Association for Cancer Research and published on *Cancer research* 65, (6), 2397, 2005



Press briefing on taxanes - Milan, 28th April 2005

INDENA 30: QUALITY YOU CAN COUNT ON



The Indena 30 Quality logo

The Quality System developed by Indena is based on over 30 different controls covering every phase of production from start to finish designed to ensure the safety, consistency and traceability of every single batch. This leading-edge system is a uniquely reliable foundation on which the manufacturing process of a botanical extract is built. In line with current QA procedures, the quality of herbal products is constructed throughout the manufacturing process starting from the very outset, even before the plant sees the light of day. The

high quality of the raw material is an essential precondition, which affects all subsequent steps. As part of our Good Agricultural Practices, preliminary inspections are carried out therefore on harvesting methods and periods, drying conditions and storage, before the biomass ever reaches our warehouse. Botanical identification and checks for any contaminants follow. The raw material can then be released for production, which complies fully with GMP, following well-defined procedures and analyzing all critical phases. All the data are thoroughly documented, detailed and double checked in order to build up a Master Batch Record. Once the manufacturing process is complete, the finished product undergoes final analysis and controls to assure compliance with its standardized characteristics and quality, employing leading edge technology equipment such as HPLC and NMR and applying validated analytical methods.

This Quality System is an Indena hallmark that demonstrates the company's commitment to continuous research and quality improvement.

INDENA HOSTS THIRD MEDICINAL CHEMISTRY GROUP MEETING

The Third Medicinal Chemistry Group Meeting took place last May at the Indena headquarters in Milan. The meeting, which was coordinated by Indena's Research Manager Gabriele Fontana, brought together the main research centers cooperating with Indena on the identification and development of new taxanes for anticancer applications.

The aim of the working group was to analyze critically the results obtained on the active principles belonging to the taxanes group in order to select the proper candidates for pre-clinical investigation. The chemical and pharmacological profile, as well as the peculiarities of the new molecules were evaluated, and four new compounds selected



The Medicinal Chemistry Group

for additional pharmacological evaluation. The good results obtained to date are a confirmation of the important synergy which has developed between Indena and its collaborating research centers of excellence.

CHINESE MEDICINE OPENS TO WESTERN SCIENTIFIC APPROACH

The holistic vision of Traditional Chinese Medicine (TCM) considers the human well being as the result of a complex balance between psychology, energy, physiology and spirit, far from the scientific and schematic approach of western medicine.

These two mindsets were brought a step closer last June when a meeting took place at the University of Milan between a Chinese delegation and Italian experts.

This initiative emerged from an agreement signed last May by the Chinese Ministry for Science and Technology and the Italian Ministry of Health. The aims of this agreement were to evaluate possible synergies and opportunities for substances used by TCM.

The Chinese consider nature to be an immense resource for human well being and for many centuries their traditional medicine has made use of a whole range of natural substances. By both building on the TCM tradition and adopting a western scientific approach, new active ingredients might well be investigated as innovative opportunities to be developed.

According to Paolo Morazzoni, Indena's Scientific Director, "Chinese tradition offers several pointers for the study of new plants using our scientific methods: but it is only the standardization of botanical extracts which allows exact reproducibility and gives a guarantee of efficacy and safety".

With a view to giving the Chinese delegation a more complete picture and a better understanding of the western approach, a presentation of European GAP and GMP was made by Indena.

INDENA MANAGERS DON CAP AND GOWN

Indena's educational thrust is becoming more university oriented: a growing number of students in various disciplines are in fact attending lectures and seminars given by Indena's professionals. As part of the Milan University Drug Chemistry PhD program, Gabriele Fontana¹ presented the process of drug discovery of anticancer molecules, focusing on Camptothecin and its derivatives. Fontana has also given lectures on drug discovery from natural substances within the Masters program on Drug Design and Development at Pavia University, and led a seminar on the historical case of Paclitaxel at the prestigious European School of Medicinal Chemistry in Urbino.

The complex issues of botanical identification,

botanical sourcing and quality control of biomass were examined by Renato Iguera² at the University of Turin. His colleague, Andrea Giori³ considered the criteria of industrialization and standardization and the development of new extracts, for the same post-graduate course, while Roberto Seghizzi⁴ and Massimo Ronchi⁵ lectured on formulation and regulation issues. Closer ties with universities mean bringing the industry into the heart of the academic world and for Indena sharing know-how with tomorrow's managers is a great way of investing for the future.

1. Dr G. Fontana, Research Manager
2. Dr R. Iguera, Botanist
3. Dr A. Giori, Development Laboratories Director
4. Dr R. Seghizzi, Technical Director
5. Dr M. Ronchi, Head of Formulation Development

BEWARE OF PHYTOTHERAPIC INFORMATION ON THE WEB

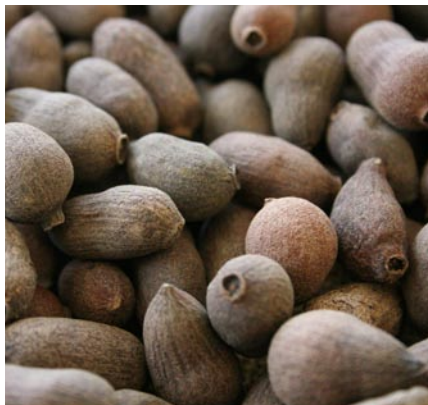
A recent investigation led by the Italian Center for Natural Medicine has shown that the information available on the Internet on specific herbal products is lacking in critical aspects, such as toxicity concerns or restrictions, and that banned products are even available on line. These findings have prompted Indena once more to reaffirm its commitment to the quality and the safety of botanical derivatives by defending phytotherapeutic ingredients and the scientific information behind herbal actives.



Ginkgo biloba

A NATURAL WAY TO MAINTAIN HEALTHY BLOOD SUGAR LEVELS

Type 2 diabetes is increasing worldwide in epidemic proportions, and hyperglycemia is recognized to be the main feature indicating a pre-diabetes phase which, in most cases, lasts several years. Though physical exercise, an appropriate diet and a healthy lifestyle provide the best approach to a pre-pathologic condition, normal glucose levels may also be maintained by means of a new patented ingredient, MADEGLUCYL[®], a botanical derivative obtained from the seeds of *Syzygium cumini*. This edible plant, also named *Eugenia jambolana*, has long been used as a remedy in Madagascar folk medicine, and toxicological and pharmacological data confirm that Madeglucyl[®] is devoid of any side effects. The efficacy of Madeglucyl[®] has been demonstrated by clinical data obtained from studies conducted in Madagascar, Germany and the USA, where it has been shown to perform its pharmacological activity after a mere 15 days'



Syzygium cumini fruits

treatment without any hypoglycemic effect being observed in healthy subjects. Indena recently presented the new dietary ingredient at Vitafoods, the nutraceutical market's prestigious international showcase in Geneva.

ANIMAL HEALTH: NEW PROSPECTS FOR INDENA

As for nutraceuticals in humans, a similar trend is developing in the animal health sector, both in livestock management and in pet care. The attention to supplements, mainly of natural origin, that may increase wellness and prevent diseases is in fact growing, and within this scenario Indena is investigating new opportunities in the veterinary market, focusing on innovative products. Patented botanical extracts have been developed as alternatives to growth promoter antibiotics in livestock to be banned from 2006. Some supplements of botanical origin are already available on the market: Silivet[™] for example is currently used in periparturient dairy cows to prevent lactation-related diseases and improve milk production.

Indena is also turning its attention to pet

care, since from a medical care standpoint, pets are beginning to emulate their masters sharing a range of pathologies from allergies to cardiovascular disorders, from degenerative joint disease to neoplasm.



INDENA'S EXHIBITIONS AGENDA

- **Health Ingredients Japan 2005** - Tokyo, Japan
October 5 - 7, 2005
Tokyo Big Sight Exhibition Center, Stand H - B402
- **6th International Symposium on the Role of Soy** - Chicago, USA
October 30 - November 2, 2005
Renaissance Chicago Hotel
- **CPhI 2005** - Madrid, Spain
November 1 - 3, 2005
Feria de Madrid, Stand 7G11 - Hall 7
- **Supply Side West 2005** - Las Vegas, USA
November 9 - 11, 2005
Sands Expo, Stand 5021 - Hall C
- **FCE Pharma 2006** - San Paolo, Brazil
April 18 - 20, 2006
Transamerica Expo Center, Stand 474
- **Vitafoods International 2006** - Geneva, Switzerland
May 9 - 11, 2006
Geneva Palexpo, Stand 444
- **Ingredients Beyond Beauty** - Paris, France
September 11 - 13, 2006
Paris Nord Villepinte, Stand F4 - Hall 4
- **Health Ingredients Europe 2006** - Frankfurt, Germany
November 14 - 16, 2006
Messe Frankfurt, Stand G31 - Hall 3.0
- **CPhI 2006** - Paris, France
October 3 - 5, 2006
- **Informex 2006**

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