



# Newsletter

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## WELCOME TO THE SECOND ISDB NEWSLETTER OF 2024

This issue provides information on several ISDB Members' publications and activities:

- A presentation of "*Boletín Informativo CIM - Centro de Información de Medicamentos*", a new ISDB associate member from Argentina, accepted earlier this year by the Executive Committee.
- An article on how drug regulation in the United States is failing patients, with proposals for change (provided by *PharmedOut*, US)
- Two articles on treatments for weight loss: one to be published in the forthcoming issue of the *Boletín de Información Terapéutica de Navarra, Spain* and the other published in *Prescrire International* (France, June 2024)

Last but not least, you will find a presentation of the Mario Negri Institute for Pharmacological Research (Italy), which was recently awarded the Edinburgh Medal. Enjoy your reading!

## THE NEXT NEWSLETTER IS PLANNED FOR SEPTEMBER 2024

We welcome comments, suggestions and articles. Please send them to [rkessler@prescrire.org](mailto:rkessler@prescrire.org) by end August 2024.

## ANNOUNCEMENT

### 2<sup>nd</sup> International Conference on Deprescribing, September 26-27, 2024, Nantes, France

Featuring the following interventions by ISDB Members:

Workshop 7 - Deprescribing long-term antidepressants: strategies for clinical practice: Ellen Van Leeuwen and Thierry Christiaens, CBiP-BCFi, Belgium

Workshop 12 - Finding the sweet spot: choosing glycemic control wisely for older adults with diabetes: Wade Thompson, Therapeutics Initiative, Canada

More information on the program and practical information [here](#)

Apparently, virtual attendance is possible.

## Presentation of a new ISDB associate member in Argentina

Boletín Informativo CIM - Centro de Información de Medicamentos, Argentina

By María Luz Traverso and Milena Bros

The Medicines Information Center (CIM) is a functional unit that operates within the Healthcare Pharmacy Area (Cátedra de Farmacia Asistencial) in the Pharmacy Department, of the Faculty of Biochemical and Pharmaceutical Sciences of the National University of Rosario.

CIM's main objective is to respond to the demand for information on medications, objectively and timely, contributing to the correct selection and rational use of medications, as well as how to optimize pharmacotherapy provided to patients and the community.

Its purpose is to make available information supported by scientific, objective, updated and carefully evaluated literature, which supports decision-making in the use of medications, promoting evidence-based health care, to improve the quality of care provided.

Our CIM has been operating since 1982, and from its inception it has published the Bulletins on a bimonthly and uninterrupted basis. It should be noted that the teaching area operates within a University Hospital, which is part of a huge network of the health system, this gives us greater interaction with the healthcare team and task force groups related with use of medicines.

The Bulletin summarizes relevant scientific information on effectiveness, safety, recommendations for use, economic evaluation, and drug policies... useful for the daily practice of health professionals, and to advise patients and the community: many times, the newsletter itself, or an attached brochure, is given to patients. The Bulletin is aimed at members of the healthcare team, and especially at pharmacists who work in the different pharmaceutical services of our health system: community pharmacy, hospital pharmacy, primary health care pharmacy.

It is currently disseminated through the Faculty's website, email and social networks of the Faculty and the College of Pharmacists of the province of Santa Fe 2nd Circ.

The CIM has a section within the web page of the Faculty, considered as a service provided to the community. Available at: [https://www.fbioyf.unr.edu.ar/?page\\_id=1022](https://www.fbioyf.unr.edu.ar/?page_id=1022) and <https://www.fbioyf.unr.edu.ar/evirtual/course/view.php?id=321>

where it provides access to information that contributes to the safe and efficient use of medications. Besides all the Bulletins CIM, is also available information on pharmacovigilance, pharmacoepidemiology, pharmacotherapeutics recommendations, and publications from the Argentine Network of Drug Information Centers (RACIM) are presented.

The professors of the Area develop activities in relation to the organization/edition of the Bulletin: selection of the topics for each edition (based on the queries received and the interaction with pharmacists, health team of the university hospital, and patients through the Pharmaceutical Care Service that is developed in the Area), scientific information management, writing and reviewing the newsletter. The group of professors that prepare the bulletin has no conflict of interest, but if we need help from other professional, they should declare a formulary of "conflicts of interest". As the Faculty is part of a public university, the professors follow professional standards, added to ethical conduct. The Faculty gives us full autonomy to write the Bulletins, they support us because they know that we are interested in the rational use of medications and the strengthening of the skills of health care professionals. Our University is public, based on the ideological principle of autonomy and academic freedom, advocating the independence of knowledge and science from government and party politics.

At this time, in our country, both locally and nationally, important modifications are being made to medication policies, which require the application of evidence-based health care. The CIM must contribute through the management of scientific information, so that these policies ensure accessibility to effective, safe and affordable medicines.

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# Drug Regulation in the United States is Failing Patients: Proposals for Change

Sharon Batt, Judy Butler and Adriane Fugh-Berman

**P**harmedOut, a rational prescribing project (and ISDB member) at Georgetown University Medical Center, recently released an important report on improving drug regulation that focuses on the United States but has implications for many countries. *What Needs to Change at the FDA: Protecting and Advancing Public Health*, relies on recommendations of an expert working group to improve regulatory processes. The report was primarily written by Sharon Batt, PhD, of Dalhousie University in Halifax, Canada; other writers included Adriane Fugh-Berman MD and Judy Butler MS, both of PharmedOut, at Georgetown University Medical Center.

Although the United States Food and Drug Administration (FDA) once set a global standard in using science to defend the public interest against harmful, ineffective, or falsely advertised drugs, repeated regulatory failures over the last 30 years and a shift in the FDA's mission from protecting public health to speeding drugs and devices to market has tarnished the agency's reputation and harmed patients. Illustrative case studies include discussions of lecanemab, ranibizumab, pregabalin, bevacizumab, flibanserin, eteplirsen, gefitinib, and rofecoxib, among others.

The FDA's mission should be to defend public health in the face of commercial pressures, using the best scientific evidence available. Although patients and clinicians interpret FDA approval to mean a drug is safe, effective, and innovative, this is no longer true. The paper examines four main themes regarding problems at the FDA: transparency and accountability, innovation, pre- and post-market standards of evidence, and value in healthcare. A sampling of issues and recommendations follow.

## Transparency and accountability

Transparency and accountability are fundamental to ensuring trust in the agency's processes and decisions, but the FDA has not been transparent about controversy on specific therapies or on when and how advisory committees are assembled.

The agency's conflict of interest policies are deficient. The FDA must address the ways in which industry funding amplifies some patient perspectives, while silencing others. The FDA should ensure that the voices of patients independent of industry are heard and exercise greater control over industry-funded patient testimony. All participants in open public hea-

tings at advisory committee meetings should be required to disclose financial conflicts, both personal and organizational.

It is vital for the opinions of FDA and industry to be separate and clearly delineated. Joint briefing documents for advisory committee should be eliminated. If a general overview is presented at an advisory committee meeting, FDA staff should present it.

FDA communications should emphasize the complexity of drug approval decisions, acknowledge reservations that reviewers have about therapies that they approve, note unanswered questions that remain at the time of approval, and disclose the plan for addressing those questions.

## Innovation

Few "new" drugs are superior to existing treatments. The term "innovation" has been inappropriately attached to virtually all drugs that the FDA approves, when most "new" drugs are not innovative at all. The FDA should not use the terms "innovative" or "breakthrough therapy"; that is marketing language better suited to industry.

Industry-sponsored patient groups who provide emotional testimony about how a drug helped or might help them can undermine the democratic goals of public participation, since those whom the drug harmed, who experienced no benefit, or who want the agency to base decisions on rigorous scientific evidence, seldom have the same resources to prepare for and attend hearings. The FDA should be as proud of its rejections of inferior therapies as it is of its approvals of new drugs.

## Pre- and post-market standards of evidence

The FDA has decreased regulatory standards by shifting away from approving drugs and devices based on rigorous tests of safety and efficacy, and towards faster approvals based on preliminary evidence. Expedited approval pathways allow companies to market drugs that have only been tested on surrogate outcomes (for example, lab tests) rather than direct patient outcomes: how a patient feels, functions, or survives. While it is expected that confirmatory studies with patient-oriented outcomes will be conducted after approval, those studies are often not completed in a timely manner. When post-marketing studies show a drug or medical device is ineffective—or harmful—it often stays on the market for

years. While it is in industry's interest to keep selling disproven products, the FDA should take a stronger stand in forcing unsafe or ineffective products off the market.

### Value in health care

Although the FDA does not take cost into consideration when deciding about a product's approval, agency decisions affect drug prices. The FDA's use of patent extensions based on the approval of multiple indications for the same drug distorts the purpose of patents and results in increased drug costs. Market exclusivity is the most important factor that allows manufacturers to set high prices. Generic drugs are the only effective source of price competition, because competition between brand-name products has not been shown to reduce prices. Backlogged FDA approvals can delay generic drugs reaching the market.

Rare disease drugs are a troubling category of treatments that incur extremely high costs. Drugs for rare diseases are often approved despite scant evidence that they meet acceptable standards of efficacy and safety.

The FDA's financial dependence on the industry it regulates has neutered its effectiveness. A victim of "regulatory capture," the FDA has strayed from its fundamental mission of protecting the public interest, and now primarily serves the interests of the pharmaceutical and medical device industries. Sufficient government funding must be provided to abolish industry user fees and reinvigorate the agency with a renewed commitment to the public.

*What Needs to Change at the FDA: Protecting and Advancing Public Health* is available for free download [here](#); an executive summary is also available.

## Glucagon-like peptide 1 receptor agonists and the problem of obesity - A pharmacotherapeutic analysis from a public health perspective

By Arana-Ballestar S<sup>1</sup>, Bartolomé C<sup>2</sup>

The article will be published in the forthcoming issue of the *Boletín de Información Terapéutica de Navarra, Spain*

Interest in the weight loss effect of Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) has been growing for the past year and a half. In a world with an obesity epidemic, the demand of the population and the enthusiasm of professionals has led to an increase in prescribing, often off-label, which has caused shortages of type 2 diabetes GLP-1 RAs formulations.

In a forthcoming issue of the *Boletín de Información Terapéutica de Navarra*, we analyze the results of clinical trials of GLP-1 RAs in overweight and obese adults without diabetes and discuss their role in the obesity problem.

First, trials that have studied the effect of GLP-1 RAs on weight, up to 2 years of follow-up, prove their efficacy for weight loss while maintaining treatment. According to the thresholds established by the FDA and the EMA, based on the benefits in several surrogate measures (blood pressure, HbA1c, cholesterol, etc.), this weight loss is clinically significant.



However, it should be noted that no clinically significant outcomes were measured in these trials. In addition, the lost weight is progressively regained after discontinuation of GLP-1 RAs. Other limitations include uncertainty regarding efficacy in overweight individuals, given their minimal presence in trials, as well as high discontinuation rates that limit efficacy and adverse event reporting.

The most frequent adverse events of GLP-1 RAs treatment affect the gastrointestinal and hepatobiliary systems. Although mostly mild, the incidence of serious adverse events is relevant in these studies. No increased incidence of pancreatitis or neoplasms was observed in the trials, although this should be monitored given their association in animal models and observational studies.

Second, the SELECT trial studied the effect of semaglutide in overweight or obese people with established cardiovascular disease (mainly a history of myocardial infarction). After

a 3-year follow-up, semaglutide produced an absolute reduction in the incidence of the composite end point (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) of 1.5%. Statistical significance was not calculated for each variable separately, although the numerical results were consistent with the main analysis.

In this trial, serious adverse events were more frequent in the placebo group, perhaps because events of the efficacy outcomes were also included as adverse events. However, as in the weight loss trials, the discontinuation rate in both groups was high, and dropouts due to adverse events were more frequent in the semaglutide group.

In short, in non-diabetic adults, GLP-1 RAs could be useful in the treatment of obesity and in the secondary prevention of cardiovascular disease. It is important to distinguish between these two indications so as not to misjudge the benefit-risk balance.

The trial in patients selected for their very high risk of cardiovascular disease, and despite some uncertainties that will need to be clarified, semaglutide modestly reduced the incidence of clinically significant events.

In contrast, in its indication for obesity, since the clinical trials did not measure morbidity and mortality outcomes, its role in the primary prevention of obesity complications remains to be defined. In addition, the fact that the lost weight is regained when the treatment is abandoned, together with poor adherence due to adverse effects and their high cost, make them an inefficient alternative.

Despite these results, and despite significant unresolved questions, in some contexts, the chronic prescription of these drugs to all overweight and obese people is being promoted as the solution to the obesity epidemic. At the same time, debates are flourishing to define obesity as a biological disease. Often, both positions are closely related to the need for pharmaceutical companies to determine market share and to the conflicts of interest of many of the physicians involved.

However, obesity is far from being just a medical issue. Unlike other conditions such as hypertension or diabetes, excess

weight is a visible condition strongly associated with certain socio-economic and aesthetic values. These issues, which are at the core of weight bias and stigma, may explain some of the perhaps disproportionate enthusiasm for GLP-1 RAs and may foster pharmacological overtreatment of excess weight, for reasons other than health.

In the same sense, the obesity epidemic is not a problem of a biological nature. Quite the opposite, this epidemic is due to changes in the context that encourage behaviors associated with excess weight. In this obesogenic environment, that also harms the health of those with normal weight, the influence of the food industry is particularly prominent.

It is undeniable that the individual management of people with obesity needs to be improved. Above all, accessibility to intensive lifestyle interventions must be ensured. Within these programs, some well-selected patients (e.g. patients with severe obesity, obesity with comorbidities or cardiovascular disease) may benefit from these drugs. In any case, at present, there is insufficient data to recommend GLP-1 RAs as a chronic treatment. In this regard, independent research focused on health outcomes will be essential to clarify the role of these drugs, maximize their efficacy and monitor adverse events.

In any case, even if these interventions are improved, they will only benefit a minority of the population. Given that the drivers of excess weight operate at a systemic level, the solution to the epidemic requires upstream policy intervention on the social and commercial determinants of health. We strongly believe that clinicians must intensify their efforts in communicating this reality to the public and to governments, advocating for policies that make health improvement reach as many people as possible.

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## Semaglutide in secondary cardiovascular prevention in overweight or obese patients

In a placebo-controlled trial in patients at high risk for cardiovascular events, their incidence was 1.5 percentage points lower in the injectable *semaglutide* group than in the placebo group, with no reduction in mortality and at a cost of frequent, and often troublesome, adverse effects.

As of late 2023, two injectable GLP-1 agonists, *liraglutide* and *semaglutide*, are authorised in the European Union for weight loss in people who are overweight and have at least one weight-related comorbidity, or who are obese (1). These drugs have frequent and sometimes serious adverse effects, including nausea, vomiting, diarrhoea, constipation, intestinal obstruction, gallstones and pancreatitis. Pancreatic and thyroid cancers have been reported. Reports of depression, suicidal thoughts or suicidal behaviour led the European Pharmacovigilance Risk Assessment Committee (PRAC) to launch a review of these risks in July 2023 (2). The evaluation data on *liraglutide* showed that patients lost weight, but did not show that it prevents the clinical complications associated with excess body weight (1).

In 2022, when *semaglutide* was authorised for obesity or overweight, its evaluation suggested more marked weight loss than with *liraglutide*. The “Select” clinical trial to determine whether *semaglutide* prevents cardiovascular complications was still ongoing at that time (1). It was conducted in patients without diabetes, aged 45 years or older, with a body mass index (BMI) of at least 27 kg/m<sup>2</sup>, who had peripheral artery disease or had had a stroke or myocardial infarction at least 2 months previously (1,3).

Results from this trial were published in a medical journal in November 2023, during a *semaglutide* shortage (4-6). The main results are reported below.

**A trial in which most patients had already had a stroke or myocardial infarction.** This double-blind randomised trial compared *semaglutide* at the dosage already authorised in obesity (2.4 mg once-weekly by subcutaneous injection) versus placebo. This weekly dose was to be achieved gradually, starting at 0.24 mg per week, and increased at 4-week intervals to 0.5 mg, then 1.0 mg, then 1.7 mg, and finally 2.4 mg (4). If unacceptable adverse effects occurred, patients received one of the lower doses.

17 604 patients were included, 72% of whom were men. Their average age, weight and BMI were 62 years, 97 kg and 33 kg/m<sup>2</sup>, respectively. 71% were obese (BMI of 30 kg/m<sup>2</sup> or

more). About 76% had had a myocardial infarction, 23% a stroke and 9% had peripheral artery disease. 82% had coronary heart disease, and 24% had chronic heart failure (4).

The main exclusion criteria were diabetes, a cardiovascular event within the previous 60 days, heart failure causing symptoms even at rest (New York Heart Association [NYHA] functional class IV), end-stage kidney disease, acute pancreatitis within the previous 6 months or chronic pancreatitis, cancer within the past 5 years, or a major psychiatric disorder that could compromise participation in the trial (4,7).

The mean duration of follow-up was 3.3 years (3). 27% of the patients in the *semaglutide* group discontinued treatment before the end of the trial, versus 24% in the placebo group. About 75% of the patients in the *semaglutide* group who did not discontinue treatment reached the dose of 2.4 mg per week, and the others stayed at a lower dose due to dose-dependent adverse effects (4).

**Fewer cardiovascular events, no demonstrated reduction in mortality.** The primary endpoint stated in the trial protocol was a “composite” endpoint that took into account whichever of the following 3 cardiovascular events occurred first: death from cardiovascular causes, myocardial infarction or stroke (3,4,7).

One of these events was reported in 6.5% of patients in the *semaglutide* group, versus 8.0% in the placebo group (statistically significant difference;  $p < 0.001$ ) (4).

Cardiovascular mortality, the first of the secondary endpoints according to the protocol, was about 2.8%, with no statistically significant difference between the groups (2.5% versus 3%,  $p = 0.07$ ). All-cause mortality, another secondary endpoint listed in the protocol, was about 4.7%, with no statistically significant difference between the groups according to the protocol (4.3% versus 5.2%) (4).

On average, patients lost about 9% of their baseline body weight in the *semaglutide* group, versus about 1% in the placebo group. This weight loss occurred during the first 9 months, with mean body weight subsequently remaining stable for the rest of the trial (4).



**Discontinuations for adverse events: about 17% with semaglutide versus 8% with placebo.** About 17% of patients in the *semaglutide* group permanently discontinued treatment during the trial because of an adverse event, versus 8% in the placebo group (4). The main reasons for stopping treatment were gastrointestinal disorders (10% versus 2%) or biliary disorders (2.8% versus 2.3%). A psychiatric disorder was responsible in 0.4% of cases, versus 0.3%; the published article does not specify the number of reported cases of suicidal thoughts or behaviour (2,4).

The article provides no new information about *semaglutide*'s adverse effect profile. However, it skates over the incidence of psychiatric disorders, and the follow-up period was too short to evaluate the risk of cancer, in particular thyroid cancer.

**In summary.** This trial evaluated *semaglutide* in cardiovascular prevention in adults with a history of cardiovascular disease (i.e. secondary prevention), most of whom had coronary heart disease, and all of whom were overweight or obese, but none of whom had diabetes. According to an article published in a medical journal, after a mean follow-up of about 3.3 years, the risk of experiencing a cardiovascular event was lower in the injectable *semaglutide* group than in the placebo group: 6.5% versus 8%. However, no reduction in mortality was demonstrated, and adverse effects were frequent and often so troublesome that the drug was discontinued (by about 17% of patients in the *semaglutide* group, versus 8%) or administered at a lower dose than planned (in about 25% of the patients who received *semaglutide* throughout the trial). These data are consistent with those from the "Sustain-6" trial, which evaluated *semaglutide* (0.5 mg or 1 mg once weekly) in patients with diabetes at high risk for cardiovascular events, with an average age of 65 years. This trial also found fewer cardiovascular events than with placebo, but no reduction in mortality (8).

As of late 2023, the European Medicines Agency (EMA) had not yet published a detailed report on the Select trial. Drug regulatory agencies have access to far more data than those presented in medical journals, and their public assessment reports are generally more comprehensive than journal articles. These data (as well as the subsequent pharmacovigilance data) will help clarify *semaglutide*'s harm-benefit balance when used for cardiovascular prevention in overweight or obese patients.

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- 1- Prescrire Editorial Staff "Semaglutide (Wegovy®) for excess body weight. No proven efficacy against clinical complications as of late 2022" *Prescrire Int* 2023; **32** (245): 36-38.
- 2- Prescrire Editorial Staff "GLP-1 agonists: depression, suicidal thoughts or behaviour?" *Prescrire Int* 2024; **33** (258): 103-105.
- 3- "Semaglutide effects on heart disease and stroke in patients with overweight or obesity (Select. NCT03574597". [clinicaltrials.gov](https://clinicaltrials.gov) accessed 24 October 2023.
- 4- Lincoff AM et al. "Semaglutide and cardiovascular outcomes in obesity without diabetes" *N Engl J Med* 11 November 2023: 12 pages + supplementary appendix: 48 pages + protocol: 251 pages.
- 5- APM "Obésité avec maladie cardiovasculaire: réduction de 20% du risque d'événement cardiovasculaire majeur sous sémaglutide" 8 August 2023: 1 page.
- 6- APM "Novo Nordisk débourse 1 milliard pour étoffer son portefeuille dans l'obésité" 10 August 2023: 3 pages.
- 7- Ryan DH et al. "Semaglutide effects on cardiovascular outcomes in people with overweight or obesity (Select) rationale and design" *Am Heart J* 2020; 229: 61-69 + supplementary materials 2 pages.
- 8- Marso SP et al. "Semaglutide and cardiovascular outcomes in patients with type 2 diabetes" *N Engl J Med* 2016; **375** (19): 1834-1844..

### EMA: EU actions to tackle shortages of GLP-1 receptor agonists, 26 June 2024

EMA and the Heads of Medicines Agencies (HMA) have issued recommendations to tackle shortages of the glucagon-like peptide-1 (GLP-1) receptor agonists. The use of GLP-1 receptor agonists for cosmetic weight loss in people without obesity or people with overweight who do not have weight-related health problems has been mentioned frequently in news outlets and social media and is worsening existing shortages.

Member States should consider, jointly with marketing authorisation holders, measures to control and optimise the distribution of these medicines.

Marketing authorisation holders are recommended to increase manufacturing capacity and to continue engaging with regulatory authorities to ensure coordination. In addition, and in accordance with national law, marketing authorisation holders of GLP-1 receptor agonists will need to ensure that the messages they use to promote these medicines have been approved by regulatory authorities. Claims made by companies in the context of such activities should align with rational medicine use and public health goals. Marketing authorisation holders should also consider implementing awareness campaigns on weight management and educational activities on the ongoing shortage and its implications for clinical practice. [Read more](#)



# Istituto di Ricerche Farmacologiche Mario Negri

By Silvio Garattini

## Introduction

My name is Silvio Garattini and I am the founder of the “*Istituto di Ricerche Farmacologiche Mario Negri*” (*IRFMN*), a “non-profit” research institute devoted to pre-clinical and clinical studies in various areas of pharmacology, toxicology and medicine. *IRFMN* has been in operation since 1963 and the experimental and clinical studies over the course of its sixty years of activity have resulted in the publication of over 17,000 articles in peer-reviewed scientific journals (average impact factor: 6.3) and 271 books, which highlights the excellent scientific productivity of the Institute. Until January 2020, I acted as the Scientific Director of *IRFMN*, which is now directed by Prof. Giuseppe Remuzzi. I still exert an active role in the institute, as I am the President of the *IRFMN* Administrative Board. Given the recent attribution of the Edinburgh Medal to the Institute, the present newsletter provides some basic information on the history and the characteristics of *IRFMN*.

## The birth and evolution of IRFMN

I am an MD and obtained my MD degree in 1954. In 1952 during the third year of my MD, I started to work full-time in one of the laboratories of the *Institute of Pharmacology* in the *State University of Milano*. Here I did a number of studies aimed at the development of technologies for the quantitative determination of specific drugs and corresponding metabolites in human blood as well as blood and organs of experimental animals. After obtaining my MD degree, I continued to work in the *Institute of Pharmacology-State University of Milano* for a number of years. During these years, I developed an increased concern about the limited possibilities for research in an Italian State university environment because of the lack of funds and the level of bureaucracy.

Given this concern, I started to develop an interest for other countries, such as the *USA*, which seemed to have much better resources for ground-breaking research in medicine. With this in mind, I managed to obtain a grant from the *Italian National Research Council* to visit a number of *US* research institutes. The grant enabled me to travel from the East to

the West coast for two months and visit several pharmaceutical companies, public and private universities, the *National Institute of Health (NIH)* and non-profit research foundations. The trip in the *USA* generated two fundamental items of information: 1) Research was not an occasional activity and required a longer commitment. This concept was not in line with the idea that research was just a side activity relative to teaching, which was considered the main duty in Italian universities; 2) Non-profit private research foundations had minimal bureaucratic burdens and had the advantage of working for the common good, particularly in the fields of life-science, for personal and public health.

After coming back to Italy I shared my experience with the group of 20 colleague scientists who were conducting research in the *Institute of Pharmacology-State University of Milano*. The long discussion of the above difficulties associated with research in an Italian university setting resulted in two potential and practical solutions to these problems. The first possibility was to move to the *USA*, while a second, more innovative solution was to establish a non-profit private foundation entirely devoted to biomedical research. All the



colleagues were in favour of the second solution, although finding the financial support to create the foundation was an obvious major requirement, which appeared to be extremely difficult. Initially I moved in various directions with limited results, mainly because I was considered too young to embark on the establishment of an independent private research foundation, as there were no examples of these institutions in Italy.

Nevertheless, I never abandoned the idea of founding a non-profit private research institute and my efforts eventually resulted in the opportunity to establish *IRFMN*. Towards the end of 1958, I met Mario Negri, a jeweller in Milano, who became extremely rich after developing a network of stores selling industrial jewellery after World War Two. Given the uncertainty of the post-war economic situation, like many other Italian entrepreneurs Mario Negri invested his resources in various fields, including the pharmaceutical industry, which was under great development in those years. Mario Negri had already founded the pharmaceutical company known as *Farmacosmici*, which acted as the Italian distributor of the pharmaceuticals produced by *Burroughs Wellcome*, an English company investing its income in research through the *Wellcome Trust*. Mario Negri came to visit me asking for advice about potential studies that could be conducted on a number of chemical compounds that an academic chemist was synthesizing in Trieste on behalf of *Farmacosmici*. During the talk, we discussed the importance of studying drugs not only in terms of benefits, but also in terms of pathological side effects. We agreed that these types of studies would be of extreme interest in terms of public health and could not be conducted by a pharmaceutical company, as they could affect its sales. For this last reason and on the basis of what I learned on my trip to the *USA*, I suggested to Mario Negri that these studies could be conducted by a non-profit research institute to be set up in Italy for the first time. I ended the talk by asking Mario Negri the following question: "Why don't you help me to build and organize a non-profit institute specifically devoted to research in the field of pharmacology?" I noticed that my proposal aroused Mario Negri's interest and this resulted in a number of other collaborative meetings that took place during the entire course of 1959.

Sadly, Mario Negri died of a colon carcinoma on the 6th of April 1960. In his will Mario Negri left 100 million Lira and the majority of the *Farmacosmici* stocks to me with the aim of founding and building a new research institute to be named "*Istituto di Ricerche Farmacologiche Mario Negri*". The will also indicated that I was to become the future director of the Institute. I am not going to elaborate on the strong pressures that I received to bring these financial resources to the *State University of Milano*. Suffice it to say that I was

offered an immediate professorship if I continued to work in the University. Nevertheless and despite the mass of necessary bureaucratic work, I was so determined to found *IRFMN* that I managed to arrange set up the non-profit foundation within a year. In the meantime and thanks to the fundamental help of Dr. Franco Russo, one of Mario Negri's nephews, the newborn foundation bought a piece of land in Milano on which to construct the original building containing the laboratories and offices of the Institute. In addition we sold all the *Farmacosmici* stocks to guarantee the complete independence of *IRFMN*. On 1 February, 1963, the group of 20 colleague scientists and myself moved into the completed building and started research at *IRFMN*. From the beginning, the activities of *IRFMN* were based on three pillars: 1) research; 2) training young scientists; 3) information to the general public. To pursue aim 2), it is important to mention that we established an active independent training school for young laboratory technicians inside the newborn *IRFMN*. Over the course of the years, the training activities of *IRFMN* have been expanded substantially. Currently the training programs consist of: a) an internal school of pharmacology for laboratory technicians and young doctorates in biomedical disciplines; b) a Post-doctoral school organized with the Italian Ministry of Research which provides a certified degree of "Dottore in Ricerca"; c) a PhD school organized with *The Open University*, UK. During all these years *IRFMN* has trained over 10,000 young scientists.

Over the course of the next 40 years, the expanding number of scientists working in the *IRFMN* led to a number of logistic problems, as the original building was designed to allow the work of no more than 300 scientists and administrative officers. For this reason, in the 2000s the CdA directed by Dr. Paolo Martelli decided to build a new and bigger structure in a nearby area capable of housing more workers. We started building the new institute in 2004 and completed it in 2007 thanks to several donations and a loan from the BEI. The entire *IRFMN* staff moved into the new location during the second half of 2007.

The *IRFMN* organization consists of two other structures in Bergamo and Ranica, a nearby small town. In 1984, I decided to open a new research institute in Bergamo, my native town, in collaboration with the Department of Nephrology of the Ospedali Riuniti di Bergamo, where the present *IRFMN* scientific director, Prof. Giuseppe Remuzzi, used to work as a clinician. With the financial support of three banks in Bergamo, we managed to restructure an old convent to contain laboratories and offices for an initial number of 30 scientists doing research in the field of nephrology. Given the progressive increase in the number of scientists working in this location, we eventually moved in 2010 the entire structure to

a larger new building - Negri Bergamo - in the technology park known as *Kilometro Rosso (KM-Rosso)*, which is also in Bergamo. This building was constructed thanks to an endowment in the will of Mrs. Anna Maria Astori. In the 1990s we also opened a new research structure devoted to studies on rare diseases, which is located in Ranica near Bergamo, and contains a few patient rooms enabling clinical studies. This structure is located in a historical building named *Villa Camozzi*, which was purchased with the financial contribution of the *Banca San Paolo di Torino* and was restructured thanks to an endowment by Mrs. Cele Daccò after whom it is named (*Center for rare diseases Aldo e Cele Daccò*). It should be mentioned that *IRFMN* was appointed as an *IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico)* with an article of law issued by the Health Minister Renato Balduzzi in 2013. This made *IRFMN* an active component of the Italian National Health System.

As a last piece of information regarding the history of *IRFMN*, I would like to mention that the *Cassa del Mezzogiorno*, a public financial organization of the Italian State, enabled the Mario Negri Institute to organize and build the Mario Negri SUD, a new research institute, that was part of the *IRFMN* network, in the 1980s. It was located in Southern Italy, in Santa Mario Imbaro (province of Chieti, Regione Abruzzo) and was partially supported by public funds. The Institute was operational for almost 25 years before its closure which was consequent to the 2007 financial crisis in the Italian State.

### The current structure and characteristics of IRFMN

*IRFMN* is a non-profit private institute devoted to basic, translational and clinical research in various areas of medicine, pharmacology and toxicology. The broad areas of interest are biochemistry, molecular biology, neuroscience, oncology, organ transplants, kidney diseases, specific rare diseases, environmental health, health policies and health economics.

*IRFMN* is structured in 10 Departments coordinated by a single Department Head. Each Department consists of one or more laboratories whose work is coordinated by a Laboratory Head. Eight departments are in Milano: 1) Acute Brain and Cardiovascular Injury; 2) Biochemistry and Molecular Pharmacology; 3) Clinical Oncology; 4) Environmental Health Sciences; 5) Experimental Oncology; 6) Health Policy; 7) Medical Epidemiology; 8) Neurosciences. Two departments are in the headquarters of Bergamo and Ranica: 1) Biomedical Engineering; 2) Molecular Medicine.

In addition the structure of *IRFMN* is complemented by four separate centers devoted to research in the following fields: 1)

Regulatory policy of the Italian health system; 2) Social and health politics; 3) Mass-spectrometry for environmental and health studies; 4) Clinical research in rare diseases.

Currently the Institute staff consists of approximately 715 units, of whom approximately 500 work in the Milano headquarters, while the remainder are located in Bergamo and Ranica. The scientists (permanent staff: 302) in the three headquarters are supported by approximately 50 members of administrative staff.

As a non-profit private institution, the research conducted in *IRFMN* is totally independent from pharmaceutical companies, government agencies, state universities, political parties and financial or religious institutions. In addition, the Institute's research and discoveries are freely available to everyone, including the scientific community, patients and general public. This guarantees the absence of confidentiality agreements and data secrecy issues. Finally *IRFMN* follows the policy that no discovery or product of the research carried by the Institute can be patented. I feel that it is of extreme importance not to patent our research products, as this maintains the non-profit spirit and characteristics of *IRFMN*. As the mandate of *IRFMN* is to serve the public interest, the Institute is under no obligation to submit to profit-making principles and it works with the typical efficiency of private organizations, with the utmost freedom of initiative and action.

The major problem of a non-profit/private research institute like *IRFMN* is finding the financial resources necessary to cover the stipends of the personnel, the general costs of the structures and the expenses associated with the research. In the last five years, the average costs of *IRFMN* have amounted to approximately 30 ML euros per year. In the same period, the participation of single scientists in Italian and European public calls for research projects in the realms of bio-medicine, pharmacology toxicology and environmental sciences has resulted in the coverage of approximately 50% of the yearly budget. Approximately 15% of the budget is guaranteed by personal donations and individual wills. Although *IRFMN* has never developed and synthesized new drugs, some of Institute's research programs, such as the organization of clinical trials and pre-clinical studies on the cellular and molecular mechanisms underlying the therapeutic action of potential or established drugs, require the collaboration with pharmaceutical companies.

In case of collaborations with pharmaceutical companies, the research protocols must respect all the ethical issues which are established and validated in agreement with *IRFMN*. In addition, we do not accept collaboration that does not permit the publication of results in appropriate scientific journals. In fact, one of the requirements of *IRFMN* is that data must be published regardless of the positive or negative

conclusions. The incidence of specific collaboration contracts with pharmaceutical and other private companies on the yearly budget of *IRFMN* amounts to approximately 35%. Over the years, the annual contribution of pharmaceutical and private companies to the budget has been fairly constant (31% to 37% in the last five years). In addition the pressure of pharmaceutical companies on *IRFMN* work has always been limited, as the Institute's position towards collaborations has always been extremely clear since its foundation.

## Conclusions

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*IRFMN* has been the first Italian non-profit private research institute working in the field of bio-medical sciences. Despite the obvious difficulties of finding the financial resources necessary to run a relatively large structure like *IRFMN*, the Institute has survived for more than 60 years and it is still very active and productive in terms of scientific results. It is my opinion that one of the major values of *IRFMN* is not only independence from the pharmaceutical industry, but also independence from the academic world. In fact, most of the work conducted in the universities in the realm of pharmacology and bio-medicine *via* collaborations with scientific and patients associations depends essentially on the sponsorship of product marketing companies. Given the experience ma-

tured over the course of these 60 years, it is also my opinion that the *IRFMN* example may facilitate the founding of similar research institutes in other European countries. However, with respect to this, it is clear that the main hurdle is represented by finding adequate resources to run this type of non-profit private institutions.

In the present article, I discussed only research and training, two of the pillars *IRFMN* is based on. I conclude by stating that the third pillar is represented by the dissemination of scientific knowledge. Indeed, the Institute contributes to disseminating scientific research and information through various initiatives and tools and it continuously informs the scientific community of new developments and breakthroughs. In addition, *IRFMN* maintains a close relationship with citizens (especially patients) by sharing information on the use of pharmaceuticals and updates them regularly on matters involving scientific research and health. In Italy, this last aspect makes *IRFMN* a major source of independent information to the public.

Silvio Garattini  
15 May 2024

See also Lancet article March 30, 2024 "*Research focus: Mario Negri Institute*" [Read more](#)