**Testimony of Clive Meanwell**

**Before the House Energy and Commerce**

**Subcommittee on Oversight and Investigations**

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Good morning Chairman Stupak, Ranking Member Shimkus, and Members of the Subcommittee. My name is Clive Meanwell and I am a physician, medical researcher and the Chairman and Chief Executive Officer of The Medicines Company, a small, New Jersey maker of acute care medicines used in hospitals. We have one product currently approved for use – bivalirudin, which we sell under the name Angiomax – and we have other products in our pipeline. Bivalirudin is an intravenous blood thinner and, in its approved uses, a substitute for heparin. In 2005, I authored a chapter titled Antithrombotic Drugs and the Pharmaceutical Industry dealing with the research, development, regulation and commercialization of blood thinners, including heparin and novel alternatives, worldwide.[1] Prior to my current role I was head of worldwide regulatory affairs at a major pharmaceutical company which marketed heparin.

I appreciate the invitation to appear before you today. Based on many years of experience in helping to develop and commercialize blood thinners and other drugs for U.S. and European pharmaceutical companies, and my experience of working within both U.S. and European regulatory systems, I hope to offer some perspective on the issues with which the Congress, the FDA, health care professionals, patients, and the pharmaceutical industry are now grappling. Let me also say, in the interest of full disclosure, that my company has pending applications with the FDA to extend the use of

[1] Meanwell CA. Antithrombotic Drugs and the Pharmaceutical Industry. In: Becker RC and Harrington RA (eds). Clinical, Interventional and Investigational Thrombocardiology. Taylor & Francis, Boca Raton 2005. pp 696

bivalirudin to patients with pre-heart attacks and patients with heparin allergy undergoing heart surgery. Further, we have been requested by the FDA to study the drug in children and that study is ongoing. Finally, we also have interest in pending legislation that is relevant to our capacity to extend bivalrudin to other treatments where heparin is currently used, including open heart surgery and stroke, but I am not here today to address that legislation.

**Historical Perspective – Medical Crises Have Led to Constructive Change**

Throughout history, medical disasters and scandals have spurred many forms of innovation. The innovation has been legislative – new laws to regulate medical products. It has been regulatory – new FDA regulations to control problems like adulteration or misbranding. And it has been scientific – as inventors, innovators and regulatory scientists in the United States have time and again come up with new solutions to improve the safety, health and welfare of patients in need.

The current heparin crisis is another tragic chapter in this story, and highlights the critical importance of such innovation – now on a global basis.

Dangerous adulteration and misbranding of foods and drugs was a common practice worldwide in the 19th century. Quinine-containing cinchona bark powder sold to the United States army was made more profitable, but much less effective and safe, by cutting it with just about anything from oak bark to mahogany dust.[2] Formation of the Division of Chemistry in 1862, pioneering work by its Chief Chemist from 1883, Harvey Washington Wiley, and passage of the Food and Drugs Act by Congress in 1906,

[2] Cyclopaedia of Six Thousand Practical Receipts, and Collateral Information: Published 1854. D Appleton & Co.

established federal ways and means to protect Americans from the most egregious adulteration.[3] An even better solution came from the American Nobel Prize winning chemist, Robert Burns Woodward in 1944 – an important time for American inventiveness – when he synthesized pure quinine salts and paved the way for industrial production.[4,5]

A horse named Jim was used to incubate an antitoxin for diphtheria in the early 1900s. After the deaths of 13 children who received the antitoxin, authorities discovered that Jim had developed tetanus, and contaminated the antitoxin. Congress passed the Biologic Control Act of 1902, giving the government regulatory power over antitoxin and vaccine development. Incubation in eggs – and more recently recombinant DNA techniques – have since provided high-tech solutions to many of the problems of vaccine production, purity and safety.

It took another therapeutic disaster to propel new legislation through Congress in 1938. The year before, in an effort to make sulfa drugs more widely available in the United States, a chemist mixed up sulfa with a substance called diethylene glycol (which we now use as antifreeze). There was no legal requirement to study the product in humans or even in animals before making it widely available, no such studies were done, and the result was a therapeutic disaster that caused at least one hundred deaths, many in

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[3] History of the FDA. http://www.fda.gov/oc/history/historyoffda/default.htm. *Accessed* 27th April 2008

[4] James, Laylin K., ed. (1993). *Nobel Laureates in Chemistry 1901–1992*. Washington, DC: American Chemical Society; Chemical Heritage Foundation.

[5] In 1970, Milan R. Uskokovic´ and coworkers at Hoffmann-La Roche in Nutley, N.J., disclosed the first total synthesis of quinine, although stereocontrol was still incomplete. Chemical and Engineering News: http://pubs.acs.org/cen/coverstory/83/8325/8325quinine.html *accessed* April 23, 2008.

children. Legislative and regulatory innovation followed immediately. FDA conducted the first large-scale recall of a product, in some cases using its staff to go from pharmacy to pharmacy to pull the product off the shelves. Congress passed and Franklin D. Roosevelt signed the Food, Drug, and Cosmetic Act of 1938, requiring for the first time that FDA be given the opportunity to review New Drug Applications demonstrating the safety of a product before it could be marketed.

Yet another therapeutic disaster compelled passage of amendments to the food and drug law in 1962. In the early 1960s, thalidomide, a sedative used by pregnant women, caused thousands of grossly deformed newborns in Europe. The disaster was averted in the United States because the New Drug Application for the product was still under review by FDA at the time the European problem became well-known. But Congress nevertheless reacted to this international crisis by tightening the regulation of drugs in the United States in many important ways, including requiring proof of efficacy as well as safety prior to marketing a drug and giving FDA authority over manufacturing processes and the clinical investigations of drugs. In addition, Congress mandated a review of a long list of drugs that had been introduced between 1938 and 1962, a list that included heparin.

In addition to triggering regulatory innovation at FDA, the 1962 amendments set off a wave of scientific innovation. FDA's issuance of regulations explicating the efficacy provisions of the new law was accompanied by intensive work by clinicians and scientists, both inside and outside of FDA, to design and carry out new and better studies of drugs. FDA's issuance of regulations governing good manufacturing practices was accompanied by intensive work by chemists and process engineers, both inside and

outside of FDA, to develop methods to assure that manufacturing processes reliably produced drugs that were as safe and effective as they were intended to be.

But now we are reminded, because of the heparin situation and others like it, that the need for innovation – legislative, regulatory, and scientific – is constant. No matter how good the legislation, or the regulation, or the science, old problems recur, and new ones occur. And we find this particularly true in the last 25 years as the nature of drug development, commercialization and manufacturing has gone truly global. A large proportion of this manufacturing has moved to India and China.

**Heparin – Current Challenges**

Heparin is practically ubiquitous in U.S. hospitals, with more than 10 million patients receiving the product each year. The main FDA approved uses for heparins are to prevent or treat blood clots in peripheral veins and arteries; in the lungs; during arterial and cardiac surgery; and during heart rhythm disturbances when there is a risk of stroke. Heparins may also be given to diagnose or treat serious blood clotting disorders, or to thin the blood during blood transfusions, kidney dialysis and while patients are on heart-lung machines. A staggering 79 million dosage units of standard heparin, 55 million units of low molecular weight heparin and 47 million units of heparin flush (used to keep injection lines open) are used each year in U.S. hospitals.[6]

Heparin was discovered in the late 19th century, and by 1935 researchers recognized its therapeutic value as a rapid and powerful blood thinner.[7] In the early days,

[6] Third party hospital audit data on file: units may be single or multiple use vials, pre-filled syringes or other dosage forms.

[7] Mueller RL and Scheidt S. Circulation 1994; 89:432-449

heparin was extracted from dog liver, beef liver, or on an industrial scale, from beef lungs. But in the 1980s, the emergence of "mad cow disease" led manufacturers to switch to pigs.[8] Today, most heparin is manufactured from pig intestines. Current manufacturing and analytical methods are based on those developed in the 1950s in which the tissue is coagulated in boiling water and subjected to prolonged and repeated digestion using pancreatic enzymes. The concentrated digest is separated with ethanol then purified with aluminium silicate and further ethanol. This gives a crude mixture of sulphur-containing sugar chains which can be further separated into crude heparin and other residual complex sugars.[9]

It is estimated that at least half the world's crude heparin supply is produced in China, and the supply chain there often includes a variety of participants, many of them unregulated. Some heparin processing facilities in China are modern and well-equipped, but, according to some experts, as much as 70 percent of China's crude heparin comes from small producers. Extraction and production facilities can be quite rudimentary, as has been recently reported. Some are family-operated, unregistered workshops that collect and process pig intestines. Press reports recently described some of these workshops as dilapidated and unheated with drainage channels and large puddles on the floor, and families living in a back room of the same building. These small producers may not keep records of the source of pig intestines or other critical in-process information. After they've produced the crude material, they often sell it to middlemen. This creates a supply chain with many players and little, if any, documentation.

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[8] Meanwell CA. Antithrombotic drugs and the pharmaceutical industry. In: Becker RC and Harrington RA (eds). Clinical, Interventional and Investigational Thrombocardiology. Taylor & Francis, Boca Raton 2005. pp 696

[9] Jaques LB and Bell HJ. Determination of Heparin. Methods of Biochemical Analysis. Volume 7. Interscience. 1959

Earlier, I described the remarkable volume of heparin use in the United States. But the average unit price – usually enough to treat a patient for one or more days - is only $1.75. Thus, an essential hospital product used in very sick people is priced well below a box of Bandaids. While low cost medications can represent an enormous benefit to patients, we need to be mindful that razor thin margins can also carry risk if producers are unable to invest in manufacturing improvements and quality control throughout the global supply chain.

In a Warning Letter it sent to one Chinese manufacturer, FDA concluded that there were significant deviations from U.S. Current Good Manufacturing Practice, citing four main concerns: that (1) the plant had not established impurity limits for heparin or shown that it could consistently remove impurities; (2) the plant had failed to establish adequate systems to evaluate the suppliers of heparin materials or the crude materials themselves; (3) the plant's testing methods could not reliably detect and quantify the presence of proteins in the API; and (4) the equipment used to manufacture heparin is unsuitable for its intended use, with "unidentified material" stuck to the inside surfaces of tanks, scratched surfaces of the tanks and unqualified cleaning methods for tanks.[10]

Apart from the specific manufacturing problems that the FDA is investigating, heparin has therapeutic limitations even when manufactured correctly. As a natural animal extract, heparin comprises a heterogeneous mix of complex sugar chains of different lengths and inter-linkages, which can vary from manufacturing batch-to-batch. Although heparin has come to be regarded as the workhorse blood thinner in hospitals,

[10] US FDA Warning Letter April 21 2008 to Changzhou SPL Company Ltd.

this lack of chemical consistency imposes well known limitations on its performance as a drug.[11]

**Solutions as We Look Forward**

With that as background, I would like to provide a perspective on how innovation can help to prevent problems, and mitigate them when they occur.

First, manufacturers need to develop innovative global business processes and take responsibility for methods, components and final product quality, whether drugs are produced in or outside the United States, by themselves or by third party contractors. There is no reason to believe that FDA should shoulder these complex responsibilities – though FDA obviously needs to create the regulatory framework and hold the industry to world-class standards. Manufacturers cannot assume, nor should they be allowed to assume, that FDA will take care of the quality control. As Professor Alastair Wood put it last week: "Although the desire to obtain the lowest cost supplies is understandable, this shift comes with additional responsibilities for manufacturers who must ensure the quality, chain of custody, and integrity of their supply chain, especially by supervising the manufacturing process in countries whose regulatory environments are more lax than ours."[12] Nobody wants to cut costs by cutting corners.

Second, FDA and other regulatory authorities need to conduct inspections and allocate resources in a manner that is matched to the globalization of medical manufacturing. According to an article in last week's *New England Journal of Medicine*, the proportion of active pharmaceutical ingredients supplied by U.S. and European

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[11] Hirsh J and Raschke R. Heparin and low molecular weight heparin: The seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:188S-203S

[12] Wood AJJ. New England Journal of Medicine 2008;358:1774

manufacturers has declined from 90% to less than 20% in the last two decades.[13] That means far more inspections of the plants should be taking place outside the United States, and that FDA must align its inspectional staff accordingly.

Third, and following on the same point, there needs to be much better co-ordination between regulatory bodies. In testimony last week, FDA Commissioner von Eschenbach suggested the need to coordinate inspections of medical products plants with the regulatory agencies of other countries, including the European Community. With the need for more inspections outside the U.S. ever more evident, we need to find ways to work with the European Community and others whose regulatory authority and inspections are as rigorous as ours to avoid duplicative inspections of plants in other countries, thus multiplying the number of inspections we can do. Working across borders is challenging – even for scientists. So the agencies involved, including the FDA, will need to continue to develop transnational attitudes and skill sets that have generally proved challenging in our 21st century world.

Fourth, we need to apply better science to manufacturing and testing processes. Scientific alarm bells were set off by the Report of the FDA Subcommittee on Science and Technology last year which concluded that science at the FDA is in a precarious situation, not positioned to meet current or emerging regulatory responsibilities.[14] There is no way to test every drug for all possible contaminants and adulterants – unless you have some idea of what you are looking for, you cannot test for it. But with its recent publication of two articles on contaminated heparin associated with adverse clinical

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[13] Schweitzer SO. New England Journal of Medicine 2008; 358:1773-1777

[14] FDA science and mission at risk. Report of the Subcommittee on Science and Technology. Rockville MD. Food and Drug Administration, November 2007

events, FDA has shown that it is capable of performing outstanding interdisciplinary science very quickly when the need arises.[15,16] What other kinds of interdisciplinary regulatory science can be applied to the analysis of adverse events, chemical structure of drugs, and other indicia of possible difficulties? Last year also, Congress established the Reagan-Udall Foundation to identify and address unmet scientific needs in the development, manufacture and evaluation of the safety and effectiveness of FDA-regulated products, including post-market evaluation. The foundation will establish scientific projects and programs to address those needs and help accomplish the scientific work FDA needs to support its regulatory mission. If there is more to do to nurture and advance these key regulatory science capabilities, it should be done.

Fifth, and as illustrated very well by heparin, we need to not only seek to assure safety in the production of existing drugs that may be useful but limited, but also to encourage innovation in new manufacturing processes and new products. Heparin, as noted, has served us well since the 1930s, but it has limitations. Scientific innovation has produced a variety of next generation substitutes for heparin over the last years. These include the important advance of low molecular weight heparins as "standard heparin," whose innovative manufacturing methods have produced a much more homogeneous product, although they are made from pigs. Other recent innovations include injectable blood thinning products not derived from animal sources. The short synthetic form of a heparin sugar chain, fondaparinux, has been introduced into the world market with some

[15] Takashi KK et al. New England Journal of Medicine 2008; www.nejm.org April 23, 2008 (doi: 10.1056/NEJMoa0803200)

[16] Guerrini M et al. Nature Biotechnology 2008; published online 23 April 2008 (doi:10.1038nbt1407)

success among patients with leg vein thrombosis.[17] In addition, biotechnology has produced the so-called direct thrombin inhibitors which include lepirudin[18] and argatroban[19] to treat specific forms of immune reactions induced by heparin, and bivalirudin,[20] which is now used by preference over heparin in almost half of the heart angioplasty procedures performed in the United States each year. There is a real expectation that American innovation can take us way beyond heparin.

In summary, Mr. Chairman, history tells us that innovation can move us beyond medical tragedy. With the current challenges of heparin in mind, innovation can include legislative, regulatory, manufacturing and product improvements that will substantially enhance the safety and welfare of patients – and reaffirm U.S. leadership in life-sciences worldwide.

[17] Arixtra®, GlaxoSmithKline

[18] Refludan, SanofiAventis

[19] GlaxoSmithKline

[20] Angiomax®, The Medicines Company