

When does a Nanotechnology Device Become a Drug? Size Versus Smarts

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Nanotechnology is an emerging field that has the potential to positively impact multiple areas of modern medicine. But what is nanotechnology exactly, and how does the definition of nanotechnology affect classification of its products as devices or drugs?

One definition of note for nanotechnology is provided by the United States Food and Drug Administration (US FDA)

[1] The US FDA states that

“Nanotechnology is an emerging technology that has the potential to be used in a broad array of FDA-regulated products, including medical products, foods and cosmetics. Nanomaterials, developed using nanotechnology, are measured in nanometers--equal to about one-billionth of a meter--so small that they can't be seen with a regular microscope. These nanomaterials can have different chemical, physical, or biological properties than their conventionally-scaled counterpart materials used in many products regulated by FDA”.

According to the US FDA, a nanotechnology product is one which

1. Is an engineered material or end product
2. Has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm)
3. Exhibits properties or phenomena that are attributable to its dimension(s)
4. Has a size range of up to one micrometer (1,000 nm)

In 2011 IBM's nanotechnology experts engineered the smallest ever 3-D map of Earth and set a Guinness record. The entire Earth measured just 22 by 11 micrometers. The map included a 25 nanometer high 3-D replica of the Matterhorn [2,3]. The IBM team created their miniscule map to demonstrate a breakthrough in the miniaturization of complex structures.

The IBM team expects their techniques to open new prospects for developing nanoscale objects in a variety of fields including electronics, pharmaceuticals and medicine. Nanotechnology can already be found in devices, chemicals, or combination products that contain both devices and chemicals. Advances in atomic force machines will likely blur the lines between these in the coming years. As nanotechnology devices reach molecular scales and exert forces of molecular magnitude, will they be classified as drugs?

The US FDA defines *medical devices* as products which do not achieve their primary intended purposes through chemical actions within or on the body of man or other animals and which are not dependent upon being metabolized for the achievement of any of their primary intended purposes [4]. Conversely, if the primary intended use of the product is achieved through chemical action or by being metabolized by the body, the product is usually a drug. Companies sometimes push to have a product classified as a device because devices, in general, are perceived as easier to approve by the FDA. The testing requirements and trials for drugs are often more stringent and expensive.

In order to achieve clearance by the FDA, a device has to be placed into one of three regulatory classification categories. Class

I medical devices have the least amount of regulatory control and present minimal potential harm to the user. Examples include tongue depressors and arm slings. Class II devices typically require pre-market notification by submission and FDA review of a 510 (k) clearance to market submission. Examples of Class II devices include x-ray systems, pumps, and surgical drapes. Class III devices are tightly controlled because they usually support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury to the patient. Typically a Pre-Market Approval (PMA) submission to the FDA is required to allow marketing of a Class III medical device. Examples of Class III devices are replacement heart valves and silicone breast implants.

Many devices currently on the market are cleared through the 510(k) process because they are considered substantially equivalent to a pre-existing device. Molecules (unless they are simply generic copies of an existing drug molecule) cannot claim similarity to a pre-existing molecule to avoid extensive clinical trials, and instead must go through a more stringent approval process whereby the drug molecule is first tested, then evaluated by teams of physicians, statisticians, chemists, pharmacologists, and regulators.

A major challenge facing the FDA is the control of hybrids, or combination products, which use combinations of devices, biologic agents and chemicals, and are approved based on the primary mode of action (PMOA) [5]. These products fall under the Office of Combination Products (OCP) at the FDA. Regulation of emerging combination products such as nanobubbles and nanoparticles is tricky because determining the PMOA is difficult [6] because the medical device component of some of these products requires electronics, perhaps moving parts, external transmitters and constant monitoring to function, should the PMOA be considered physical? Or does the accompanying molecule(s) being used make the PMOA chemical and regulated like a drug, since it is being used to combat medical conditions like cancer and diabetes?

When is a nanotechnology product a drug product, when is it a device product, and when is it a combination product? Is size all-important in defining nanotechnology devices? When a nanotechnology product becomes small enough, the forces it exerts may become on the order of the forces that exist in chemical bonds like O-H, C-H and C-C. Such a nanotechnology device's actions may appear to be chemical. Even here we see the possibility of hybrid definitions. Enzymes are sometimes referred to as molecular “factories” that alter other molecules without

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being changed themselves. Enzymes are regulated as drugs, however. RNA polymerase, which is about 14 nm in size, is said to act by chemical means. Would we still say that if RNA polymerase could be reprogrammed in to operate different ways again and again?

A few years ago, Ehud Shapiro and his colleagues at the Weizmann Institute of Science in Israel developed a molecular computer based on DNA. It was capable of performing simple computations. In this biological nanocomputer, strands of DNA served as software that programmed the activity of enzymes [7]. Later, the team expanded the concept and engineered a miniature medical computer from DNA that could detect cancer genes in a test tube and respond by releasing a drug [8]. The researchers programmed this computer for treating two types of cancer, prostate cancer and a form of lung cancer. For each cancer, the team targeted four genes that become either overactive or underactive in patients with the disease. To detect changes in gene activity, the researchers designed their computer with three components. The first consisted of short strands of DNA, called transition molecules that bound to a segment of the messenger RNA that each cancer gene produced. The scientists synthesized those segments for their experiments and added various amounts of them into test tubes to simulate the presence or absence of cancer. The second component was a computation module made up of a long DNA strand. This molecule contained a series of nodes, each of which participated in a logic operation that determined a diagnosis from the RNA in the test tube. Each operation relied on a series of reactions in which the transition molecules directed an enzyme to cut the module in one place or another. This long DNA strand also harbored the computer's third component, a therapeutic fragment of DNA that bound to and suppressed the activity of a disease-causing gene.

In a positive diagnosis of malignancy, the computer's transition molecules detected changes in the activity of all four of a cancer's genes. When the molecules determined that all four genes had abnormal activities, the enzyme cut the computation module so that it released the drug. However, even if the activity of only one of the four genes was normal, the diagnosis was "not cancerous." In these cases, the enzyme cut off a different strand of the computer's DNA, which neutralized the drug. If the computer released the drug by accident, a separate component kept the system in check by simultaneously releasing the drug suppressor.

Enzymatic molecular "factories" and DNA computers can be on the order of the same size. Are they both drugs? What factors make each category (drug or device) unique at nanoscales? Does the amount of effort required to operate or monitor a nanoparticle give a particular classification as device or drug more weight in determining the PMOA? Devices act by physical means and chemicals by chemical means, but where is the line drawn? Is it drawn at *programmability*?

Nanodevices promise to increase in complexity and capability. A decade ago John Rice, on the faculty of Computer Science at Purdue University, gave an example of smart nanoprobes sent to other planets [9].

Nanotechnology produces devices and processes at very, very small scales. Eventually we expect to see machines the size of molecules and even complex machines will be the size of complex molecules. In the near term we expect to build devices only 5 or 20 atoms wide. This technology is still in its infancy but many experts project that it has the ability to produce, for example, machines that go inside the body to kill, nurture or modify various cells; machines inside automobile tires that to sense imminent failure and signal a car to stop; machines in our food that detect the presence of a few cells of *Salmonella* or *E. coli* and

then sound an alarm. This microscopic scale of technology is already well developed in electronics; we should expect it to be extended to mechanical, chemical and biological processes.

Professor Rice noted that scientists on Earth already prefer to send robots instead of astronauts to explore other planets like Mars, Venus, Jupiter and Saturn. Our robots are smaller and cheaper to send than humans, who require large and complex life-support systems. Rice even envisioned a future in which highly advanced nanotechnology devices would be used for interstellar space exploration.

The big barrier to space travel (as we now understand physics) is mass. It requires enormous amounts of energy to move even ordinary sized masses across inter-stellar space rapidly. So we should expect space travelling aliens to be very small. An advanced technology would use micro space ships with some basic sensors (sound, images, etc.) and that carry nano-robots (nanobots). These nanobots are very intelligent, self replicating (using common materials) and capable of building many other types of nanobots. Once an alien ship arrives in our solar system, it parks in space and sends the nanobots out to build facilities, more sensors and, perhaps, more micro space ships. The actual alien life form need never get close to us; it can use remote sensors to provide direct input to its mind. Indeed, the alien mind could be some combination of organic life and manufactured devices (electronic, molecular and ???). This approach allows the alien to travel "reasonably" close to the speed of light using "reasonable" amounts of energy and to visit many star systems at once.

It is not hard to imagine similar "smart" nano devices being injected into patients to cure diseases. Clearly, it would be difficult to call such a nano device simply a chemical, or to classify it as a drug. Computers made from DNA already exist, and they suggest certain questions: When does a medical device become so small that it begins acting like a chemical? When does a "chemical" become so "smart" that it begins acting like a device? Is the FDA's definition of nanotechnology going to continue to be adequate and useful in the 21st century and beyond?

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