Commentary *Highlight article*

The U.S. Food and Drug Administration, the mechanism of action, and other considerations for cell-based therapy candidates

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Impact Statement

The use of cells to provide therapeutics has been used for many tens of years without regulation. In these cases, simple blood or marrow products, such as for a blood transfusion, are regulated by good manufacturing practices. However, new generations of cells are now being used to instruct a patients' immune system to attack cancers, or to provide broad range therapeutics, as in the case of mesenchymal stem cells (MSCs). All of these cell-based therapies are now being regulated as if they are drugs. This oversimplification affects their fair and logical evaluation, and the new medicine of cell-based therapies needs to be re-thought on a variety of levels. This Commentary addresses some of these issues.

Abstract

The focus of this Commentary is to introduce cell-based therapy in the context of how I believe the U.S. Food and Drug Administration (FDA) might establish criteria for the approval of clinical trials that could eventually lead to the final marketplace approval of these medically relevant, cell-based therapeutic products. It is important to emphasize that regulatory agencies have set up practices and procedures that are based on many years of evaluating pharmaceutically provided drugs. To consider cell-based therapies as single action drugs is inappropriate given the complexity of this technology. The regulatory agencies have been slowly reevaluating the criteria by which they allow clinical trials using cell-based therapies to proceed. This commentary focuses on a few key aspects of such considerations and provides suggestions for modifying the standard criteria.

Keywords: Cell-based therapy, FDA, nonresponders, MSCs, chimeric antigen receptor, medicinal signaling cells

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Introduction

This article is a point of view and should be taken as one person's opinion although I know other professionals have a similar opinion. It is important to stress that this is not a critique of the U.S. Food and Drug Administration (FDA), but it is directed at understanding the relationship between the FDA and the medical community and how and why certain medications come to market. The focus of this document is to introduce cell-based therapy in the context of how I believe the FDA might establish criteria for the approval of clinical trials that could eventually lead to the final marketplace approval of these medically relevant, cell-based therapeutic products.

Chimeric Antigen Receptor–T cell technology

The motivation for this article is to introduce a new player to the medical community in general and, in particular, to emphasize this new player called cell-based therapies which I believe will be a huge medical game changer. This is already completely obvious when talking about chimeric antigen receptor (CAR)–T cell technology, which educates a patient's immune system to attack their resident cancer cells.[1,2] The fact that immune cells can be trained to go after and destroy cancer in one's body by using one's own immune cells is now an established technology in the marketplace and FDA-approved.[3] This technology saves lives, and although it was developed in an academic environment,[1,2,4] its validation comes from the fact that a large pharmaceutical company has taken over the technology and has brought the technology to approval by the FDA.[5] And, indeed, here is the difficulty which is that the pharmaceutical company is charging close to ½ of $1 million for this treatment with a money-back guarantee. This ½ of $1 million does not reflect the company's investment made to generate this technology because almost all of it was developed and perfected in an academic environment. Perhaps if it remained in the academic environment (perhaps as a public-private partnership), the price point could have been much lower making the therapy more accessible to all of those in need.

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This article is not meant to criticize the pharmaceutical company but rather aims to understand the environment in which they have set this very high price. Moreover, it is to understand the environment in which this technology was FDA-approved for use in the medical community. The approval of CAR-T was based on clinical trials in the USA and Europe with 86% of the patients reported as being responsive and 69% complete responses with many being essentially cured of their blood-borne cancer with 2–3 years of follow-up.[2,6] It is not my aim to summarize the CAR T sector since the references provided[1,2–6] are sufficient to provide both an update and a historical perspective. The entire industry has expanded, and it is not appropriate here to detail the new logics and technologies nor to do more than emphasize that this is the dawn of cell-based therapy as anticancer clinical protocols are continuing to evolve.

Many companies are now pursuing a similar, but not identical logic for getting cell-based therapies to attack specific cancers, including solid tumors, which represent a huge challenge for this technology. These other companies are using a variety of logics or, indeed, investing huge amounts of money to perfect the technology and to make their way through the FDA-controlled approval process. Not only does this take large amounts of money and investment but it also takes place over large periods of time.[4,6] Other countries have provided early, partial approval of products to short-circuit both the time frame and the amount of money necessary to get a product into the marketplace.[7,8] This is emphasized below where treating a few thousand people in a clinical trial can provide evidence for efficacy and approval but in the end, the truth of the value of a particular drug or therapeutic is in the marketplace where many millions of people have access. Importantly, as discussed below, the complications and serious failings of a drug or technology become obvious with both the passage of time and multiple patients uses.

MSCs

Another cell-based therapy that is extremely popular with over 1000 clinical trials listed on *clinicaltrials.gov* involves mesenchymal stem cells (MSCs). The most popular use of MSCs is as an allogeneic-based technology. In this case, someone else's MSCs are isolated from fat,[9] bone marrow,[10] or from the umbilical cord[11] and put into cell culture and expanded using technologies in which patents were first written in the late 1980s and early 1990s.[12,13] MSCs have been documented to have a variety of therapeutic potentials.

In 1990–1991, I named a cell which attached to plastic cell culture dishes, derive from bone marrow as mesenchymal stem cells, MSCs.[14] I felt justified in calling them "stem cells" since, in culture, I could induce them into a variety of mesenchymal phenotypes such as cartilage, bone, muscle, fat, etc. Indeed, in the 1990s, I assumed that this multipotent cell was present in all of the mesodermal tissues of the body and was responsible for the replenishment of cells which naturally expired. The dogma in those days was that what you saw in culture represented what happened *in vivo*. This view was completely incorrect and when it became obvious that MSCs could be isolated from a huge variety of tissues, it became clear that the marrow-MSC was not the replenishment progenitor of other tissues in the body. An important publication clearly documented that MSCs were derived from perivascular cells that were present on every single blood vessel throughout the body.[15] Because of this, I changed the name of these cells to Medicinal Signaling Cells to represent the fact that MSCs function at sites of tissue damage and are highly secretory.[16] At this time, several clinical trials were being reported which showed that MSCs had the broad healing activity with a large and complex secretory capacity.[17,18]

Part of the legacy-driven requirements for FDA approval has been set up in the last 50 years as a result of the interface of pharmaceutical companies and this criterion is quite suitable (as discussed below) for small molecule drugs but is not suitable for cell-based therapies at this stage of our technological competence. One focus of the issues discussed here revolves around the mechanism of action (MOA) requirement and how this currently is not useful for most cell-based therapies that function in various *in vivo* environments. By trying to provide MOAs in these diverse situations would, indeed, negate good scientific practices since this would require overly speculative responses. Rather, MOA could be an important component of the manufacturing details and the release criteria use for batches of therapeutic cells. Again, this is not a criticism of the FDA; all of the approval requirements and experience of the FDA have been centered on products involving small molecule drugs and recombinant proteins, not cells. In science, we are often educating our students to be critical of all of the data which is disseminated in published manuscripts. This focus on criticism is hugely prevalent now in our society and is propagated and enlarged by social media. This article is a suggestion for how the FDA might view the new cell-based therapies that come before it during the many steps prior to final medical marketplace approval.

The MOA

The MOA for purified small molecule drugs is an obligatory piece of any FDA filing for the approval for the medical use of such drugs. There are many drugs on the market that have been approved with a specified and detailed MOA which is useful in assisting with both the publicity associated with a drug and its actual medical use. Take, for example, the MOA of statins (completely inhibiting HMG-CoA reductase). These small molecules inhibit at various points along the cholesterol biosynthesis pathway within cells.[19,20] My wife and I started taking statins at the urging of our general physician many years ago. My wife, shortly after starting to take these drugs, would be awakened during the night with leg cramps, particularly in the calf muscle. When this cramping first started, I remember going to dinner with my very good friend, Professor Richard Hanson, and his wife. Richard, now deceased, at this point was the chairperson of the Biochemistry department at CWRU and a brilliant biochemist. He immediately grabbed a paper napkin on the table, took his pen out, and drew the many steps of the cholesterol biosynthesis pathway. He admonished me for not understanding that the statin that we were taking inhibited cholesterol biosynthesis at a point before the synthesis of Coenzyme Q, and therefore, I should have considered that

Table 1. MSCs.

MSCs arise from their release from perivascular locations.[15,46]
MSCs survey, sense and respond to their microenvironments.[29]
MSCs modulate the immune system.[18,27,28]
MSCs secrete proinflammatory or antiinflammatory molecules based on the environment.[29]
MSCs are immuno-evasive and, thus, allogeneic MSCs can be used.[27]
MSCs manage pain by secreting molecules that occupy opioid receptors.[33,47,51,53]
MSCs secrete molecules that are mitogenic to tissue-intrinsic committed progenitors.[48,54,55]
MSCs secrete angiogenic molecules.[55]
MSCs secrete proteins that are antibacterial/antiviral.[18,49]
MSCs inhibit scar formation.[50]
MSCs suppress microglial activation and modulate neuroinflammation.[51]
MSCs modulate T-cell proliferation and suppress systemic inflammation.[27,52]
MSCs are eaten by Ly6Clow monocytes which then change T-cells to Regulatory T-cells which can account for long-term therapy.[52,53]
MSCs are NOT Stem Cells.[16,18,56]

MSC: mesenchymal stem cells.

the cramps were due to diminished mitochondrial function. For someone who did his PhD thesis on understanding how the inner and outer membranes of the mitochondria function, and could be separated,[21,22] I was embarrassed to have not remembered the fact that there were molecules within the electron transport chain, which were provided by the cholesterol biosynthesis pathway. Dr Hanson's solution to the problem was to daily take the smallest dose of Coenzyme Q that we could purchase over the counter. To this day, we still take 50 mg a day of Coenzyme Q along with our statin of choice. Coenzyme Q is a cofactor in the transport of electrons down the electron transport chain within mitochondria, and that's the cause of an energy deficiency in my wife's calf muscle which caused the cramping.

This MOA of drugs is an important aspect of their being approved by the FDA and especially in the paperwork used to ask for permission to conduct Phase 2 and 3 clinical trials. Such descriptions of the MOA do not necessarily mean that the drug actually functions in the body in this exact manner or that it is safe. A case in point is the history and acceptance (i.e. in 1999, FDA approval following a Phase 3 clinical trial) and then withdrawal of approval in 2004 of Vioxx for knee osteoarthritis (OA) from the pharmaceutical marketplace. The maker of Vioxx clearly identifies the MOA of this drug to be a cyclooxygenase-2 (COX-2) inhibitor. The pharmaceutical company also understood that people who had blood problems and/or vascular issues particularly those identified with cardiac or stroke risk should not take this strong drug.[23,24] The drug was taken off the market after a number of males were reported to have died from cardiac events and it is now retrospectively estimated that 140,000 people had heart attacks and strokes due to the functioning of this drug with 88,000 who died.[25,26] Thus, FDA approval after a successful Phase 3 clinical trial and the understanding of the MOA of a particular drug does not guarantee that it will be safely used or administrated by medical practitioners. As discussed below, if postmarketing follow-up was standard for all drugs and approved therapies, the pharmaceutical company would have been forced to disclose the adverse events among the first group of males who died from cardiac complications. This would allow a pharmaceutical company to more strongly and publicly require that individuals with cardiac or vascular issues not take this drug. In the case of Vioxx, a country cousin called Celebrex is now in the market and does have a much-reduced risk for cardiac and/or stroke problems although that risk is not zero. Since there are no registries or post marketing follow-up, the long-term benefits and/or risks related to the use of this drug have not been reported and may, indeed, not be known.

The point of the above is to emphasize that for any small molecule drug, the detailed MOA can help us understand how it can be used therapeutically and how its safety might be questioned. That said, the MOA of cell-based therapies currently in the clinical trials is for me meaningless. This is because once the therapeutic **CELL** enters the bloodstream of the patient being treated, we do not have a ghost of an idea of where it docks, what it secretes in the bloodstream or at the docking site, or the cascade of events that its presence in the bloodstream or at a particular site will initiate. The case in point for me is for the MOA of MSCs, and their use in clinical trials. It is well documented in *in vitro* studies that MSCs have an immune-modulatory capacity[27,28] and additionally produce a number of molecules that can have various positive effects on the regenerative capabilities of individual tissues where they reside or where they dock.

In the accompanying list (Table 1), with a few references, all of the activities that have been shown to be attributed to the MSCs when tested *in vitro* and for these individual activities when tested in animal disease models. In addition, there are several clinical studies whose results support the therapeutic use of MSCs as indicated in this table. That said, the MOA (including cellular interactions and the transfer of cellular components) of these cells is totally unknown once they enter the body of the test individual. The need for the FDA to require the MOA for approval of any clinical trials is for me out of context with the reality of the use of these cells and their exhibited safety within a medical context.[28] This is not to say that given the new analytical technologies that are continually emerging that we will not be able, someday, to noninvasively follow the cells and their molecular products very precisely, and, thus, be able to very precisely and with high confidence describe their MOA.

It should be noted that MSCs have been shown, in a number of *in vitro* assays, to have direct effects on various aspects of immune cell function.[27–31] Very complex and detailed analyses of the immuno-modulatory activities *in vitro* have

been documented for MSCs. More importantly, MSCs have been shown to have dramatic immuno-regulatory effects on patients whose immune systems are dysfunctional.[30,31] These observations clearly support and extend the observations that have been made in *in vitro* test systems. This immune-modulatory activity is, in itself, highly complex and whether the paracrine secretions of the MSCs themselves, or the MSC-instructed members of the immune and hemopoietic system such as Regulatory T-cells, are the causative agents for the therapeutic effects that are observed in patients is a much-debated issue.

Another example is that MSCs have been used to mediate pain in a number of animal studies[32–36] and especially, in clinical trials focused on OA. Pain modulation in a number of diverse medical situations is an excellent outcome parameter and is used in many clinical trials for both cell-based therapy and for drugs. The question arises as to whether the primary effect of MSCs is actually to fabricate molecules that directly affect nerve endings (in this case opioid receptors)[35] or that their primary function is in inflammatory modulation with the reduction of swelling at sites of such inflammation. In my opinion, the pain modulation effect of MSCs involves both the antiinflammatory effects and mediation of pain receptors both at peripheral and central nervous system sites. Of course, there is no direct proof for this last hypothesis in humans because we do not have noninvasive analytical technologies that can quantitate either the MSCs' neurological effects or the immuno-modulatory effects. The hope is that new technologies will arise in due course, which will allow us to provide such analysis noninvasively in patients that have been treated not only with cell-based therapies but also with commonly used drugs. The availability of such noninvasive analytical tools will allow many of the MOAs to transition from robust hypotheses to realistic measurements.

Manufacturing cells and MOA

There is no question that a proposed MOA for cell-based therapy could be a useful yardstick for understanding aspects of the manufacturing steps and for identifying release criteria for batches of cells. In this case, it should be understood that the MOA is totally hypothetical and that its use is an important aspect of the quality control aspects of the manufacturing protocol. The stringent criteria for manufacturing cells that are going to be used for therapeutic purposes is an evolving art form and not as precise a scientific endeavor as is to be expected for the fabrication of small molecular drugs.

Thus currently, it is to be expected that the MOA will be useful for the FDA to better understand the detailed steps of the manufacturing process associated with the production of therapeutic cells. This is easily understood for the production of CAR-T cells and their *ex vivo* modification before their reintroduction into the patients who provided the cells in the first place.[36,37] In this case, very precise chemistry is required for both the modification of the cells and for their subsequent release and reintroduction into the patients from which the cells were obtained. All of this is described in great detail in the manufacturing protocol to which the FDA pays very close attention. In this case, the MOA provides huge information and is obligatory for the use of these cells in a clinical setting and in clinical trials. That said, it is to be understood that the MOA is, at the very best, a hypothesis that in no way describes the complex mechanism of action of cells once inside the body and for that matter, the complex interactions of simple drugs inside the body. This is particularly evident in the case of statins which after many 10s of years in the marketplace are now reported to have a variety of effects outside the liver-controlled biosynthesis of cholesterol.[38,39] Again, this does not negate the need to specify a proposed MOA and to design manufacturing and quality control criteria for the release of a specific therapeutic whether it be a cell preparation or a small molecule drug. Again, for emphasis, well-controlled clinical trials with long-term follow-up should be required for any cell-based therapy or small molecule or recombinant drug to establish both safety and efficacy.

The placebo control versus the nonresponders

In the medical sciences, the gold standard for acceptance of a new medical procedure or drug centers around Phase 3 clinical trials that are randomized, placebo-controlled, and double-blinded. Double-blinded refers to the requirement that the individual administering the therapeutic material or placebo to the patient should not be the same person who evaluates its medical effects on that patient. The issue of placebo-controlled is, likewise, a very important parameter in the case of drug studies and especially in the case of soluble preparations that are injected or infused. It is well known that there is a 20–40% placebo effect depending on how a particular drug or preparation is administered to the appropriate patient.[40] In the case of cell-based therapies, it is important to make this distinction because, in all of these cases, the cells are introduced by injection or infusion and such technologies generate the highest placebo effects. Thus, it is important to consider the placebo effect in all clinical trials regardless of the material being tested and or the mechanisms used to deliver the therapeutic preparation.[36]

That said, there is another strong issue that must be evaluated in any drug or cell therapy preparation during a clinical trial. This issue is the fact that there will be some patients who do not respond to the drug or cell preparation. These patients are referred to as nonresponders and in drug situations, the nonresponders can represent as much as 30–50% of the population of patients exposed to this drug. If you have a headache and you take Tylenol (Acetaminophen), and it does not work, you are a nonresponder to Tylenol because it is effective against most headaches. In the case of cell therapies, especially when allogeneic cells are used, there could be two situations for a mismatch and, thus, observing a nonresponse. The first is the fact that the genotype-controlled secretome of the cells being used may not interface with the patients who had their own genotype-controlled response profile.[41] In the case of MSCs, we know that every initial tissue (marrow, fat, etc.) donor has a different genotype and that the quantitative aspects of the secretome are dependent on this donor-unique genotype. Although MSCs from a variety of donors all, more or less, secrete the same spectrum of molecules, the absolute amounts of each of these molecules

is dependent on the genotype of the donor and can vary greatly in absolute amounts.[41] Second, it may also be that the patient will not optimally respond to the molecules and/or effects of the cell being presented. This may simply be due to the density of receptors on the cells that are at the site where the effector cells dock thus soliciting a suboptimal response. Not considered here is, of course, the variation that nutrition, exercise habits, and other environmental influences may have on either the donor cells or the response profile of the recipient patient.

These considerations mean that there will be a baseline that one could establish with regard to therapeutic efficacy established by the nonresponder which would automatically take into consideration any placebo effect. If all the patients received the same preparation (called "open label") in the same way (thus eliminating the need to "blind" the administrator to who is providing the trial therapeutic or the placebo), the nonresponders could represent the floor on top of which efficacy would have to be statistically demonstrated in the responder group. This would have to require the same level of statistical validation as if the nonresponders were the placebo control group. The complexity here is that it is hard to evaluate the actual placebo effect in both the nonresponders and the responders, therefore making the statistical analysis of these two groups more complicated. This becomes important because at this stage of our technical competence, we could expect, and have seen in some cell-based therapy clinical trials, a higher percentage of nonresponders than in most drug-related clinical trials. These are very important considerations and would require that the FDA fully embrace the nonresponder concept. Likewise, a company or academic institution that wishes to use this logic would have to clearly propose this responder–nonresponder logic in the documentation necessary to receive approval from the FDA to conduct a Phase 2 or 3 clinical trials.

Postapproval follow-up

In my opinion, the long-term postmarketing surveillance of the clinical efficacy of any therapeutic should be required. In the case of cell-based therapies, this should be obligatory and necessary for following both the long-term safety and efficacy of the use of therapeutic cells within a defined medical context. Although it costs the cell-therapy and pharmaceutical companies more money to accumulate postmarketing follow-up, in the case of Vioxx,[23–26] the timely reporting of this would have saved thousands of lives and would have emphasized the careful and restricted use of this effective drug for patients with OA who have a low risk for cardiac or stroke issues.

In this regard, all patients have cell phones and an app on each patient's phone that is specific to an administered medical procedure or newly prescribed drug could be used to report a variety of self-reported outcome measures (like pain scores) on a daily basis. This data could be deidentified and crowdsourced for efficacy outcomes and identifying safety problems. Such apps would require internal software to statistically consider the idiosyncrasies of the individual patients and score for recording consistency. A patient with a high tolerance for pain would score differently than a patient who has a low tolerance for pain. Such considerations can be normalized within an individual app's software component before such data are outsourced and made public. In the end, such data would be accumulated and posted in registries or other display formats so that the long-term effects of a particular cell-based therapy and/or drug could be independently and publicly evaluated. The use of phones and everyday app-technology to follow-up on outcome parameters for clinical trials using cell-based therapies will also make it easier and more accessible for the physicians, themselves, to follow patients even after and, separate from, the FDA approval process.

Registries

In response to this need for postmarketing follow-up, several medical professional societies and organizations have set up registries for Cell and Gene Therapies[42,43] for listing and following the therapeutic effects and long-term efficacy of a variety of cell preparations, devices, procedures, and drugs. Such registries do not preclude rapid reporting to the FDA of serious adverse events (SAEs) but can be used to mine data when an SAE is reported to determine if there are similar/related events in the database. Long ago in Sweden, the orthopedic community required the use of a registry[43] for every implantable device particularly those used for knee and hip replacement. The detailed temporal listing of the outcomes of the implantation was so that their long-term stability and use could be shared among practitioners. In this case, a particular knee or hip implant device could be shown to have long or short lifetimes within patients. These registries were used by orthopedic surgeons to make judgments about which devices to propose for young patients based on the longevity of a particular device. If a device was shown to have a very long lifetime in patients, one would expect that this device would be used in younger patients. This is a perfect example of how long-term follow-up has advantages for the medical community and for understanding both the positive considerations and downstream difficulties of individual devices, procedures, or drugs.

At the 2023 AAOS meeting, there was an FDA and physician "Town Hall Meeting" on device innovation. There was a discussion of the FDA's efforts[44] to create an Orthopedic Coordinated Registry Network (Ortho-CRN), which captures reliable real-world data for a variety of devices. Real-world use is necessary to fully comprehend the effectiveness and risks associated with a variety of devices. In this regard, several registries have recently become available for both veterinary and humans the new group of biological products that are being introduced into the orthopedic community and for some cell-based therapies. It would seem to me that both the medical community and the corporations would be best served by publicly accessible registries to understand which medical techniques, products, and procedures stand the test of time. With the introduction of AI, some of the real-world data that was being accumulated could be statistically analyzed in real time. This could predict potential adverse events that might occur downstream and provide a relative level of confidence in such predictions. Such predictions might save lives and avert downstream patient discomfort.

Outcome analysis is a very complex and cumbersome task. For example, in a registry where one would list one set of knee outcomes in knee OA, an entire set of SAEs involving heart issues could be missed that impact patients. This is likely more concerning for systemic therapies as opposed to those delivered locally. The issue here is that drugs compared with cell-based procedures delivered locally could miss the systemic effects. In my case when I receive steroid injections into my OA knee, within a few days, my arthritic shoulder feels the impact of the fact that the steroid delivered locally has become a systemic drug. I call this a halo effect in which no matter where I get a steroid injection, other joints benefit from systemic exposure to this steroid. In this regard, cell-based therapies and any clinical trial that focuses on one set of outcomes may actually be blind to SAEs that affect the patient because it is out of focus of the other important and potentially dangerous outcomes. Such out-of-focus adverse events that affect patients are what long-term follow-up should record and be expeditiously made public.

Because of my age, and also the fact that baby-boomers represent such a huge percentage of the world's population, it is of interest that MSCs may have distinctive benefits for aging fragility and quality of life of people above the age of 50. Because systemically introduced MSCs, home to sites of tissue damage and/or inflammation, and at these sites, they seem to secrete therapeutic factors, a large number of the members of the aging population are, of course, interested in improving the quality of our aging lives.[57] Compared with the use of CAR-T to cure cancers, one could expect that MSCs given to people who are aging to improve the quality of their lives would be an indispensable product. Again, I would suggest that the analysis of clinical trials in this regard, become difficult when trying to ascertain, in a quantitative way, that quality of life has been improved by being exposed to MSCs. Again, if the regulatory agencies continue to treat cell-based therapies as if they are single action drugs, improvement of the aging process will never become an outcome that would find favor among regulatory agencies. Again, the logic of analyzing cell-based therapies, and their appropriate outcomes, should not, in my opinion, be done within the pharmaceutical or drug context but rather, by broadly approved clinical criteria. In the case of CAR-T, this would be the elimination or remission of a particular form of cancer. In the case of MSCs, it could be diminution of pain, healing of wounds without scar or protection of kidney or heart from fibrosis which affects assayable organ function. Thus, rather than describe a detailed molecule MOA, the articulation of clear clinical endpoints, some of which can be quantitated, would be a corollary to the pharmaceutical logic but distinctive for cell-based therapies.

Conclusions

Although cell-based therapies were first commercialized in the 1990s, only about a dozen have been approved for use in Europe and other countries.[45] There are very few cell-based therapies that have been approved in the USA. It should be clear that the use of cell-based therapies is out of context of the established criteria that has been an accepted for small molecule or recombinant drugs. It is certainly more difficult to make judgments about a complex cell-based product then for chemically and quantitatively analyzed drugs. We don't have a mass spectrometer for cell-based therapeutic products to ensure their purity and, thus, chemical safety. Because the FDA is rightfully concerned with both the safety and efficacy of cell-based products, the criteria for their acceptance and approval are slowly being developed.

Above, are the reflections of someone who has worked in the cell therapy industry and the academic environment for many 10s of years. The suggestions made are based on long and vigorous discussions with my colleagues with this article as the product of such discussions. The emphasis of this article is to encourage the FDA and both private and public sector organizations to act expeditiously to bring cell-based therapies into the medical marketplace where I believe they will change the practice of medicine.

AUTHORS' CONTRIBUTIONS

The author generated the entire text of this commentary and is fully responsible for the views and opinions expressed herein.

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