NATIONAL MS SOCIETY

Science/Safety

1. What is immunogenicity? Why is immunogenicity a special concern for biologics and what are the risks to patients? Do immunogenicity risks vary depending on the type of biologic?

Immunogenicity is of great interest to the National MS Society and all those living with MS. Immunogenicity is a body's response to foreign protein (such as occurs with transplantation). Immune responses to biologics often have no effect on patients' clinical outcomes, but occasionally the responses can be clinically significant; consequently, immunogenicity must be considered as part of the product development process.

This is true for all biologics. All biologics have intrinsic risks, including immunogenicity, as well as relative risks, including in relation to alternative treatments. In sum, immunogenicity is a consideration common to all biologics, and it is not unique to follow-on biologics.

Moreover, if analytical, preclinical, and, as necessary, clinical comparability are demonstrated for a follow-on, then that follow-on will share the risk of the reference (brand) biologic. In the one well-publicized case of immunogenicity in patients, Eprex, the innovator did not undertake this type of comparability demonstration and failed to identify its own comparability failure with its innovative product.

The Society, and those we represent, appreciate that risks do vary depending on type of biologic, the indication, and the patient population. However, we equally understand that these factors are independent of the business model of the biologic sponsor (i.e., regardless of whether the sponsor is an "innovator" or "follow-on" company). The fact that an innovator failed its patients on immunogenicity with Eprex demonstrates this point well.

Carefully monitoring pre- and post- licensure is important for all biologics, as is documentation at the dispensing level recording which patient received which product and when (this applies to all medicines).

2. To what degree, if any, is immunogenicity testing necessary? Should immunogenicity testing be mandated by statute for all follow-on biologics (FOBs) or should the Food and Drug Administration (FDA) be given discretion to determine whether such studies, and what types of studies, are needed on a case-by-case basis?

Biotechnology has a very good safety record in the U.S. Consequently, continued application of the current science-based, data-driven, regulatory standards to all biologics by FDA is appropriate.

As has always been the case for innovator biologics, FDA should be given the authority to apply its expert discretion to follow-ons without legislative mandates meant to discourage competition. The legislation should have the same high standards as those for innovative products.

Patient risk of possible immune responses is equally present for both innovator and follow-on biologics, and the innovator biologic is always the product FDA knows the least about at the point of initial approval – particularly because the company developing an innovative biologic had no comparator biologic with which to make relative assessments. Accordingly, recognizing the availability of state-of-the-art techniques, especially those relevant to intrinsic immunogenicity, FDA should be authorized to exercise its discretion in evaluating an immunogenicity assessment head-to-head against the innovator by analytics and preclinical measures to determine the risk of immunogenicity relative to the reference product.

For all biologics, it will remain important to monitor for immune responses as part of post-marketing safety commitments (i.e., pharmacovigilance).

> 3. Has FDA exercised appropriately its discretion whether to require immunogenicity testing for manufacturing changes? Should immunogenicity testing for manufacturing changes be mandated by statute, or should FDA be given discretion to determine whether such testing is necessary?

FDA's history with innovator biologics in this regard is excellent—even though innovator biologics are the ones FDA knows the least about at their point of initial approval.

No statutory mandate is necessary nor in patients' interests, as it will unnecessarily impede patient access. Instead, what is crucial to emphasize is consistent application of appropriate science-based and data-driven standards. This applies both in the context of innovator manufacturing changes and of follow-ons as, in both contexts, it is possible to do comparability studies relative to a reference product (pre-manufacturing change and marketed innovator, respectively) and thereby manage the risk (of the post-manufacturing change product and of the follow-on, respectively) – steps that unfortunately were not initiated for Eprex.

Instead, as has always been the case with innovator biologics, FDA should be granted discretion to make **case-by-case, data-driven decisions** on what testing is needed for a follow-on, and then to evaluate that data and make an approval/disapproval decision based upon the ensuing data generated and submitted by the follow-on sponsor. FDA has proven to be a conservative Agency and there is no reason to undermine the trust

the country has put in its work. No one believes the FDA will not require the data needed to provide safe and effective product, just as it does with any product it reviews.

> 5. Under the Food and Drug Administration Amendments Act of 2007, Congress established new authorities for FDA to enforce drug safety. How should the new post-market authorities enacted in this legislation be applied to FOBs? Are post-market studies always needed for FOBs? Are there situations in which FOB applicants will need to conduct post-market studies that are different from those that have been required and/or requested for the reference product?

In the interest of patient safety, **consistent standards** should be applied for both innovator and follow-on products with regards to post-market study expectations. The greatest variation can be expected to be dependent upon the type of biologic and its therapeutic use, not its sponsor's business model (the latter of which should be irrelevant to FDA).

FDA has many years' experience using sound judgment and discretion when applying consistent standards for all currently-marketed biologic products. This should be respected and reinforced by giving FDA the authority to also regulate interchangeable follow-on biologics that can enable patient access to affordable medicines. No treatment is effective if it is unaffordable.

However, same standards does not necessarily mean same specific data, and thus, for example, scientific progress following the initial approval of the innovator (reflected in publications generated from clinical use of the innovator and the like) can be taken into account by FDA in establishing case-by-case standards for follow-ons – just as FDA does today for innovators.

In all cases, without exception, it will be essential to keep comprehensive records at the dispensing level of which patients have received which products, be they innovator or follow-on.

> 6. Should non-interchangeable FOBs be required by statute to have different non-proprietary names from the reference product? What should the standard be for interchangeable FOBs? What are the advantages and disadvantages of requiring different non-proprietary names, including any affect on patient safety? What alternatives are available?

No, as FDA has indicated in supporting application of the existing INN system to follow-ons, follow-ons should share the same INN as the innovator reference product. (See http://www.fda.gov/cder/news/biosimilars.htm.)

Similarly, in the EU, follow-ons (biosimilars) have the same INNs as their innovator reference counterpart (unless the sponsor of the follow-on chooses to apply for a different INN).

Indeed, given that existing INNs are issued based on the active ingredient, it could be proposed that all biosimilars and follow-on products must have the same INN, since a follow-on cannot actually be a follow-on if it is not comparable to its innovator reference product (which includes comparable such that the follow-on can carry the same INN).

The current INN system, administered by WHO with the concurrence of 193 member countries, has worked well for over 50 yrs and has included biotechnology products. The INN applies to the active ingredient (and is not a name for the product itself). **Accordingly, several innovator products are marketed in the U.S. with the same INNs even though they have never been compared (multiple epoeitins, interferons, human growth hormones, and insulins).** And yet, these innovators do not need to be compared to share INNs and for the INN system to continue to serve its original purpose to healthcare systems/providers in the interest of global public health.

It would be inappropriate and contrary to public health globally for the U.S. to create a system on naming for follow-on biologics that is incompatible with the naming system applied by the rest of the world. A separate naming system for U.S. follow-on products would be confusing and could lead to serious safety consequences for the patient.

It also would impede patient access by blocking interchangeability of comparable biologics. Given that an INN is assigned for the life of the product, a non-interchangeable follow-on with a different INN could not subsequently become an interchangeable biosimilar with the same INN (as proposed in Senate H.E.L.P.).

Moreover, distinct INNs are unnecessary. All follow-on biologics will be uniquely named and traceable independent of the INN based upon label information identifying the manufacture, plus brand name, plus INN, plus batch number. Hence no patient safety issue arises that is unique to follow-on biologics (and any suggestion to the contrary is a thinly-veiled attempt to preclude substitutability).

7. Is it important that an innovator and an FOB have the same mechanism of action? Why or why not? If the mechanism of action of the reference product is unknown, should the FOB applicant be required to determine the mechanism of action and ensure that both products share the same one? Why or why not?

For people living with MS and others needing access to affordable treatments to maintain quality of life, it is recognized that the globally-accepted standard of comparability when applied to follow-on products means that follow-ons will by definition share the same mechanism-of-action as their innovator reference products.

This is because a follow-on cannot be comparable and have a different mechanism of action.

As with small molecule drugs, if the mechanism of action of a biologic is unknown for the innovator reference product, then adherence to specifications plus all other studies within a comparability assessment (analytical, functional, and, if necessary in FDA's expert judgment, clinical studies) becomes more important for the follow-on sponsor as they would for the innovator's initial development.

This reinforces the necessity for application of consistent regulatory standards for all biologics. The amounts of data itself necessary to meet those standards will always vary, and may be more or less, and will always be different for each sponsor's product, but can nonetheless demonstrate achievement of the same standard and enable patients to be confident in the safety and efficacy outcomes.

> 8. How much variability in chemical structure is there in individual brand biologics: (1) batch-to-batch, and (2) as a result of manufacturing changes? What are the implications, if any, for FOBs testing requirements, naming, and interchangeability?

The National MS Society recognizes that all biologics contain variation with respect to certain attributes (chemical structure is more variable than for a small molecule drug, plus other components of the product that may be important may vary as well). However, the people represented by the MS Society also recognize that consistent application of the principles of comparability to both innovator and follow-on products will mean that **there should be no difference in safety, purity, or potency** for a follow-on if it remains within the same range of variation as its innovator reference product. If a follow-on is within the same range as its innovator reference product, then the products should be considered comparable to the innovator – just as different batches of the reference product are considered comparable to each other.

In terms of naming, there are no implications from the Society's perspective. An innovator does not change its biologic's INN when making manufacturing changes based upon comparability if it stays within its target range of variation, nor should a follow-on approved based on comparability having the same variation range be required to adopt a new INN. If both products are equally variable in the same range, both products are comparable and interchangeable for patients.

However, if comparability is no longer good enough as the basis for interchangeability of products in the context of manufacturing changes, then this industry practice and regulatory approach may need to be reconsidered. Currently, changes are often made by innovators of their biological products, including new cell lines and new manufacturing plants. These changes are reviewed by the FDA, with supporting data, and the FDA determines if any clinical trials are needed (which can be as little as 1% of cases). Therefore changes in product are made without the knowledge of any physician

but instead by careful evaluation by the FDA. If this is not acceptable, then innovator companies and patients will suffer increased cost, decreased innovation and less access.

9. Should human clinical trials be mandated by statute for all FOBs or should FDA be given discretion whether such trials are needed on a case-by-case basis? Would not requiring human clinical studies of FOBs result in these products having a more difficult time reaching market acceptance? Why or why not?

The **PHS Act today does not even require, in the statute itself, that innovator biologics be subject to clinical trials, so too would it be** inappropriate and inconsistent mandate clinical trials for follow-on biologics across the board. **Mandating science is not the role of Congress.**

The biotech industry has a very good safety record with very few serious adverse events reported, which demonstrates that FDA has done a good job applying its existing authority – **even though that authority does not mandate clinical trials for biologics, and even though a number of biologics have been approved with limited or no clinical trials.**

For people living with MS, acceptance of follow-ons will depend on FDA's application of consistent regulatory standards that build trust and confidence. That is why the Society believes FDA should be given discretion to apply consistent and appropriate standards to all biologics.

The National MS Society understands that the patient-centric outcome of access to affordable MS therapies will not be achieved by passing legislation that erects new barriers to entry and that makes it more difficult to produce high-quality, safe, efficacious, and more affordable versions of biological drugs. What people with MS want and need is for Congress to make biological therapies more affordable for people living with MS – and this requires simple authorization for FDA to get on with the business of approving interchangeable follow-ons.

10. What studies have been required for past approvals of protein products under section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA)? Have any been approved without clinical trials?

There are a number of instances in which FDA has approved protein products under Section 505 of the FFDCA – so called biologic drugs – without requiring any clinical trials

or less than full clinical studies, and the marketed products have not shown any unusual safety issues:

No clinical trials required for generic menotropins (approved January 30, 1997)—which were approved in an FFDCA 505(j) ANDA albeit never marketed. Limited allergenicity studies – skin tests in ~ 100 patients – were all that FDA required for hyaluronidases, which FDA approved in FFDCA 505(b)(2) NDAs. None of these products were fully characterized.

Very limited clinical trials were required for recombinant calcitonin and glucagon, both also approved in FFDCA 505(b)(2) NDAs.

In the case of the first and still only follow-on biologic that is itself a recombinant product, and that references a recombinant reference product (Genotropin), Omnitrope (somatropin), was approved on May 30, 2006, on the basis of a demonstration of comparability at the analytical, functional, as well as the clinical levels. This approval shows that the concept of comparability can and has been used by FDA for the evaluation and comparison of a follow-on and of two products from two entirely separate sponsors, and done so in a manner that assured patients of comparable safety and efficacy outcomes with the follow-on.

Likewise, the use of comparability with innovator products has shown it is a very high standard. "It sends a very loud message and sets a very high bar," according to Alison Lawton, Genzyme's senior vice president for regulatory affairs. See http://www.pharmalot.com/2008/04/fda-says-genzyme-cant-copy-its-own-biologic/.

11. Omnitrope is approved in the U.S. (albeit as a 505(b)(2)) and in Europe (as the first biosimilar).

    a. Have patients experienced any problems?

    b. Have patients been switched to Omnitrope from other recombinant human growth hormone products?

    c. If the answer to part b is yes, how are payers handling the availability of this comparable product?

The National MS Society is not aware that there have been any reports of any problems with Omnitrope or that there is any indication that patients are reacting differently to Omnitrope than they have to the innovator reference product Genotropin. We have the same understanding with respect to the epoetin alfa biosimilars in Europe.

Regulatory/Administrative

1. Some believe Section 505 of the FFDCA provides a regulatory pathway for approval of biosimilars for reference products approved under Section 505. Should a newly created biosimilar regulatory approval process include all biologics approved under the FFDCA as well as those regulated under the Public Health Service Act?

Consistent with the Omnitrope approval, as well as those for the hyaluronidases and recombinant calcitonin, the National MS Society recognize that there is absolutely no need to sweep FFDCA biologic drugs regulated under section 505 into a new biosimilars pathway. A well-paved pathway already exists for biologic drugs and people relying on those drugs don't want it change.

What people with MS want is for Congress to focus on the issue at hand – an expedited pathway for interchangeable follow-on biologics that reference PHS Act licensed innovator products when their patents expire. People have no interest in Congress spending time fiddling with an existing pathway for FFDCA biologic drugs where FDA already has authority and experience. People want Congress to concentrate on the pathway where that authority is lacking – for the PHS Act biologics.

Unfortunately, a range of affordable options do not exist for most medicines approved in the U.S. to treat multiple sclerosis. Many MS treatments are biologics produced from living cell cultures rather than synthesized chemically like traditional drugs. Biological MS therapies such as Avonex, Betaseron, Rebif, and Tysabri can cost MS patients $16,500 to $30,000 each year. These are all PHS Act biologics. No follow-on versions of these biologics are available because FDA does not yet have the authority to review follow-on biologics. People with MS recognize that Congress and the President can eliminate this barrier to access with the stroke of a pen. So let's create that pathway as soon as possible and keep it as simple and unencumbered as the PHS Act is today.

2. The current statute gives FDA discretion to decide whether a change in an approved biologic requires assessment through a clinical trial. Do you think this statutory discretion has been appropriate or adequate? What has been its effect on patient safety?

Comparability has been used by FDA since the mid 1990's to make approval decisions when sponsors have made manufacturing changes to innovator products, and clinical trials have not been routinely required by FDA in that context. The comparability standards FDA uses have been so successful and universally-recognized that they were subsequently developed into globally-applicable regulatory principles (ICH Q5E). **That now-harmonized standard became the basis for the even more successful European system of follow-on biologics (biosimilars).**

Notably, although the question refers to the statute, the entire system of comparability was developed and implemented as guidance. It is not a statutory-based system other than through FDA's exercise of the broad discretion granted to FDA by statute. Significantly, the guidance development process for comparability was not blocking, and thus it did not preclude comparability demonstrations in the meantime.

The National MS Society is well aware of the potential impact and value of the robust and internationally-applied comparability standard, because **the FDA has already applied comparability in the context of MS therapies in what stands today as one of the most prominent examples of how the longstanding principle of comparability can significantly reduce regulatory burden** — and enable patient access, in this case, patient access of particular interest to the Society and the people living with MS we serve because the access was to Avonex.

The Avonex approval is particularly relevant in the context of this question referring to the statute, given the points addressed here about comparability being implemented by FDA (and ICH) by guidance. That very guidance was challenged in connection with the Avonex approval – as was the approval itself – and both were ratified by the D.C. District Court, *Berlex Laboratories, Inc. v. FDA*, 942 F. Supp. 19 (Oct 7, 1996), and both the Avonex approval and the comparability guidance have withstood the test of time over the past 12 years.

Notably, a company marketing a competing MS therapy challenged the approval and the comparability guidance on the basis **that FDA had not required full clinical trials in approving Avonex**; "Biogen and FDA acknowledge FDA's past insistence upon clinical trials of each drug being considered for approval, but they contend that no statute or regulation requires it and submit that the use of data on "comparable" drugs is within FDA's discretion." 942 F. Supp. at 24.

The Court dismissed this challenge and deferred to FDA and the Agency's scientific expertise in applying comparability: "FDA conceded that it had never before approved a new biological drug on the basis of a clinical study of a "comparable" drug, but FDA demonstrated by reference to public documents that the principle of comparability was not unknown and that, in fact, it had been previously applied in other situations. FDA argues that its extension of the comparability principle in this case reflects a reasonable interpretation of the statutory grant of its regulatory authority, particularly given the rapidly changing scientific and technological context in which FDA regulates biological products. The record contains ample support for FDA's comparability determination and for its finding that Avonex is "safe, pure and potent" as required by the statute. This court may not substitute its own judgment for that of the FDA, an agency created by Congress to address difficult scientific issues such as the one at the center of this claim. " 942 F. Supp. at 25.

Congress should do no differently and no less here – Congress should simply and expeditiously proceed to give FDA discretion to make data-driven comparability decisions regarding follow-ons.

If we trust FDA for decisions on innovator medicines – and people living with MS, and their physicians, did with Avonex – then we have to trust FDA on follow-on biologics. FDA has shown it can appropriately apply the robust comparability standard to MS therapies and should be enabled to do so with respect to follow-on versions of those therapies.

Should Avonex be pulled because no clinical trials were ever conducted on a product that was made with a new cell line, in a different laboratory in a new country? Of course the answer is no, because the company did eventually show comparability.

4. What standards are required to assure sufficient similarity between the FOB and the reference product? Is the requirement that the FOB be "highly similar" to the reference adequate or should an applicant be required to establish that the FOB is "as similar as scientifically as possible"? How would FDA assess these requirements?

The same standard FDA already uses today for innovator products making manufacturing changes – after which FDA and the innovator effectively treat the pre- and post-manufacturing change products as interchangeable for patients. That standard is comparability. This is precisely the same standard FDA used 12 years ago to approve a pioneering therapy for people with MS, Avonex, and it is exactly the same standard FDA should be enabled to utilize 12 years later to enable comparable follow-on versions of that and other biologics to compete in the marketplace and enhance access to affordable therapy for people living with MS.

FDA can readily apply this globally-accepted standard to follow-ons that reference previously-licensed PHS Act innovator biologics, just as FDA already has done for the FFDCA biologic drug Omnitrope and as it has done with the PHS Act biologic Avonex for treatment of MS.

For patients, the veracity of this conclusion is reinforced by the fact that our European counterparts are securing access to affordable follow-ons as a result of Europe's application of the same comparability standard when approving follow-ons in the EU.

5. Should FDA be required to promulgate regulations and guidance before reviewing applications? Why or why not? Furthermore, should FDA be required to issue and permit public comment on product-specific guidance before submission of applications? What are the advantages and disadvantages? How

long will it take to put a regulatory framework in place, including new regulations and guidances for FOBs?

For a pioneering breakthrough new class of MS therapy, people should not be deprived of a safe and effective medicine while FDA implements regulations and guidance. Similarly, people living with MS should not be denied access to affordable follow-on versions of existing MS therapies while FDA goes through the process of developing and securing input on guidance and regulations. Patient treatments and patient access should not be held captive to guidance or any other form of so-called "public participatory process".

A simple statute creating a straightforward regulatory pathway to authorize FDA to approve interchangeable follow-on biologics based on the established regulatory standard of comparability does not need any new regulations or guidance.

FDA already has extensive experience using comparability with innovator products, including application of comparability in the context of MS therapies shortly after the guidance-issuance process that resulted in FDA's comparability guidance. The comparability guidance, ICH Guidance Q5E (http://www.fda.gov/cder/guidance/6003dft.pdf), was developed in collaboration with industry in 1996, and it has been further refined by regulators in the U.S., Europe, and Japan ever since, during which time it has already gone through a universal public participatory process.

For people living with MS and other disease, time can quickly become a life/death issue, particularly if access to medicines is impaired or impeded while the clock is running. For patients, promulgating regulations and issuing guidance will do nothing more than take time. These are inordinately time-consuming processes and should not be used to delay applications or approvals. This is particularly true when any guidance adopted, even when final, is not binding on either the Agency or the industry, and the approval of each application must be evaluated on a case-by-case basis.

Moreover, FDA already has adopted a guidance, its longstanding comparability guidance, and both FDA and industry have a wealth of experience with its application, including in the context of a critically-important MS therapy (Avonex). The validity of FDA's existing comparability guidance has been affirmed by the Judicial Branch, *Berlex Laboratories, Inc. v. FDA*, 942 F. Supp. 19 (D.D.C., Oct 7, 1996), and the Judicial Branch has appropriately deferred to FDA's expertise in that context. In the interest of patients and affordable access to medicines, it is now time for Congress to do the same by adopting a simple legislative solution that enacts a straightforward and robust pathway enabling FDA to apply its established expertise to follow-ons.

Interchangeability

> 2. In general terms, what types of testing or data would be necessary to establish that two biologics are interchangeable?

FDA should be given discretion to make case-by-case, data-driven decisions on interchangeability (just as FDA does today in evaluating comparability and thus interchangeability of innovator products pre- and post-manufacturing changes – where interchangeability is presumed). The standards for interchangeability should remain high.

Just as FDA has long ago been given the authority to ensure that innovator biologics meet the statutory criteria of the PHS Act, so too the National MS Society believes Congress can delegate to FDA the responsibility to ensure that follow-on biologics meet those same statutory criteria – criteria that have not changed in over a century.—i.e. safety, purity, and potency.

We recognize that there is a distinction between the standard and the data necessary to achieve that standard. The standard can be consistent and required within a statute and applied to all products now and into the future. In contrast, the data necessary to meet that standard will be specific to a given product, confidential to an individual sponsor, variable on a case-by-case basis depending upon the nature of the product, and evolving in terms of the expectations of what the data can show as the science progresses and the understanding of the disease being treated evolves.

In all cases the physician-patient relationship must be recognized and given precedent. The physician must always have the authority to prescribe any drug, including a brand name, for their patient and a patient should not be forced to take a follow on product.

> 3. How should product-specific requirements for demonstrating interchangeability be established? Should the statute prohibit interchangeability assessments or give FDA the authority to determine interchangeability as science permits? Please explain your answer.

Today, for innovators, pre- and post-manufacturing change, FDA effectively treats the products as interchangeable for patients. Physicians never know of these changes. This standard works today for MS patients and it can work tomorrow for MS patients demanding access to affordable follow-ons.

Because of the confidentiality of every regulatory filing, only FDA will be able to evaluate the data submitted and make data-driven decisions on whether or not a sponsor has proven its assertion that two biologics are interchangeable.

The statute can set the standard of comparability, and FDA can implement the standard, and apply it consistently to all sponsors. In the interest of patients, such a straightforward approach would allow the actual data requirements of the Agency to evolve as the science evolves.

In all cases the physician-patient relationship must be recognized and given precedent. The physician must always have the authority to prescribe any drug, including a brand name, for their patient and a patient should not be forced to take a follow on product.

4. Should there be product specific guidances, with opportunity for public comment, on establishing interchangeability before submission of applications? What are the advantages and disadvantages?

For a pioneering breakthrough new class of MS therapy, patients should not be deprived of a safe and effective medicine while FDA develops guidance. Similarly, people with MS should not be denied access to affordable follow-on versions of existing MS therapies while FDA goes through the process of developing and securing input on guidance. Patient treatments and patient access should not be held captive to guidance or any other form of so-called "public participatory process".

Just as it is with guidance for innovator products, it should be left up to the FDA to decide what guidance, if any, is appropriate for any particular group of biologics, follow-on or innovator, interchangeable or not. Guidance should not be mandatory, nor should it be blocking, as guidance merely represents advice and the current thinking of the Agency – by definition, guidance is not binding.

More fundamentally, for patients, guidance in this context merely impedes access and could undermine access to affordable follow-ons if the guidance-making process becomes so cumbersome and unworkable as to eliminate any real ability for follow-on sponsors to use the pathway.

The standard of comparability has already been established by the regulators and industry representatives from the U.S., EU, and Japan in their very public development of ICH Q5E alongside industry. It would be unnecessary and a real disservice to patients to repeat the public participatory process that was undergone globally for comparability or that was undertaken in Europe to generate guidelines for follow-ons (biosimilars).

The National MS Society recognizes that Congress and the President can eliminate the barrier to access to affordable follow-ons with the stroke of a pen. The Society also understands that this patient-oriented outcome will not be achieved by passing legislation that erects new barriers to entry and that makes it more difficult to produce high-quality, safe, efficacious, and more affordable versions of biological drugs. Consequently what people with MS want and need is for Congress to make biological

therapies more affordable for people living with MS by adopting a simple statute with a straightforward pathway for follow-ons without artificial and inappropriate barriers to entry.

> 5. What are the potential risks to patients from interchangeability of one biologic for another? If FDA finds two biologics interchangeable, should physicians, pharmacists, and patients feel comfortable with substitution by pharmacists? Why or why not? How would interchangeability affect patient access to biologics?

Patient trust can and should be placed in the FDA to apply consistent regulatory standards and to make data-driven decisions regarding comparability-based interchangeability for follow-on biologics once Congress bestows that authority on the FDA. This trust exists today for all other drugs.

Biotech has a very good safety record in the U.S. and **patients are routinely switched between products that have never been compared in the practice of medicine today.** This includes both within product "classes" and between pre- and post-manufacturing change biologics. (Unfortunately, no FDA advice is provided to physicians, and data on such routine switching is not captured.) Additionally, in Europe, while there is no formal designation of interchangeability and biosimilars have been available for only a short time, we understand switching is occurring and there is no evidence of any problems for patients being switched between a biosimilar and its innovator counterpart.
The National MS Society believes that industry and FDA should continue working together, along with patient advocates such as ourselves, to ensure that sound post-market monitoring is occurring. In addition, there can be greater emphasis on working with providers across the health care system to ensure comprehensive track and trace at the dispensing level of medicines dispensed so that any reduced efficacy or safety issues with any biologic, innovator or follow-on, can be identified as soon as possible.

The Society believes it is essential for FDA to drive this process by being authorized to make interchangeability decisions as it implicitly and effectively has been doing for biologics for a decade. **Absent FDA involvement, heath plans will be the ones switching patients between products.** The Society believes it is much better to have FDA involved in the process and making interchangeability determinations based on data.

If FDA applies the same standards across the board, patients and providers can have equal confidence in all products approved by the Agency. Patients recognize that adverse events can never be eliminated entirely, but we also recognize that there is not a scintilla of data to support the notion of an increased risk of occurrence because of interchangeability. Instead, this represent the intrinsic risk:benefit ratio (new medicines include unmet medical need and FOBs include access) in making any medicines available to patients.

Patents

> 2. The Hatch/Waxman Act restored innovator patents up to 14 years, and further provided manufacturers with 5 years of data exclusivity. Is this a good model for biologic manufacturers? What lessons can we learn from the Hatch-Waxman Act, and apply towards Congress's discussion about FOBs?

The 14-year patent term restoration is the only provision of the Hatch-Waxman Act that applies to PHS Act biologics. In giving biologics innovators this significant R&D incentive in 1984, Congress did not give patients a countervailing benefit in a pathway for follow-on biologics but instead limited patients to the now-24-year-old generic drugs pathway for drugs approved under the FFDCA.

PHS Act biologics (manufacturers) have applied for and received patent term restoration under this provision. These extensions have allowed the extended patents to be protected and remain in force against all competitors – not just follow-ons, and thus have added considerable value to the individual product and beyond.

The National MS Society recognizes patents are important to sponsors of innovative products, and we do not want patents undermined. However, when patents end, we and people living with MS want to see competition that can enable greater access to these critical medicines more affordably.

The relevant lesson from Hatch-Waxman is that when patents end, competition begins, and patients get more innovation as well as affordable access to medicines – we want that for biologics too, and we want it now.

Achieving such a patient-beneficial outcome, however, will not be possible in the face of cumbersome patent provisions and never-ending patent disputes such as would be fostered by all proposals to date. Just as the BLA pathway today is devoid of patent provisions, so too should the follow-ons pathway not be subjected to patent linkage. In this context, patent provisions simply are a distraction from the main objective of interest to patients – an authority for FDA to implement a straightforward and workable pathway for interchangeable FOBs. Patent rights for biologics are covered by the Patent Code and should stay that way.

> 4. What procedures, if any, should be included in legislation to enable reference product companies or third parties to identify potential patent infringement claims by a biosimilar company and to ensure timely resolution of legal disputes?

None, because authorizing FDA authority to review and approve follow-on biologics would not alter the current rights of biologics patent holders. Those rights are fully protected for biologics, as they are for all other products, in Title 35.

From its inception, the biotech industry has not only functioned but flourished without linking patents and regulatory review, and it can be left that way. That is the way patients want it. While patent linkage will help patent lawyers, it will do nothing to enhance patient access to affordable follow-on biologics.

In short, as reflected throughout the history of biotech in the U.S. and the history of the entire biopharma industry in Europe, there simply is no need or compelling public policy objective served by coupling regulatory procedures to any patent rights under Title 35. All the laws on infringement remain intact, and all the patent rights conveyed under Title 35 will remain unaffected by follow-on biologics. In the interest of patients and access, these rights should be left up to the Courts to reconcile as needed without encumbering the regulatory process or follow-on sponsors' development programs.

Incentives/Exclusivity/Investment

2. What types of assessments have been conducted to determine the minimum term of exclusivity that will enable a robust industry for discovery and development of biologics?

For the National MS Society, exclusivity for a particular innovator biologic means that an application for a competing comparable product cannot be submitted to FDA or approved for a set period of time established by Congress.

While exclusivity is not an alternative to patents, exclusivity can significantly assist in sustaining innovation in future biologic medicines for people with MS and those living with other disease, because exclusivity ensures a fixed period of certainty against a competing comparable follow-on product. This certainty will enhance R&D planning, help to minimize patent litigation, and positively impact the associated risk and costs of development for both innovator and follow-on companies.

In terms of assessments, the Society has found that it is very difficult to obtain data that is meaningful. Although merely anecdotal, the Wall Street reaction to the Senate H.E.L.P. Committee-reported legislation, with its 12 years of exclusivity, was favorable in that investment in the biotech industry was not reduced. This investment reaction suggests that that bill was not interpreted as being contrary to the R&D interests of the innovator industry. It was also noted that many innovator companies worked on that legislation and have indicated support.

Exclusivity is very different from patents and both have value, but when they end, competition and patient access should begin.

5. Do you think biologics should receive a different period of data exclusivity than drugs? Why or why not?

The National MS Society recognizes that, generally speaking, biologics are complex and take considerable effort and time to discover, research, and develop whereas small molecule drugs, although trending to have greater development costs as well, on average are still less expensive to develop and manufacture. Similarly, we understand that small molecule drugs are not subject to the same degree of regulatory challenges with respect to, for instance, getting extra dedicated capacity on line, and that small molecules generally benefit from having more options by way of raw material supplies. We recognize that these factors warrant a different exclusivity period for biologics.

6. What policy considerations justify that patent protections be the principal form of intellectual property protection for biologics and drugs?

Exclusivity and patents are complementary in ensuring the health of the biopharma industry and together increase the probability of further and sustained innovation on behalf of patients and the health care systems delivering medicines to patients. Consequently, the National MS Society believes exclusivity is a fair, equitable, and predictable mechanism through which to foster innovation while also delivering the promise of patient access.

7. If a follow-on biologics pathway was created without additional incentives—beyond existing patent protections—for continued innovation, how would innovation be affected either positively or negatively? What additional incentives, if any, would be necessary to support continued research and innovation, including at American universities?

Patents, although immensely valuable, do not create market certainty in a challenging R&D climate and uncertain regulatory environment. Perhaps recognizing these factors, Europe adopted 8+2+1 data exclusivity at the same time it adopted its follow-ons pathway (biosimilars).

In the absence of an exclusivity incentive, molecules and processes on which little or no patent protection was available would become lower priorities for further development regardless of their potential in treating or curing patients. Patient outcomes should not be driven/dictated by the absence of an R&D incentivizing exclusivity system.

Exclusivity and patents are complementary in ensuring the health of the biopharma industry and the patients they serve. Together, exclusivity and patents increase the probability of further and sustained innovation leading to newer and better medicines for patients.

Economic Impact

1. How much savings would a generic biologics pathway create and in what period (taking into account the time it will take to implement any new law, and the time

needed by manufacturers to develop products and submit applications)? Please describe the evidence on which you base your answer.

No one disagrees there will be savings as a result of follow-ons, it's just that everyone disputes how many tens of billions of dollars will be saved over what period of time. At one level, patients don't care whether it's one billion or 100 billion – savings in the billions of dollar ranges will translate into more patients having more access to costly medicines.

Several recent studies released over the past 18 months (by PCMA, ExpressScripts, Avalere, and Insmed in order of publication) have estimated savings from follow-ons to be billions and billions of dollars over 10 years. Although the studies make different assumptions and attribute savings to different groups of medicines and different U.S. populations, all the savings estimates for follow-ons are significant.

The most substantial savings were projected in the Insmed report, which predicts a price discount of 25-35% over a 10 and 20 year period, with anticipated savings of $67 billion to $108 billion over the first 10 years and $236 billion to $378 billion over 20 years. The report assumes a follow-on pathway is approved in 2008 and those products already off patent could be approved by 2010.

For people living with chronic disease, any kind of savings – much less savings in these stratospheric ranges – are extremely important and translate directly into greater access to more affordable medicines through competition.

These savings will help lessen the burden on an already crumbling health care system that is increasingly passing high costs on to consumers. People with MS more often are forced to pay high co-pays as insurers pass along ever increasing drug prices to those who can least afford the extra costs. Biological drugs carry the highest cost and present a constant struggle for access.

3. What implications would a follow-on biologics pathway have on U.S. economic competitiveness and leadership in protection of intellectual property rights?

Head-to-head **competition by follow-on biologics will incentivize further innovation** by the innovator biotechnology companies who will need to replace the products subject to competition in their portfolios, as occurs with small molecule drugs today.

More affordable follow-ons will free up more health care dollars for further investment in both new medicines and additional follow-ons.

Consequently, the new pathway can be expected to stimulate and enhance U.S. economic competitiveness generally and of the biopharma industry in particular, as occurred after 1984 with the enactment of Hatch-Waxman.

For people living with MS, in addition to translating into more affordable medicines, follow-ons will mean multiple manufacturers will be producing product, which gives patients a better assurance of continued supply in the event an innovator has a manufacturing hiccup.

4. What implications does the treatment of patents in the context of a follow-on biologics approval pathway have for the future of biotechnological innovation?

Patents are crucial to the biotech industry. However, cumbersome patent provisions, or any patent provisions for that matter, are extraneous and wholly unnecessary for a follow-ons pathway. For patients, our biggest concern in this regard is that patent linkage – heretofore nonexistent for biologics – could disincentivize use of the pathway.

If the statute gives exclusivity to each innovator biologic for a set period running from the original date of a biologic's initial FDA licensure, the pathway would enhance the certainty of finite protection of innovator products and incentivize utilization of the pathway for affordable biologics for patients.

Moreover, the protection afforded through exclusivity will enhance the investment in innovator products due to the investment value of that greater market certainty, and thereby help increase the upward cycle of enhanced biotechnology innovation. Meanwhile, patents provide a complementary protection based on innovation but are also finite. With patents and exclusivity combined, biotech companies can better trust the future and let competition occur with their old products.

European Model (abbreviated approval pathway)

1. The European Union (EU) regulatory system for biosimilars requires the development of product-specific guidances which detail the standard for approval that would need to be met by a biosimilar in a defined product class. Do you think these guidances would provide similar benefits to industry, healthcare providers, and patients in the U.S.?

The EU biosimilars pathway is based on the comparability standard with which both the EU and FDA regulators have extensive experience.

Although the EU process included a non-statutorily-mandated process for development of certain general and product-class-specific guidelines, this process and these guidelines were not blocking on applications or approvals while they were being developed. Applications and approvals continued concurrently, and some biosimilar applications even contributed to the substance of the guidelines.

With the EU having developed a series of guidances through a public participatory process that has included all stakeholders – including many from the U.S. – it is not in the interest of people with MS to repeat that process here as it will impede access.

2. Legislation passed by the European Parliament encourages innovation by providing 10 years of market exclusivity, extendable to 11 years for select new indications of use, for innovator biologics, thereby preventing the introduction of FOBs during that period. Should the U.S. be guided by treatment of drugs and biologics in the EU with respect to exclusivity periods?

Given that the U.S. has a very distinct healthcare model, we believe it is best to consider the EU approach only as a model for exclusivity.

Given the degree to which exclusivity would enhance innovation and investment in new medicines, we support a fair period of exclusivity along with a workable, competitive pathway to interchangeable follow-ons.

3. If the U.S. adopts incentives for innovation in biologics that are substantially less than those afforded in Europe, what could the potential effect be on U.S. competitiveness?

Those living with chronic disease in the U.S. are demanding what their counterparts in Europe already have: a workable pathway for affordable follow-ons. A pathway in the EU for follow-ons (biosimilars) already is generating follow-on products that are being reviewed and approved, as a result of which these follow-ons are becoming available to European patients first. Their availability is triggering reductions in prices and greater access to important off-patent medicines that cannot presently occur in the U.S. unless sponsors are prepared to invest in and undertake a complete biologics development plan and file a full BLA.

Exclusivity will help provide incentives for continued innovation, and given that the EU already has this incentive in place and the U.S. does not, the disparate R&D incentive frameworks will affect where biologics are developed and where they are first marketed. This will remain particularly true if the U.S. continues to lack a straightforward pathway to expedited approval of interchangeable follow-ons.

4. To what extent do you agree or disagree with the EU's current model when it comes to access to needed biologics, patent protection, patient safety considerations (including interchangeability), and the length of time needed for

the approval of a new product? What are the advantages and disadvantages of the EU's model? Are there other models that the U.S. can examine? If yes, what are the strengths and weaknesses of their models?

While regulatory approval is necessary in the EU and the U.S., it is not sufficient by itself to enable access and availability of biologics, as the payor and reimbursement systems play a critical role.

They payor and reimbursement systems are different between the U.S. and the many individual EU countries. While it will be appropriate to standardize the regulatory requirements as much as possible, other aspects then must also be considered.

Interchangeability will help foster availability and greater price competition as healthcare providers and patients will have greater confidence with FDA involvement in that assessment.

Once approved by the regulators, immediate market access is key for patients, and here in the U.S., that process is quicker than most other countries. This will be the same as for all other biologics.

5. FOBs are now approved in Europe, and FDA has approved a number of follow-on protein products under the FFDCA. Have these shown any problems with respect to safety or efficacy? In what ways are these different from any safety problems seen with brand products? Have there been any safety/efficacy problems here or in EU? If not, can we just say they have a good safety record and the risk of a safety/efficacy problem is irrespective of whether it's a brand or follow-on product?

To the knowledge of the National MS Society, no safety problems have been attributed to biosimilars in Europe or to those biologic drugs approved in the U.S. under 505(b)(2) of FFDCA. We are not aware of any data showing that a marketed biosimilar is in any way different from its reference or not comparable. In fact, **the use of FOB's in other countries, including Europe, proves that follow on biological medicines can be produced safely despite the scare tactics that some try to use.**

The use of the same science-based and data-driven regulatory standards for all biologics will make the risk of a safety or efficacy problem with any given biologic equally consistent. If the same standards are applied to all products then they will not represent a greater risk to patients, but will enable greater access through competition that creates more affordable medicines.

The continuing unmet medical needs – whether cost-based or therapeutic-based – demand that follow-ons like all biologics should be made available as expeditiously as possible, and should service as a reminder that risk to patients must always be balanced

by the benefits for patients. In this context, while follow-ons will enable greater access and fulfill very important public health goals, follow-ons will do so without any increased risk and while fostering innovation in the process. All that is required is the pathway.

The Society recognizes that Congress and the President can eliminate this barrier to access with the stroke of a pen. The Society also understands this patient-centric outcome will not be achieved by passing legislation that erects new barriers to entry and that makes it more difficult to produce high-quality, safe, efficacious, and more affordable versions of biological drugs. More affordable follow-on versions could provide safe and effective alternative treatment options and help alleviate the cost burden on families dealing with MS and other diseases. A competitive FDA pathway also will incentivize innovation in our country, as competition will help spur new investments and speed up development of newer and better therapies.