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Citizen Petition

Biologics Nomenclature and Public Information: Suitably Descriptive Names/Identifiers and Public Disclosures are Needed

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Dear Sir or Madam:
The undersigned submits this petition under relevant statutory sections of the Federal Food, Drug, and Cosmetic Act, Public Health Service Act and/or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs under 21 CFR 5.10 to request the Commissioner of Food and Drugs to consider the information and take the specified actions cited below.

A. Actions Requested

Request Summary: In simplest terms, this petition is rather straightforward. Currently, there are no non-proprietary names [and no related nomenclature system(s)] for FDA-approved biologics that reflect the nature of the products (and active agents), what they are, which is largely dependent on their CMC, bioprocessing and quality-related aspects; and insufficient related public information concerning product identity. This petition requests FDA assign both unique and biosimilar/(bio)generic-type (or class) names/identifiers for approved biologic products and their active agents, along with disclosures of sufficient public information to enable an adequate understanding of product identity, what the products/agents are.

In expanded but still simple terms,, this petition seeks FDA to assign both unique/distinct and biosimilar/(bio)generic-type (or class) names and/or other identifiers for approved biologics and their active agents that are science/product/entity-based, not constrained by regulatory uses/requirements (e.g., Established names), and that reflect product identity, what the products/agents are (including CMC, bioprocessing and quality aspects). The unique product and agent names/identifiers must be sufficiently specific/descriptive and be clearly linked to Web site-published product/agent approvals review-related public documents including sufficiently-informative disclosures to enable clear understanding of product identity (what the products/agents are) at any specific time and an understanding of related, including biosimilar, biologics' similarities and differences. This includes unique names/identifiers being unencumbered by existing regulatory requirements. Prior to BLA approvals, product/agent nomenclature and related information (including CMC, bioprocessing and quality aspects) must be publicly

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disclosed for at least some minimal professional feedback/peer review, including discussion at any BLA approvals-related advisory committee public meetings.

Note, this petition does not concern and makes no requests concerning either biosimilars regulations or any regulatory-required currently-existing biologics names/identifiers, including Established, USAN and Proper Names and NDCs.

Additional and related information, not formally part of this petition, is online at www.biopharmacopeia..com.

Current Situation Summary:

In simplistic terms, the current situation concerning approved biologics is that:
1) Functional/useful names for products and active agents do not exist. Biologics are now recognized as each being unique, yet there exist no suitable non-proprietary unique names/identifiers, i.e., reflecting product identify (the collective information that describes/characterizes biologic products and active agents from a science/product/entity-based perspective}. Also, there are as yet no suitable biosimilar/(bio)generic-type non-unique names or class names yet available for biologics.

Biologics nomenclature is in a pitiful state. Lacking suitable non-proprietary names, the same established/compendial/USAN names are nearly universally used for *both* finished products and active agents, with full ambiguity! Making the situation even worse, these established/USAN names are regulatory artifacts, including being insufficiently descriptive and inherently generic (not unique/specific enough).

The non-proprietary names FDA currently officially has a role in designating include Established Names, related USANs/compendial names, and Proper Names. These names each have specific regulatory-constrained purposes; do not track the science/product/entity-based identity of products/agents (what they are); do not reflect changes in products/agents, including 'product drift;' derive from legacy, pre-recombinant protein, nomenclature systems not adaptable for modern biopharmaceuticals; and otherwise are severely constrained in their usefulness. [Again, this petition does not concern Established or any other regulatory-required nomenclature, nor implementation of biosimilar regulations.].

2) Nobody knows what the products/agents are! There is now often negligible or even no product/agent identity-related information, including concerning CMC, bioprocessing and quality aspects, being disclosed by FDA in the public domain. FDA review documentation nowadays often includes *no* descriptive or summary product/agent identity-related information (see Appendix 3), with the few meager sentences in product inserts often more informative than all approval review-related public documentation. This situation is unacceptable in the context of current science, understanding of the nature of biopharmaceuticals, and expectations and legal requirements for FDA making the most basic public disclosures about its approved products.

3) More precise names and more product/agent-defining information are needed. Both unique and biosimilar/(bio)generic-type (non-unique) non-proprietary names designed to be optimally descriptive (both unique and generic) and not constrained by regulatory requirements are needed for approved biologic products and their active agents; and these names need to be associated with relevant sufficiently-descriptive product/agent identity-reporting public information disclosures, including concerning CMC, bioprocessing and quality aspects.

4) FDA is the only organization able to rectify this situation: Manufacturers and FDA are the only authoritative sources for information about approved biologics. Manufacturers are not suitable sources for non-proprietary names, and are restricted from disclosing product/agent-specific information due to fears about off-label information dissemination. FDA is the only organization capable of doing (disclosing) what is needed.

Introduction:

Many aspects of federal biologics regulatory information management have not changed in over 100 years of federal biologics regulation. This includes approved biologics (biopharmaceuticals), both the products (drug products) and active agents (drug substances), lacking suitably descriptive non-proprietary unique names/identifiers (names), particularly names that reflect product and agent identity (vs. being regulatory artifacts), including names linked to bioprocessing and quality-related FDA-disclosed public information needed to understand what these products/agents are and enabling meaningful comparisons between products and different versions/iterations of products. And in recent years, the FDA-disclosed public information about biologics has even regressed, become less in quantity and less informative. This, particularly, includes the public approvals' review-related documentation online at FDA's Web site, which is often totally devoid, 100% redacted, of all bioprocessing and quality-related information (see Appendix 3).

Biologics are now recognized as each being inherently unique vs. most classic/pre-recombinant biologics being designed and/or treated as rather generic, even interchangeable, e.g., most classic vaccines and blood products. And now with biosimilars coming and expected to rapidly outnumber established reference and new innovator products, it is clear that FDA's current biologics nomenclature and related product/agent-related public information regimes are inadequate, even dysfunctional, and contrary to U.S. economic and public health interests. The present biologics nomenclature and product/agent identity-related public information regimes are clearly legacies, not visibly changed or updated since FDA assumed biologics from NIH decades ago!

Terminology Used: Note, the term "name," for the purposes of this petition, includes names and/or other identifiers that adequately serve the purposes discussed. Ideally, these "names" will be usable as and look like names, i.e., be predominantly text-based, pronounceable, writable, etc. However, particularly with unique names, the petitioner realizes that this goal may be difficult or impossible to attain, e.g., text-based names will likely often be long and may require appending alphabetic/numeric decimal notations and/or other artifices to be more descriptive.

It is fully acceptable, if FDA sees a genuine need, for the requested "names" to be obfuscated and designed so as not to be generally usable as short names, such as to prevent the requested names use for prescription or marketing purposes. For example, FDA could use artifices such long descriptive names, hybrid names-numbers or other alpha-numeric notations, registry numbers, long linear notations/strings of descriptors, etc. (provided that names/identifiers are unambiguously associated with suitable public disclosures of product/agent identity-related definitions/descriptions). Also, in terms of meeting the requests of this petition, FDA may elect to exclude certain classes of non-

mainstream biologics, such as community blood center-manufactured products, allergenic products, HCT/P's, and diagnostics regulated as biologics.

Scope/Coverage: Note, this petition does not involve and makes no requests concerning the various biologics regulatory names/identifiers FDA has long officially assigned -- established names (and related compendial/USAN names), Proper Names, and National Drug Codes (NDCs). These established nomenclature systems are highly evolved to serve their specific regulatory-defined purposes; and in this context are highly constrained and generally simply not suited in unmodified form for use as any of the requested types of names.

Recognizing budget constraints and facts, *this petition only requests the barest requisite minimum.* But obviously, FDA should do things right, what's really needed, including developing nomenclature and public registry system(s) fully integrating the requested and other types of biologics nomenclature the agency assigns; along with a coherent 21st century-suitable biologics public information regime, including one capable of handling the rapid ramping-up of approved products as 100s of biosimilars receive approvals in coming years.

Biologics Need Suitable Product and Active Agent Non-proprietary Names

Biopharmaceuticals are the most complex of all commercial products. Despite this and their 100+ years of federal regulation, there exist no U.S. widely-usable or relevant non-proprietary product or active agent names that reflect the products' identity (largely dependent on CMC, bioprocessing and quality aspects), nor are there often even minimally-suitable associated publically-available definitions or descriptions of what available names represent – biotechnology-derived pharmaceuticals, i.e., products/entities, in commerce.

Effective regulation by FDA and health care professional, scientific and public communications regarding approved biologics and their active agents require that unique names (and/or other identifiers) be assigned to each product and active agent, with these names/identifiers reflecting the identity of (information that collectively defines) each product and active agent. Further, biosimilar/(bio)generic-type non-unique names/identifiers are required for effective communications regarding products and active agents, including for biosimilars without and with interchangeability. And adding more complexity, biobetters (similar follow-ons too dissimilar to receive biosimilar approval), in fact, all biologics, also need suitable unique and non-unique/generic/class names.

But neither FDA, nor any other authority, yet assigns either usable unique or biosimilar/(bio)generic-type names to U.S.-marketed biologics. FDA-assigned regulatory-required Established and Proper Names are simply useless in terms of being either unique or (bio)generic. There are no suitable or usable sufficiently-unique non-proprietary names/identifiers designated by FDA for approved biologic products, and particularly none that reflect the actual identity, nature, etc. of biologic products and active agents, including their bioprocessing and quality-related aspects and the differences in products as they evolve (product drift). And there are also no usable

biosimilar/(bio)generic-type non-unique or class names for (bio)similar products. These most basic needs for names have been ignored or avoided by FDA.

Currently, the only non-proprietary names for approved biologics with any authority or usability are established names -- FDA-officially-designated non-proprietary names usable for prescription and marketing purposes, almost always USANs (which are almost always INNs), while biologics' Proper names are simply too generic and way too inconsistent, often incoherent, to be of any real use. Lacking usable names, the *same* Established/USAN names are used nearly universally, including by FDA, as non-proprietary names for *both* the finished products and their active agents – a situation with absolute ambiguity! Everyone does this – uses these same names to refer to products and/or agents. All those reading this petition surely automatically, often without conscious thought, interpret "abcdefghijk" USAN/INN or established name *in context* as referring to either the active agent, the finished product, or vaguely referring to both. This total lack of specificity and ambiguity is not acceptable in regulatory and professional communications concerning approved biologics!

Established names, with their requirements for use for specific purposes, including designating prescriptions, and their source USANs, designed for uses including as names for generic USP standards/monographs, have unique requirements that simply make *unmodified* USANs and established names useless as unique product/agent identifiers for biologics (while these names, like CAS nomenclature, may be suitable for requested uses with appropriate modifications, e.g., modifiers appended). The non-utility of these names includes their lacking any explicit linkage with sufficiently-descriptive product/agent identity information; these names remaining the same irrespective of significant post-approval changes in products/agents, including bioprocessing and quality-related changes that essentially define new products (or versions or iterations of products); and these names simply being too short to be sufficiently unique/descriptive. Similarly, National Drug Codes (NDCs) are rather useless as unique or non-unique product and/or agent identifiers. NDCs are primarily based on and vary with packaging; are not explicitly associated with any specific product/agent definitions or identity information, including bioprocessing and quality-related aspects; and do not reflect or track product identity and related changes. However, portions of NDCs, such as labeler and product codes might be usable in unique names/identifiers.

The recent 55th Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances included an initial discussion (but no actions) regarding the need for more unique, more specificity in, INN nomenclature for biosimilars (but not all biopharmaceuticals, the real problem). FDA responding to this petition stating that it intends to wait and see and hope that the INN nomenclature system is suitably redesigned and repurposed to be suitably unique/specific concerning biosimilars is thoroughly unacceptable! Even with modifications to make INNs more unique, the core INN system is still problematic and further jury-rigging will not fix its core underlying problems. With INNs controlled by WHO/UN committees and with most members (i.e., countries) having vested interests in uncritical INN name-based interchangeability/substitution, any changes to INN to allow for more unique names for biosimilars will inherently be compromises with the resulting modifications and further jury-rigging of INN likely no better than the current system.

B. Petition Requests

1) Nomenclature-related Requests:

FDA is requested to, for each approved biologic, minimally, upon any approval (BLA or sBLA) assign a:
1) unique name reflecting the finished product's identity (what the product is, which is largely based on CMC, bioprocessing and quality-related aspects).
2) unique name similarly reflecting the active agent identity (what it is).
3) biosimilar/(bio)generic-type non-unique name(s) and/or classification(s) for the products reflecting relevant similarities with other similar (not necessarily biosimilar) products; and
4) biosimilar/(bio)generic-type, non-unique name(s) and/or classification(s) for the active agent reflecting relevant similarities with other similar (not necessarily biosimilar) active agents.

As discussed below, these requested names need not be official, complex, nor involve significant additional work or expenses on the part of FDA, with the requested names *minimally* to simply be reported and used in approvals-related documentation as approvals are granted, with no official designations needed (and probably best avoided).

Nomenclature Requirements:

Further, the names/identifiers to be assigned to approved biologics *must* be:
1) derived from a biologics nomenclature system(s): Some minimally rational and coherent/consistent publicly-stated conventions, rules, etc., need to be followed - that is what nomenclature is all about. FDA adopting a policy of simply arbitrarily adopting names, following no known nomenclature conventions, just making names up as needed, would be contrary to this petition and U.S. public health and economic interests. Further, any nomenclature system must reflect sBLA-associated changes in products/agent-related information that define new products/agents or versions or iterations, including 'product drift.' Without this, any nomenclature system is useless.

The CDER-managed *Unique Ingredient Identifier (UNII)/Substance Registration System* may be (and is recommended by the petitioner as) an appropriate starting point or parent system for managing unique agent names/identifiers, presuming each biologic and agent from each product/manufacturer is considered unique. Biologics need to be integrated into FDA's chemical substance/drug-oriented databases! Ideally, biologic active agents and finished products would each have their own CAS Names and Registry Numbers (or comparable equivalents), with these names/identifiers likely better suited than other options, e.g., Established/USAN names, for use as unique names (certainly, more descriptive), with modifications to make them sufficiently unique.
2) non-proprietary - publically usable: Trademarks, which cannot be freely used, must be avoided as prominent parts of names (although they may be included strung along with multiple other descriptors as parts of longer linear notation names/identifiers). Thus, use of a product/agent name with trademark appended is not suitable, e.g., xyz name/TRADEMARK®.
3) non-commercial/non-promotional: Company and other trade names must not be used as prominent parts of names. This includes prominent use of company names, which as with trademarks, used in communications would effectively result in endless promotion/advertising and simply be unsightly and inappropriate, particularly in

scientific/technical communications. Using company names would pose other problems, with these names easily gamed, rebranded, besides normal frequent changes, and difficulties in selecting a single company name for marketed biologics. For example, would the 'company' name be for the manufacturing establishment, parent company (for U.S. or worldwide), the U.S. marketing subsidiary or licensee(s), etc., and would this be consistent for all or be customized for each product? And company names can simply be too long, e.g., Boehringer Ingelheim; and acronyms can be ambiguous, e.g., would BI refer to Boehringer Ingelheim or Biogen-Idec? Thus, product and agent names prominently incorporating commercial names are not acceptable, such as xyz product/Company. But like trademarks, company names may be used as parts of names, if just a minor portion of the name. Active agent/API and finished product manufacturers' establishment numbers may be more suitable than company names.
4) cover all products/agents regulated as biologics: Naming and information disclosure must apply to all biologics irrespective of their regulation by CBER or CDER. This includes all products now approvable as biologics, including vaccines, blood and cellular products, not just high-purity protein products. As noted above, certain non-mainstream biologics may optionally be excluded.

FDA is free to make its own decisions about how it identifies, defines and differentiates biologic products and active agents (what is assigns unique names to), as long as these criteria meet the requested requirements and are applied consistently. [But with FDA, through meeting the requests of this petition, obviously taking a leadership position in biologic products nomenclature, with this information expected to be adopted and used worldwide, the agency needs to do this right]. The basic potential approaches and criteria for defining biopharmaceuticals (biologics) and biosimilars are discussed in published articles authored by this petitioner (1,2,3,4,5,6). For example, if a hybrid entity/regulatory/commercial-centric approach is used, which is likely suitable, each product and agent with its own BLA/sBLAs and/or involving a different manufacturing company/facility would have its own unique name/identifier, likely with further modifications designating different versions and iterations.

2) Public Information Disclosure Requests:

FDA is requested to *minimally* upon approvals (BLAs or sBLAs):
1) Disclose information, including in review-related public documents, that adequately identifies (defines, describes, characterizes and differentiates) each product and active agent (including for reference products upon biosimilar approval). In regulatory terms, this means FDA disclosing a core body of diverse types of drug product and drug substance bioprocessing-related, quality-related and other descriptive (top-level, summary) information, particularly including information any of which significantly changes may well require a new approval (BLA or sBLA). Alternatively, FDA public disclosures may generally follow the topics listed in Common Technical Document (CTD) Module III (Quality) or comparable FDA CMC review checklists.

Doing this for new products is critically important. But FDA must also make informative disclosures regarding sBLAs, particularly any including any demonstration of product or agent comparability (and including those approvals simply reported in *Drugs@FDA* as involving "Manufacturing Change or Addition," with absolutely no related public disclosures of what has changed. This includes for already-approved products reporting

information that differentiates the new (new sBLA) vs. prior product/version/iteration. This information is needed for professional and public understanding of the identity of marketed products/agents (what they are), including having some basic minimal understanding of the differences and (bio)similarities between similar (but not necessarily biosimilar) products, and for the understanding and tracking of 'product drift' as products change and evolve.

As further discussed below, FDA must accept that in the context of current science and understanding of biopharmaceuticals; the current state of bioprocessing technologies, with many now rather standardized industrial platforms; biosimilars and requirements for implementation of the BPCIA; and with ever-increasing expectations for pharmaceutical approvals-supporting information to be readily available (currently, most attention directed to trials), that basic (top-level, summary) bioprocessing, quality-related and other CMC-related information is neither inherently proprietary nor biosimilar competitor-enabling! FDA must realize that the transparency, openness, etc. now demanded and on track to become common with clinical trials also must apply to product/agent identity-related information, without which the trials information is rather useless. If clinical trials designs and data, long considered even more proprietary and competitor-assisting than product/agent descriptive information, can now be disclosed and discussed in incredible depth, why not basic/top-level bioprocessing and quality-related information, which is even more critical to understanding products?

2) Include product/agent nomenclature and identity-related (including CMC, bioprocessing and quality-related) information in public approvals-related documentation, post this online, and allow some professional/peer input prior to its finalization. Obviously, names/identifiers and public product/agent information disclosures must be available online at the FDA Web site. For BLAs, this includes the requested product/agent names and descriptive public information being published in public advisory committee meeting briefings; FDA and/or sponsor staff (someone) discussing this information at these meetings; and input and questions regarding product/agent nomenclature and bioprocessing and quality-related information be allowed at these meetings. And where BLA approvals are not considered by advisory committees, FDA must disclose the requested information at its Web site and allow public or at least professional/peer comments prior to the finalization of the online postings of review-related documentation. For sBLAs, particularly any involving product/agent identity-related changes (such as involving any comparability testing), sufficiently-informative public information disclosures must be posted online.

Public Information Disclosure Requirements:

Defining, identifying, characterizing, etc. biopharmaceuticals/biologics invariably requires presenting a considerable amount of diverse types of information, with these products largely defined by their bioprocessing, quality-related, regulatory and commercial information (1,2,3; and to a lesser extent 4,5,6). Disclosing just a few descriptors or sentences describing products/agents, as is common in product inserts, with these now often more informative than all the information in related public approvals review documents, is absolutely inadequate!

Requested product/agent definitions/information disclosures could be in the form of:

a) descriptions/lists of the diverse characteristics that collectively define each product/agent, particularly bioprocessing- and quality-related information, generally following CTD Module III or comparably-rigorous FDA CMC review checklists; and/or public disclosures could simply be
b) rationally (less extremely) redacted CMC review-related documents.

This product/agent identity public information must include basic descriptive information enabling meaningful understanding of what defines/differentiates each product and agent (or each product or agent iteration or version), obviously including substantive disclosures concerning bioprocessing and quality-related aspects. Note, product identity-related information to be disclosed will, ideally, be descriptive, i.e., substantively informative, as much as possible, but when needed, such as to avoid proprietary information disclosure, the information disclosed may be indicative, more generic, and classifications may be used.

With a typical recombinant protein BLA reported to include over 1,200 distinct steps/operations/manipulations and with each of these rather complex, it is hard to believe that any disclosure of top-level/summary bioprocessing information, lists of characteristics, etc. prepared by any qualified FDA staff (that presumably can easily recognize and exclude genuinely proprietary information) can be considered either competing product developer-useful information or otherwise rationalized as proprietary and not disclosable. In this respect, FDA, seemingly particularly CDER, needs to undergo a major change in corporate culture! Bioprocessing, quality-related and other product descriptive information must not simply all be considered inherently proprietary, competitor-assisting or otherwise simply not disclosed.

Bioprocessing, quality-related and other top-level/summary descriptive information is and must be considered by FDA as inherently descriptive and informative regarding biologic products, including concerning critical safety-related aspects, and, thus, inherently publically releaseable (excluding specific, rationally-limited information identified by the sponsor or FDA staff as being truly proprietary)!

This petition's requests for basic descriptive product/agent public information include FDA disclosing some minimally descriptive/useful information regarding the nature of product identity-related changes associated with supplemental approvals ('product drift'). FDA must, particularly, make at least minimally-informative disclosures regarding sBLAs including any testing or demonstration of product or agent comparability! Unless FDA can provide a better parameter, sBLAs involving any analytical, in vitro, in vivo and/or clinical testing or demonstration of comparability between different products, versions or iterations of products are presumed to demark new products (or versions or iterations), with these generally requiring new unique product and agent names/identifiers and approval-related documentation disclosures citing what is new and different.

For example, identity-related information that *minimally, along with other information*, needs to be disclosed, ideally discussed, for approved recombinant proteins includes: primary protein sequences (including public database accession numbers); cell lines/expression systems; genetic engineering, including types of vector constructs used; overall outline of up- and downstream bioprocessing (sequence of steps); scale of manufacture (bioreactor and/or batch size); basic aspects of upstream bioprocessing (e.g., batch, perfusion or continuous culture); type of culture media; use or not of animal-derived products in manufacture; basic aspects of purification (e.g., sequence of

chromatography steps and types of media used); basic aspects of formulation and fill-finish processing; delivery system aspects and; agent/API and finished product manufacturing sites and companies, including CMOs, and their roles. Biosimilars will require further disclosures, including summary and comparative analytical data and discussion of similarities and dissimilarities with their reference product. This petition asserts that it is very rare for any *such top-level/summarized* bioprocessing- and quality-related information (e.g., that cited above) to be genuinely useful to competing product, including biosimilar, developers; and thus there is no basis for considering this information inherently proprietary or otherwise not disclosable.

But no matter what, the current practice of simply not releasing, including redacting, any/all bioprocessing- and quality-related information, somehow considering any/all substantive information about biologic products, their manufacture and quality to be inherently proprietary, is totally ridiculous (absurd; deserving of ridicule) and unacceptable! Examples of this practice are shown in Appendix 3. Also, unless truly warranted, such as for national security (e.g., not disclosing botulinum toxin manufacturing sites), there is no rationale for the current common non-release/redaction of manufacturing facilities, their identity, roles they play in manufacturing, and locations; with this a core part of the basic public record [and let's not forget that BLAs include establishments registration, what was formerly handled by ELAs, with much establishment information previously routinely disclosed now not being disclosed]. Further, in the context of biosimilars, with these soon enough outnumbering BLA-approved biologics (discussed in Appendix 2), understanding the similarities and differences between products/agents becomes even more critical.

3. New Programs, Initiatives and Expenditures Are Not Needed

This petition, other than minimally requesting FDA state some nomenclature conventions. assign related names as needed, and disclose some most public basic product/agent information - absolute basic requirements for any U.S. regulatory agency - does not request or require any significant new or additional programs, initiatives or expenditures by FDA. Once some basic nomenclature conventions are developed, the requested names and descriptive information need *minimally* only be issued upon any biologics approvals (sBLA or BLA; including for reference products upon biosimilar approvals). But ideally, appropriate names/identifiers should retrospectively be assigned to all approved biologics.

Surely, FDA must currently internally use unique and non-unique product and active agent names/identifiers for biologics in its internal information systems and communications. If not, then it is a no-brainer that these are needed in, if only in FDA's biologics-related public communications, particularly approvals review-related documents and listings. To satisfy this petition's requests concerning nomenclature, minimally all FDA may need to do is disclose relevant preexisting information. And surely, FDA must already internally as part of product reviews have relevant top-level summarized product and active agent identity-related information, summary descriptions, CMC reviews, etc. To satisfy public disclosure needs, minimally all FDA may need to do is disclose this information (summarized or minimally redacted).

FDA has considerable in-house expertise in pharmaceutical, including biologics, nomenclature. This includes FDA obviously needing to interpret the diverse names in the published literature during product reviews; and FDA developing and/or approving

multiple types of pharmaceutical names, including Established, Proper, sponsor's proprietary names and NDCs. Particularly, once the requested basic nomenclature conventions are set, someone knowledgeable, perhaps staff of the CDER-managed FDA *Substance Registry System* (SRS) or a CMC reviewer, over the long course of reviewing applications, should easily be able to propose suitable unique and non-unique names, particularly with many diverse names already in use by the time applications get to FDA, and in the context of FDA required to also officially assign Established and Proper Names and approve proprietary names. Ideally, there should be some internal and external names peer review (for which this petitioner volunteers).

FDA could further minimize any related work and likely improve its designations of the requested types of names by simply allowing or encouraging sponsors and other parties propose these names. This includes requesting suggestions and comments regarding proposed unique and biosimilar/(bio)generic-type names from sponsors during BLA reviews, and in advisory committee briefing documents coupled with allowing related public comment at these meetings. Another option for FDA, now very successfully used for about 40 years, would be one similar to that used for cosmetic ingredient labeling nomenclature (the *PCPA/CTFA Dictionary*), where an industry-based committee, here affiliated with the leading cosmetics trade association, proposes names that have almost always been accepted officially by FDA. Along these lines, see the petitioner's proposal for the *U.S. BIOPHARMACOPEIA Registry of Biopharmaceutical Products* (at www.biopharmacopeia.com), with an industry-grounded committee(s) proposing candidate names and maintaining a public registry of products (nomenclature).

Further, this petition asserts that the more substantive information FDA discloses about approved biologics, the less effort, time and money will be expended or wasted by the agency. Otherwise, with current lack of clarity in communications, products lacking needed names, continued professional and public ignorance about biopharmaceutical product/agent identities (which will only get more severe with biosimilars), and with the current FDAS practice of simply not disclosing any relevant descriptive/identity information, endless FOI requests and lawsuits seeking basic information will divert FDA.

B. Statement of Grounds

This Petition Claims Broad Representation, Including for All Biologics Information Resource Developers/Publishers: The petitioner claims, besides his own information resources/publishing company, that this petition also represents the interests of all biotech/pharmaceutical publishers and *all those needing to communicate and understand the identities of FDA-approved biologics*. This includes the biopharmaceutical, health care professional, patient, regulatory and scientific communities and the general public. This petitioner presumes he need not go into full detail about the need for suitable names for biologics and related defining/descriptive information disclosures. These are among the most basic legal requirements for FDA regulation of biologics.

Without names and basic descriptive information with any type of authority and with the products so complex, most every author and publisher rightly totally avoid getting involved with biopharmaceuticals. Publishers, including the petitioner, have been strongly inhibited from and nearly all have totally avoided developing

biopharmaceutical/biologics information resources, particularly any that treat products/agents individually, i.e., as unique rather than generic products. This is simply because no one knows how to handle these products, what the products are (their distinct identities). This includes there being no suitable unique non-proprietary product names, no biosimilar-type/non-unique or even class names, and by far worst of all, no associated sufficiently-informative public product definitions and descriptive information. The petitioner is the only information resources developer/publisher brave or foolish enough to have developed and publish a product/agent-centric biopharmaceutical information resource/reference, the *BIOPHARMA®: Biopharmaceutical Products in the U.S. and European Markets* database at www.biopharma.com (7). FDA should realize that this is not a situation that should be allowed to continue, in the sense that there should be a vast array of authors, analysts, publishers and others disseminating and adding value to biologic products/agents-related information. That such a health array is totally lacking should be a glaring warning sign to FDA of significant problems with the state of biologics information!

This Petition Further Claims Broad Representation for the U.S. Biopharmaceutical Industry and All Biopharmaceutical Information Users: The petitioner claims that the requested names and related product/agent identity-related public information are very much needed and in the vested interests of the U.S. biopharmaceutical industry and the U.S. public health. Biopharmaceuticals are among the few industries still profitable and led by U.S. companies. But regrettably, the U.S. lacks any biopharmaceuticals-dedicated trade association [and the leading most relevant biotech/pharmaceutical trade associations have committed to propounding overly-simplistic proposals for either unique or biosimilar/(bio)generic-type established names]. Until FDA rules on biosimilar established names and removes this divisive politicized issue from public controversies and politics, the trade and other organizations having taken stands on this issue may well be unable to move past this in terms of rationally considering other nomenclature and product/agent information issues (including this petition). Surely, FDA must recognize that functional names and public product identity information are absolutely critical to communications and public health, particularly with biosimilars (and more biobetters) coming, with these soon enough outnumbering current reference/innovator products (discussed in Appendix 2).

Legal, Regulatory and Historical Basis/Context

Regulatory/Legal Context:

The most recent biologics legislation, the Biologics Price Competition and Innovation Act of 2009 (within H.R.3590), failed to include any guidance concerning biosimilars nomenclature, with "name" and "nomenclature" never even mentioned. To date, FDA has totally avoided any substantive discussion of its potential approaches to biosimilar nomenclature, with this so far narrowly framed within the context of public controversies, lobbying and hype concerning selection of established names. But any reading of the BPCIA surely makes it obvious that unique and non-unique product and agent identifiers are needed for biosimilars (and all biologics), if only to support clear communications concerning biosimilar approvals.

Through the Public Health Service Act and other laws, including the BPCIA, FDA regulates marketed biologics (biotechnology-derived pharmaceuticals), and does this

separately from drugs (chemically-derived pharmaceuticals). Obviously, regulated biologics and their active agents need coherent unique non-proprietary names and/or other identifiers sufficiently specifying what is regulated and approved, with these names associated with basic public information identifying, defining, differentiating, etc. the regulated products. This should be job #1 for any regulatory agency.

But for over 100 years of federal regulation, the federal agencies regulating biologics, including FDA and NIH before that, have avoided assigning unique non-proprietary names for approved biologics! There appears to be historical basis for this. Until rather recently, biologics were essentially all designed, approved and considered to be rather generic, even fully-interchangeable products, with nearly all biologics being vaccines and blood-derived products. Even now, many, if not most (numerically), approved biologics are treated as fully generic (interchangeable), e.g., inactivated injectable influenza vaccines, even the yeast- and insect cell-expressed recombinant hepatitis B virus vaccines, many other vaccines, including most universal/pediatric vaccines, and nearly all blood-derived products, e.g., Albumin, immune globulins, Red Blood Cells and Anti-Hemophilic Factor. These are generally either designated interchangeable (if needed) in product inserts/labeling and, if not, are interchanged in practice.

Starting in the 1980s, with advancing science and technology, including recombinant proteins, biopharmaceuticals have become more varied, differentiated and science-based. Modern analytical technology reinforces the fact that biopharmaceuticals are inherently heterogeneous complex mixtures including many variants of the designated active agent and other components, largely dependent on bioprocessing. It is now universally recognized, including codified in laws, e.g., BPCIA, that biologics are very complex and unique products, with their identities, including properties and activities, largely dependent upon and differentiated from similar products, even proteins with the same primary sequence, on the basis of their manufacturing processes.

Everyone now realizes that "process = product" is very relevant to biologics, with a corollary being that no two products from different manufacturers, with unavoidably different bioprocessing, can be considered the same (for regulatory and prescription purposes, unless officially designated otherwise). But if "process = product" is in any way true (which it obviously is), then we (everyone other than sponsors and FDA) know little or nothing about approved biologics! Limited bioprocessing information is available for most approved biologics, paradoxically seemingly with less pubic information now being disclosed for more recent vs. older legacy products (back when bioprocessing technology was more unique, proprietary, etc.)

Further, biologics' manufacturing processes and the products/agents change repeatedly over time, resulting in serial sBLAs, with the product's core identity/definition potentially changing incrementally with each change/sBLA, particularly any bioprocessing or other change considered important enough for the sBLA to include testing to prove comparability. This change and evolution of products over time is commonly referred to as "product drift." Particularly, in the context of biosimilar approvals being based on comparisons with an established reference product, it is critical to have information available allowing some basic understanding of what products are at any particular time, including originally and currently, and the changes they have gone through.

Better professional and public understanding of products/agents and the changes they go through can only improve patient safety and post-marketing surveillance. This

includes clinicians being better able to associate variations in products' safety or efficacy with manufacturing changes. For example, among the 300+ deaths among Eprex (EU version of Procrit) recipients, how many might have been avoided, how sooner might problems or their cause have been identified, if this EU product's bioprocessing, including formulation and container changes, had been more readily-available public information, before large numbers of patients started dying from PRCA?

FDA's Current Biologics Public Information Regime is Dysfunctional

The amount and usefulness of the product/agent identity-related information being disclosed by FDA and, particularly, for recombinant proteins has very obviously been severely restricted. Some examples are cited in Appendix 3.

FDA now often discloses no useful or relevant information, often no information at all, concerning approved biologic products' and active agents' identity, including concerning bioprocessing and quality-related aspects! This is illustrated in Appendix 3. This includes never defining, stating or even citing what the approved products/agents are. This lack of clarity about what has been approved is intolerable, counter-productive, contrary to the laws and expectations for biologics regulation, and must be corrected! Unacceptable practices include public "review documents" often lacking any discussion at all of CMC, bioprocessing and quality-related aspects, including the totality of relevant sections in these documents being fully, i.e., 100%, redacted (see Appendix 3) with no public summaries provided. CMC reviews and summaries, particularly those covering manufacturing/bioprocessing, surely must be prepared internally. But none are included in the public review documentation; nor are summaries; nor is any such or related documentation retrievable when searching Drugs@FDA and the full FDA Web site.

Examination of recent and earlier (including decades ago) product approvals' review-related public documents shows much less information about recombinant products, particularly their bioprocessing and quality-related aspects, now being disclosed. Paradoxically, the newer and better characterized/characterizable a product is (or, perhaps a coincidence, if now regulated by CDER), the less relevant information FDA now discloses about the product/agent. This includes more information disclosed in earlier decades, when any/all information regarding recombinant proteins/mAbs, biologics and bioprocessing was inherently much more novel and commercially sensitive/proprietary/valuable in nature.

Substantive and detailed FDA public disclosures of bioprocessing, quality-related and other CMC information regarding approved biologics are nothing new (with this petitioner in the early-mid 1990s, in the context of developing *BIOPHARMA*, having received relevant public documents through filing of ~200 FOI request for all then-approved biologics). Incongruously, older review-related documents are most often significantly more informative than more recent documents! In terms of minimally meeting the product identity-related information disclosure requests of this petition, FDA could simply extend to all biologics, including recombinant proteins, many of its public information disclosure practices long-applied to many classic biologics (discussed below)!

FDA has a multi-decades record of detailed public disclosures regarding biologics, including bioprocessing-, quality- and product drift-related information. This is exemplified by the extensive information and data, including regarding purification and

viral inactivation processes, disclosed since the early/mid-1980s (with the advent of HIV/AIDS and hepatitis C) for most pooled plasma-derived products. Here, rather detailed bioprocessing information and quality assurance/specifications data are disclosed in public review documentation and even inserts/labeling for each product upon both relevant full and supplemental approvals. Also, many vaccine and cellular product inserts and review documents include extensive bioprocessing and quality-related information; and many approval reviews-related documents for many early recombinant proteins/antibodies are way more informative than currently, e.g., include details about drug substance and product specifications. Thus, FDA cannot simply dismiss this petition's request to disclose meaningful product identity-related information on the basis of the agency lacking legal or regulatory frameworks or precedents.

Are other relevant CMC-, bioprocessing- and quality-related reviews public documents not posted on the Web site available through FOI request? When asked by this petitioner, FDA staff state "No," with all public documentation online. If this information is hidden in 'public' documents only available only through FOI requests, this is unacceptable – this information needs to be genuinely publically accessible.

Other Issues Supporting This Petition's Requested Actions

References and Other Information Sources All Treat Similar Biopharmaceuticals as Generics

Lacking usable or in any way authoritative unique product and agent names and identities-related product/agent descriptive information or definitions, essentially every pharmaceutical reference treats biopharmaceuticals the same as it treat drugs, i.e., all similar products are treated as generic, particularly products having the same or similar established names/INNs/USANs, with all similar active agent products all handled in the same monograph. In terms of nomenclature, this includes all established chemical and pharmaceutical nomenclature systems all handling biologics generically, i.e., with no recognition of each product from each manufacturer being unique and requiring its own name/identifier. Thus, besides established names/INNs/USANs being inherently generic/non-unique, so are Chemical Abstracts Service (CAS) Names and Registry Numbers and related IUPAC systematic chemical nomenclature inherently fully generic in their handling of biologics. These chemical nomenclature systems are designed to provide index terms to bring together, not differentiate, similar (e.g., same or very similar established name/INN/USAN) products.

No established pharmaceutical or chemical nomenclature system yet recognizes and assigns unique names/identifiers to biologics active agents and finished products! Rather, products and active agents, for lack of any better options, use the same inherently non-unique/generic names, a perfectly ambiguous situation as with established names. All chemical and pharmaceutical nomenclature systems, to date, simply consider all products with similar active agents to be the same, e.g., single monographs for recombinant somatropins; hepatitis B vaccines; interferons alfa, beta, gamma, etc. [But CAS/IUPAC Names, much like established names, could well be adopted as the requested (bio)generic-type names for biologic active agents, and with further appropriate modifications could also be used for generic and unique product names and unique agent names]. With CAS/IUPAC names being rather systematic and descriptive, these names could well be much better suited than established/compendial

names for adaption as the requested unique names (while current Proper names, which exhibit excessive inconsistency and incoherency, are best totally avoided).

Essentially all pharmaceutical references similarly treat biologics generically. This includes generic monograph entries for biologics in those references formally recognized in practice as suitable for making substitutions in practice, e.g., *AHFS Drug Information* monographs. In this context, particularly with the advent of biosimilars, not having unique non-proprietary product and active agent names and not having information differentiating products is outright dangerous! Totally lacking any even partially authoritative descriptive product/agent names and needed product identity information, and despite biosimilars coming to market, essentially all pharmaceutical references have no choice but to continue with their status quo – treating all similar biopharmaceuticals as (bio)generic equivalents. This is obviously adverse to the nation's public heath.

Further, not designed to differentiate among products or their active agents, all current 'registry' systems (nomenclature databases) for biologics are rather useless or worse, are substantially misleading. This includes the CAS Registry System, CHEMID and other National Library of Medicine nomenclature files, and the "Nomenclature" section in *BIOPHARMA* monographs (www.biopharma.com). When it comes to biologics, lacking any authoritative names and with no authoritative linked descriptive information, all current 'registry' systems simply cumulate garbage – jumbling together diverse names for any/all rather similar products and agents from diverse sources, including erroneous names, mixing-up different products' and active agents' names, etc., with the resulting list being useless or worse, with no one knowing what names represent or mean.

Lack of Information Confounds Public Trust, Particularly in the Context of Biosimilars

The lack of sufficient in any way authoritative information about biopharmaceutical products confounds public trust in these products, the industry and FDA (8). When patients, public, physicians, pharmacists, students, formulary committee members, competitors – anybody – go to look for information about marketed biopharmaceuticals, they quickly find that the only (or rather, most) 'unique' name for a products/active agents are trademarks and that there is little or negligible information available about products' and agents' identity, what they actually are, including bioprocessing and quality-related aspects. In contrast, there is relatively near infinite information available about of medical/use-related aspects, including clinical trials. But this information that is most-available does not address the most basic issues related to biologics safety and quality that most are ultimately concerned about – what's in it?, how was it made?; who made it, where? and how was quality assessed (what criteria or specifications are met)?

In this context, particularly the lack of any descriptive product/agent identity, bioprocessing and quality information, FDA upgrading nomenclature and public product information regarding approved biopharmaceuticals can only help these products avoid from being targeted with some of the same fully-irrational, not grounded in science, allegations now targeted to genetically engineered foods. The last thing the U.S. industry and FDA needs is for recombinant biopharmaceuticals to be tagged and attacked as "Frankenbiophamaceuticals" or equivalent. With all the approval, patent and other controversies and chaos surely coming, and with all the associated press coverage and hype as hundreds of biosimilars (and biobetters) enter the market, not having useable names and product identity information available, not providing

biopharmaceuticals a suitable common denominator or baseline of public information, can only contribute to such public and professional distrust.

The more in-depth, descriptive, detailed unique names and information FDA discloses, the better for FDA, the U.S. biopharmaceutical industry and the U.S. public health and economy! This need not be costly or complex. FDA can do much as it does with other information, notably its clinical trials assessments and increasingly even sponsor's data - simply disclose it, such as in rationally-, i.e., minimally-, redacted CMC reviews. No matter how lengthy, scientifically or otherwise complex public disclosures are (they should and need not be dumbed-down), presuming disclosures are useful/descriptive enough, FDA can count on many others, including in the private sector, repackaging, analyzing, adding value and widely disseminating this information. And FDA, in the context of biosimilars, surely knows that releasing top-level/summary information about approved products will be of little genuine help to competing biosimilar developers, with there being no rationale to redact, consider proprietary or otherwise not disclose the requested public information.

C. Environmental Impact

FDA fulfilling the actions requested by this petition is projected to not have any discernable environmental impacts, either negative or positive.

D. Economic and Public Health Impacts

FDA fulfilling the actions requested by this petition will have significant positive impacts on the U.S. biopharmaceutical industry, (bio)pharmaceutical information providers and publishers, and the U.S. economy and public health. This petitioner cannot envision any economic- or safety/public health-related downsides to having useful biologics names and good product/agent information available.

The U.S. biopharmaceutical industry has for too long been hobbled by lack of suitable names, identities and understanding of its products. Having usable names and basic understanding of product/agent identities (what they are) is obviously required for effective and precise communications regarding these products. Although difficult to quantify, better understanding and information about U.S. biopharmaceuticals will clearly result in positive economic and public health outcomes.

E. Conclusion

Nomenclature and public information regimes suitable for the 21st century and for dealing with the complexities of biologics and the 100s of upcoming biosimilar (and biobetter and biogeneric/interchangeable) approvals are required. Product and active agent names and related public information disclosures regarding their identity, definitions, descriptions, etc., are needed that are primarily science-, product- and entity-based, not based on and their utility confounded by regulatory requirements (e.g., Established/compendial/USAN Names). As requested by this petition, FDA must assign both unique and biosimilar/(bio)generic-type non-unique names for finished products and their active agents; and disclose associated top-level/summary product identity information in public review related documentation, including regarding bioprocessing and quality-related aspects.

F. References Cited [PDF versions of nearly all cited references are online at www.biopharmacopeia.com]

Late addition:
Rader, R.A., "Biosimilars: The U.S. Development Pipeline and Likely Market Evolution," *BioProcess International*, "Biosimilars" supplement, June 2013 [printed version mailed but not yet online as of filing date]

1) Rader, R.A., "Nomenclature for Biosimilars Will Be Highly Controversial," *BioProcess International*, vol. 9, no, 6, June 2001, p. 26-33 [abstract and link to full article at www.biopharmacopeia.com].
2) Rader, R.A., "What Is a Generic Biopharmaceutical? Biogeneric? Follow-On Protein? Biosimilar? Follow-On Biologic? Part 1: Introduction and Basic Paradigms," *BioProcess International*, March 2007 [abstract and link to full article at www.biopharmacopeia.com].
3) Rader, R.A., "What Is a Generic Biopharmaceutical? Biogeneric? Follow-On Protein? Biosimilar? Follow-On Biologic? Part 2: Information, Nomenclature, Perceptions, and the Market," *BioProcess International*, May 2007, p. 20-28 [abstract and link to full article at www.biopharmacopeia.com].
4) Rader, R.A., "What is a Biopharmaceutical, Part 1: (Bio)Technology-Based Definitions," *BioExecutive*, March 2005, p. 60-65 [abstract and link to full article at www.biopharmacopeia.com].
5) Rader, R.A., "What is a Biopharmaceutical, Part 2: Company and Industry Definitions," *BioExecutive*, May 2005, p. 42-49 [abstract and link to full article at www.biopharmacopeia.com].
6) Rader, R.A., "(Re)defining Biopharmaceutical" *Nature Biotechnology*, July 2008, 26(7), p. 743-751 [more concerned with terminology; abstract and link to full article at www.biopharmacopeia.com].
7) Rader, R.A., *BIOPHARMA: Biopharmaceutical Products in the U.S. and European Markets*, now in 12th year/edition as an online database at www.biopharma.com. [The only biopharmaceutical products information resource/reference, further unique with its concentration on products' biotechnology and commercial aspects, not relatively infinitely available medical/use information. Last printed 7 years ago, then 2 vol., 1600+ dense pages, now much larger].
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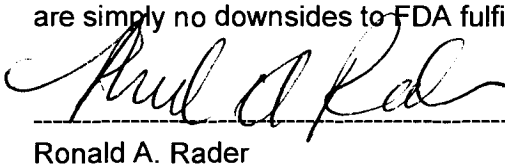
9) Rader, R.A., , BioPlan Associates, Oct. 2008, 365 pages [The only directory of expression systems and other genetic engineering technologies in use and/or available for license].
10) Rader, R.A., *Charting the Biosimilar and Biobetter Development Pipeline*, FirstWord Pharma, 428 pages, Sept. 2012.
11) Rader, R.A., *BIOSIMILARS.com: The Biosimilars Information Resource for the Biopharmaceutical Industry*, embryonic Web site at www.biosimilars.com.
12) Rader, R.A., et al, "Chemical Information Resources Directory: An Integrating Component of the Chemical Substances Information Network," in the *Journal of Chemical Information and Computer Sciences*, May, 1981, p. 78-82.
13) Rader, R.A., *Federal Biotechnology Programs Directory*, OMEC International, 162 pages, 1987; the first directory/study of federal biotechnology research, development, regulatory and funding programs.
14) Rader, R.A, *Federal Biotechnology Information Resources Directory*, OMEC

International, 151 pages, 1987; the first directory/study of federal biotechnology research, development, regulatory and funding information resources.
15) *Federal Bio-Technology Transfer Directory*, author and publisher, Biotechnology Information Institute, 687 pages, April 1994; replaced by database online until 2000.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition. [Although, the petitioner knows of no and asserts that there are simply no downsides to FDA fulfilling the requests of this petition].



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