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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Citizen Petition

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

Filed by:
Ronald A. Rader
President
Biotechnology Information Institute
1700 Rockville Pike, Suite 400
Rockville, MD 20852
E-mail: biotech@biopharma.com

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

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].
8) Rader, R.A., "Biopharmaceuticals: Lack of Information Disclosure Confounds Public Trust, Particularly in the Context of Biosimilars," *BioWorld Perspectives*, vol. 2, issue 18, May 1, 2008; online at www.biopharma.com/Bioperspectives_05.01.2008.html.
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].

---------- Date ----------

Ronald A. Rader
President
Biotechnology Information Institute
1700 Rockville Pike, Suite 400
Rockville, MD 20852
Phone: 301-424-0255
E-mail: biotech@biopharma.com

Appendix 1: **Petitioner Qualifications Regarding Biopharmaceutical Nomenclature and Information**

The petitioner, Mr. Ronald A. Rader, is President, Biotechnology Information Institute (BII), a biotechnology/pharmaceutical information resources developer, publishing and consulting sole-proprietorship company based in Rockville, MD. Mr. Rader is currently best known as author and publisher of *BIOPHARMA: Biopharmaceutical Products in the U.S. and European Markets* (*BIOPHARMA*), now in its 12 year/edition and available as an online database at www.biopharma.com (7). Mr. Rader's full resume, with links to his publications, is online at www.bioinfo.com/resume.html.

BIOPHARMA is the only information resource/reference specializing in biopharmaceuticals – currently with 671 "product" monographs, including 234 recombinant protein "products" (but with what constitutes "products" not consistently defined, with no in any way authoritative source for this information). Ideally, the unique product names and definitions requested will be usable in *BIOPHARMA* and other pharmaceutical references, formularies and professional and public communications to more coherently and consistently identify, define and differentiate unique approved products and active agents. Mr. Rader is also the author of the only directory/reference of expression systems and related genetic engineering technologies in commercial use and/or available for licensing (9).

Mr. Rader is author of the most extensive published biosimilars/biobetters pipeline (what's in R&D) study, with a book version published by FirstWord Pharma in Oct. 2012 (10), and his company (BII) launching its own more extensive biosimilars/biobetters pipeline database this Spring at www.biosimilars.com (11). Other plans for Biosimilars.com include making this the best single source for (bio)technical and commercial (i.e., non-medical/use) information about biosimilars and their reference products.

Mr. Rader is uniquely qualified concerning chemical, pharmaceutical and biotechnology information, particularly in a regulatory context, and concerning biopharmaceutical nomenclature and related classification and indexing schemes, taxonomies, etc. He has degrees in Microbiology and Library/Information Science (B.S.; M.L.S.). Graduate studies including a Chemistry department course in chemical/pharmaceutical representation and nomenclature taught by the then head of drug information, CDER. Early in his career he held various chemical/toxicology information positions providing a high level of expertise in regulatory-related chemical information and nomenclature, including Information Specialist, Gillette Co. (including developing the company's first chemical inventory) and with various government contractors including serving as User Support Coordinator, NIH/EPA Chemical Information; Chemical Editor (nomenclature), *Survey of Compounds Which Have Been Tested for Carcinogenicity* (PHS-149); Manager, Cancer Information Clearinghouse (for NCI); and Information Scientist, Toxic Substances Information Group, MITRE Corp. In this last position, Mr. Rader was the lead chemical information specialist on a full-year multi-agency-funded, including FDA, project investigating chemical structure, nomenclature and other ways of networking and

combining information and data from major chemical/toxicology, mostly regulatory agency, information systems (12).

Mr. Rader then worked for 5 years as Manager, Information Services, Porton International, then the largest privately-held biotech company, including as Editor/Publisher within the company's OMEC International publishing subsidiary. This included his serving as Editor, *BioINVENTION*, a monthly biotechnology patent abstract and news periodical; founding the *Antiviral Agents Bulletin*, which his own company continued to publish for 15 years (1987-2003); and lead author of two books: *Federal Biotechnology Information Resources Directory* and *Federal Biotechnology Programs Directory*, providing him with a full understanding of regulatory and other biotechnology information organization and use throughout relevant federal regulatory and research agencies (13,14).

Mr. Rader started his own company, Biotechnology Information Institute, in 1991, with its early publications including the *Antiviral Agents Bulletin*, a monthly periodical, and the *Federal Bio-Technology Transfer Directory*, a 687-page book and later larger online database reporting all federal agency, e.g., NIH and FDA, inventions/patents, licenses and Collaborative R&D Agreements (CRADAs) in biotech/biomedical areas (15). He launched *BIOPHARMA: Biopharmaceutical Products in the U.S. and European Markets* in 2001, last published as a multi-volume 1600+ page book in 2007 and now much larger and only available as an online database (at www.biopharma.com)(7).

Mr. Rader is also author of multiple very highly-relevant published articles (see references list), including (see main reference listing):
a) "Biosimilars: The U.S. Development Pipeline and Likely Market Evolution," BioProcess Interational, "Biosimilars" supplement, June 2013 [in print, not yet online as of date of filing]
b) "Nomenclature for Biosimilars Will Be Highly Controversial," in *BioProcess International*
c) a 2-part series, "What Is a Generic Biopharmaceutical? Biogeneric? Follow-On Protein? Biosimilar? Follow-On Biologic?" in *BioProcess International*
c) "(Re)Defining Biopharmaceutical" in *Nature Biotechnology*
d) a 2-part series, "What is a Biopharmaceutical?," in *BioExecutive*
These nomenclature-relevant articles are abstracted and accessible at www.biopharmacopeia.com.

<u>Appendix 2</u>: Upcoming Biosimilars (and Biobetters) Approvals Make Product Names and Information Even More Critical

Note: Related article by this petitioner, "Nomenclature for Biosimilars Will Be Highly Controversial," has been published in the current June issue of BioProcess International*, "Biosimilars" supplement, printed version mailed but not yet online as of filing date]*

The petitioner is the author of the most extensive published (book format) biosimilars and biobetters pipeline study to date (10), and he/his company will be bringing out an even more extensive online database this Spring (see www.biosimilars.com)(11). Besides tracking products in development, the petitioner has determined projected U.S. and EU patent and data and market exclusivities expiration dates for essentially all relevant reference products (n = 119). Note, this only include protein/mAb products, nearly 95% recombinant, with vaccines and blood products excluded. [Biobetters are defined as similar follow-on biopharmaceutical products that are too dissimilar relative to an established/reference product to receive biosimilar approval].

The petitioner's database is currently (4/30/2013) tracking >500 (n = 517) biosimilars and >400 (n = 404) biobetters, a total of over 900 follow-on biologics, in development worldwide with essentially all targeted, if not initially, then sooner or later for the U.S. market! These large numbers of biosimilar/biobetter products in the pipeline will further grow significantly, with many of the likely future major biosimilars and biobetters players, including many of the largest international pharmaceutical and generic drug companies, not yet having disclosed their specific products in development.

Even allowing for a vast majority of dropouts and product failures, FDA will soon enough be seeing many biosimilar applications, way beyond the meager number of biosimilar developers that FDA has formally met with so far. As FDA surely knows, most of the major economically-attractive biosimilar/biobetter candidates are still at least a few years off from being marketable (patents and exclusivities expiring), and most biosimilar developers have not yet even had their first formal meetings with FDA. Many or most seem to be in no rush to be the first into the market, with there being no Hatch-Waxman-like months of market exclusivity or other incentives granted to first biosimilar approvals, and patent dispute resolutions specified in the BPCIA affect early applicants more than later ones. Thus, many companies prefer others be the pioneers; and many or most are primarily interested in rounding out and expanding present product portfolios, which also need not involve them being among the very first in the market.

Further contributing to complexity and adding problems to biosimilars (and biobetters) regulation, many biosimilar applicants will be new to biopharmaceuticals and/or the U.S. market; there will be a considerable market for approved biosimilar APIs, with many product manufacturers only performing fill-finish; there will be many authorized (bio)generics, including companies relabelling products for sale by others; there will be applications from foreign countries with no precedents for U.S.-approved biologics manufacture; there will be lots of patent disputes; and other issues and events will only complicate things for FDA and confound professional and public understanding of

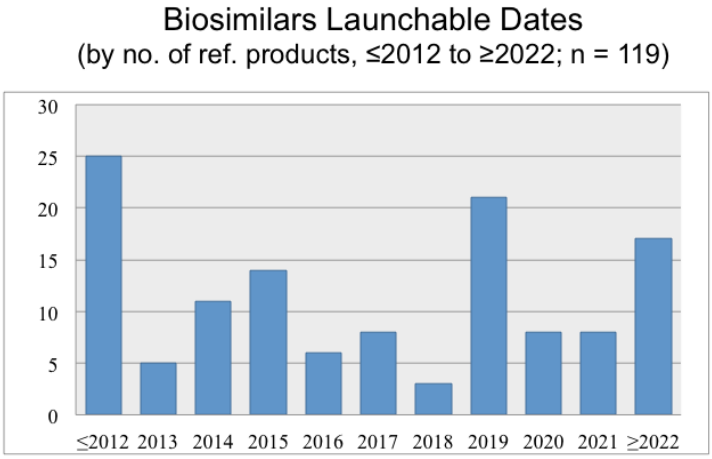
biosimilars. Not having suitable product/agent nomenclature and information available will only further complicate complexities, controversies, and simply be bad for the industry and FDA.

Although discussions tend to concentrate on reference/innovator and biosimilar products, there will be nearly as many biobetter products. Most of these are being designed to be better in in some way(s) compared to related legacy innovator products. Biobetters, by this petitioner's definition, involve innovator/reference product active agents as a component, e.g., physically in an improved delivery system, or as a chemical substructure, e.g., as a pegylatated version or albumin fusion protein. Thus, biobetters add further levels of complexity to product/agent names and identities. This makes it all the more important that suitable names and identity information be available.

Biosimilars (and Biogenerics) Will Quickly Dominate Approved Biologics

Much as 10 generic versions of the asthma inhaler drug Singulair were recently approved on the same day after patents expiration, with more expected to follow, much the same and, perhaps, even more biosimilar and biobetter versions of reference/innovator products can be expected to be filed for approvals as patent and data and market exclusivity expirations allow or shortly thereafter (after a few pioneers have set precedents). The *BIOPHARMA* database currently reports ~40 biopharmaceuticals with blockbuster, i.e., over $1 billion/year, worldwide sales, and another 35, ~75 total, with over $500,000 million annual sales (7). All of these reference products will be among the prime targets for launch of biosimilars and biobetters.

The figure below shows the petitioner's estimates of the number of evaluated reference products (n =119, nearly all rDNA) by their U.S. launchability date (expiration of patents and data and market exclusivities). This Figure agrees with essentially all other forecasts of U.S. launch(ability) timing for biosimilars, with a large number expected in a few years and another large number, including many blockbuster monoclonal antibodies, expected late in the decade.



To date, no biosimilar applications have been filed, with few of the currently off-patent, off-exclusivity reference products, e.g., the 30 biosimilars launchable ≤2013 (in Fig. 1), economically attractive or posing technical issues, e.g., insulins and analogs being very device-dependent. But as FDA should well know, starting now and through the next 10 years, over $100 billion in current biopharmaceutical sales will be launchable as biosimilar versions in the U.S.

The following Figure shows some current blockbusters followed by some major product classes with current reference product sales and the number of biosimilars and biobetters known/reported to be in development.

Biosimilars and Biobetters Reported to Be in Development

Ref. Product	Sales($B)	Biosimilars	Biobetters
Rituxan	$7.30	21	15
Avastin	$6.30	10	9
Remicade	$7.16	8	9
Herceptin	$7.30	21	12
Humira	$9.27	11	7
Lantus	$6.40	6	2
Neulasta	$4.01	13	9
Lucentis	$3.72	2	2
Aranesp	$3.00	4	2
Epogen/Procrit	$3.73	64	25
Neupogen (G-CSF)	$1.44	47	22
Insulins (all)		38	53
TNF inhibitors		38	18
mAbs & mAb fragments		130	90
Interferons alfa		45	42
Interferons beta		20	22

In this context, this petitioner believes that the biosimilars/biobetters market will be more like the generic drug market, with often over a dozen sources for major-selling reference products. Keep in mind that 10% market share of a $1 billion market is $100 million/year, likely providing up to $1 billion in revenue over the product's say dozen years of life.

The petitioner asserts that for most every reference product currently with a significant U.S. market, there could very easily be 10 more biosimilars entering the market by the end of the decade. For example, if only 3-4 Big Pharma companies, 3-4 large generic drug companies, 2-3 established biotech companies, 2-3 new biosimilars-targeting biotech companies, and 3-4 foreign companies seek approval for biosimilar versions of major reference products (with these low estimates for each type of company), one can see that there could easily be well over a dozen biosimilars alone, ignoring biobetters, entering the market for each major reference product in coming years. If there are just 10

biosimilar versions of each of the current 40 blockbusters (400 products total) and 5 for each of the other ~35 with sales $.5-$1 billion (175 total), that is a total of 575 new biopharmaceuticals entering the market in coming years, not including new innovator products and biobetters!

Thus, biosimilars alone will rapidly come to outnumber innovator products in ≤5 years. Hopefully, FDA will be ready for this onslaught, with biosimilar approvals rapidly becoming routine and not diverting agency resources, including having nomenclature systems in place for unique and biosimilar-type/non-unique names fully ready and a related public information disclosure infrastructure.

No matter what, there will be a large number of biosimilars and biobetters, 100s, coming to market in coming years, and these will rapidly outnumber traditional-type innovator products. Diverse user communities will need useful information about product similarities and dissimilarities. In this context, having usable unique and biosimilar-type/non-unique names and public product identity information allowing understanding of (bio)similarities and differences among products will be critical.

Appendix 3: Examples of Inadequate Public Information Disclosures

Various BLA-associated review documents retrieved from Drugs@FDA and the overall FDA Web site were examined for ***any/all*** disclosures of product/agent identity information, including regarding CMC, bioprocessing and quality-related aspects. The Figures presented below are screen-shots of pertinent sections of FDA's online PDF BLA approval reviews-related documents (with petitioner text in Arial and FDA screenshot text in Times-family font). Discussion concentrates on the redacted or missing information in specific relevant-titled FDA documents.

THE POINT HERE IS TO SHOW WHAT IS MISSING (PROVE A NEGATIVE) – THAT NO OR NEGLIGIBLE USEFUL INFORMATION ABOUT PRODUCTS IS BEING DISCLOSED ANYWHERE IN FDA's ONLINLE APPROVALS' REVIEW-RELATED PUBLIC DOCUMENTATION!

1) Taliglucerase alfa, BLA granted May 1, 2012

Summary: No CMC or bioprocessing review or useful descriptive information retrievable in Drugs@FDA or the entire Web site!

Chemistry Review – As the first plant cell-expressed biologic to receive approval and one of the first products to be manufactured using single-use bioreactors and other equipment, one would presume that there would be some information concerning bioprocessing in this (or some other) document. But the "Description of the Product" (figure below) provides no description of either the active agent, the finished product or bioprocessing, other than the active agent having the primary sequence of human glucocerebrosidase, its molecular weight and cites a carrot cell line as being used for protein expression.

Also, as with all the other 'Chemistry Reviews" examined, none actually discuss drug substance or product chemistries! This includes no discussions of microheterogeneity, the normal distribution of molecular variations expected and allowed in products; glycosylation patterns and variants; etc. Similarly, for this and the few other products publicly known to be among the first recombinant products manufactured using single-use/disposable (plastics-based) bioreactors and other equipment, there is no mention of this, much less needed information about leachate and extractables, their levels and safety assessments.

Also, this and none of the other reviewed documentation include any useful information about purity, potency and how these were determined, with the one or a few sentences in product inserts' often dislosing more information than cumulatively disclosed in approvals-related review public documents!

V. EXECUTIVE SUMMARY

A. Description of the Product

Taliglucerase alfa is a parenteral single use lyophilized drug consisting of human glucocerebrosidase. Taliglucerase alfa is produced in a carrot cell line and is purified to homogeneity using standard chromatographic techniques. Taliglucerase alfa is a single polypeptide chain containing the exact amino acid sequence of human glucocerebrosidase [redacted (b) (4)] The molecular weight is ~ 60,800 Da [redacted (b) (4)]

Glucocerebrosidases are enzymes that catalyze the hydrolysis of long chain fatty acid glucocerebrosides to glucose and ceramide. The hydrolysis reaction occurs via a double displacement reaction where sugar-enzyme intermediates are formed and hydrolyzed. No cofactors or metal ions are required for catalysis. Due to assay difficulties with glucocerebrosides, enzyme activity is measured by monitoring the hydrolysis of p-nitrophenyl-β-glucopyranoside (pNP-Glc) which contains the critical glycosidic bond.

Glucocebrosidases are used as standard of care enzyme replacement therapies for patients with Gaucher's Disease. Gaucher's Disease is a lysosomal storage disorder that is marked by the inability to clear cellular glucocerebrosides resulting in their accumulation in the lysosomes of tissue macrophages primarily in the spleen, liver and bone marrow. The lyophilized drug product, containing the excipients mannitol, polysorbate 80, and sodium citrate, is reconstituted in sterile water. The dosing regimen is 60 U/kg once every two weeks by IV infusion over 1-2 hours.

Manufacturing taliglucerase alfa using the carrot cell substrate has several advantages. The growth media is devoid of any mammalian derived products (including serum) thus avoiding issues with mammalian adventitious viral agents. In addition, the [redacted (b) (4)] fashion by which glycan structures are synthesized in [redacted (b) (4)] Taliglucerase alfa with terminal mannose residues is critical to its mechanism-of-action (and glucocebrosidases as an enzyme replacement therapy) since it is through the mannose receptor that taliglucerase alfa is internalized into the macrophages that have accumulated high levels of glucocerebrosides.

All information above about the active agent and its bioprocessing is missing or redacted (while irrelevant non-identity-related information, e.g., concerning agent biological activities, is retained).

All information related to manufacturers, locations and roles has been redacted, as shown below, with 94 pages cited as "Withheld in full."

Also, this and none of the other reviewed documentation includes other critically-needed information, such as regarding comparability of products used in different phases of development. How can the relevance of preclinical studies and early clinical trials be determined without knowing whether the products manufactured and used in early development are the same (comparable) or not as the marketed product? EMA EPAR documents regularly discuss this, but not FDA public documents.s

3.2.P.3.1 Manufacturer(s)

Table 1 - Manufacturers for the Drug Product

Name and Address	Responsibilities
(b) (4)	

(b) (4)

94 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

2) TBO-Filgrastim, BLA granted Aug, 30, 2012

Summary: No CMC or bioprocessing review or useful descriptive information retrievable in Drugs@FDA or the entire Web site!

Chemistry Review – The only sections where the drug substance is discussed, the last two paragraphs shown in the figure below, are totally redacted, other than the protein's amino acid length! Again, there is absolutely active agent description, no CMC, bioprocessing or quality-related information.

SUMMARY BLA 125294 Neutroval (Filgrastim)

Table 3.2.P.7-2: Primary Packaging Components: Description

Component	Description	Compliance Reference	DMF/ BMF #
[redacted]			

The product label claims that the DP is supplied as 300 mcg/0.5 ml and 480 mcg/0.8 ml. The PFS are filled to a target fill volume [redacted] and [redacted] respectively. Teva was asked to justify the overfill of [redacted] per syringe. They have provided fill weight data generated during the manufacture of the pivotal batches of XM02-DP. The data show for the 0.5 mL PFS the average weight is [redacted] with a STD [redacted] For the 0.8 mL PFS the average weight is [redacted] and a STD [redacted] Given this data Teva states that tightening of the fill weight limits beyond the original limits is operationally not feasible.

Reviewer Comment: These data indicate that the variation in the stated content is well within USP recommendations for "excess" volume and thus the applicant meets the requirements under 21CFR 201.51(g).

XM02 is 175 amino acids long [redacted]

[redacted]

As shown below, the "Summary of Quality Assessments" section is totally, 100%, redacted. The CTDL secondary CMC memo discussing "information on the approvability of this application" is simply missing; and the bottom of the page cites redaction of 380 pages.

Reviewer Comment: This memo does not cotain the summary basis of approval. For information on the approvability of this application see the CTDL secondary CMC memo.

I. SUMMARY OF QUALITY ASSESSMENTS

(b) (4)

[redacted]

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Latter, within the “Risk Assessment” section, there is one introductory sentence citing, “The product *[wrong, the active agent/drug substance]*, XM02, is a bacterial (*E. coli*) derived non-glycosylated 18.85 kDa human recombinant Granulocyte Colony Stimulating Factor (G-CSF) protein with an extra Methionine residue in the N-terminal portion.” This is the only product identity information, including bioprocessing- and quality-related, disclosed anywhere!

3) Aflibercept, approved Nov. 18, 2011

Summary: No CMC or bioprocessing review or useful descriptive information retrievable in Drugs@FDA or the entire Web site!

Chemistry Review – The following three Figures shows nearly 100% redaction of all product/agent identity information, including everything bioprocessing-related! And there is absolutely no real drug substance chemistry information, such as microheterogenity, contaminants, purity, process chemicals, etc.

visual acuity at week 52 compared to baseline. Four randomly assigned dosing regimens were (A) Eylea 2 mg administered every 8 weeks following 3 initial monthly doses; (B) Eylea 2 mg administered every 4 weeks; (C) Eylea 0.5 mg administered every 4 weeks; and (D) ranibizumab 0.5 mg administered every 4 weeks. Arms A and B were shown to have efficacy that was non-inferior and clinically equivalent to arm D.

C. Stability

Drug Product:

- Drug product is intended to be stored at 2-8°C.
- Expiration dating for the Drug Product, aflibercept injection, is 15 months from the date of manufacture when stored at 2 - 8°C, protected from light. The date of manufacture is defined as (b) (4)
- Aflibercept is light sensitive and should not be exposed to excessive light. A photostability study identified impacts to size variants, charge variants, and particulates.
- The expiration date for the packaged product, (aflibercept single-use vials, syringe, needle and filter needle) shall be no longer than the shortest expiration date of any component.
- Eylea drug product formulation does not contain a preservative; vials are intended for single use only.

The manufacturing process of aflibercept is (b) (4)

(b) (4)

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from another part of the “Chemistry Review:”

16. Regarding the description of the manufacturing process:

(b) (4)

and yet another section [How can basic product definitions be proprietary or non-discloseable?]:

DS intermediate is (b) (4)

Aflibercept **Drug Substance** (DS) is (b) (4) aflibercept formulated in 10 mM sodium phosphate, pH 6.2.

Formulated Bulk: (b) (4)

(b) (4)

As shown below, all (100%) of the “Related/Supporting Document” has been redacted. How could related DMFs, which are approvals, ever be considered proprietary or otherwise not discloseable?

14. **PRIMARY STRUCTURE, PHARMACOLOGICAL CATEGORY, MAIN SPECIES MOLECULAR WEIGHT, HOST SOURCE, MAIN GLYCOSYLATION STRUCTURE/S:**

Aflibercept is a dimeric IgG1 fusion protein. The Fc portion of human IgG1 is fused to human vascular endothelial growth factor receptor (VEGFR)-derived peptide domains. VEGFR2 extracellular Ig domain 3 is fused to the Fc region, and VEGFR1 extracellular Ig domain 2 is fused to the VEGFR2 domain. (b) (4) The theoretical (unglycosylated) molecular weight is 96.9 kD, and the experimental molecular weight is 115 kD. The isoelectric point is 5.8-8.3.

15. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]
(b) (4)	III	(b) (4)	(b) (4)	4	N/A
	III			4	N/A
	III			4	N/A
	III			4	N/A
	III			4	N/A
	III			4	N/A
	III			4	N/A
	V			4	N/A

[1] Action codes for DMF Table:
4 – Sufficient information in application

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Another section, here with 100% of comparability information redacted:

14. Regarding manufacturing process development:

a. On the subject of comparability:

(b) (4)

Regarding the decay profiles, as no primary data were provided,

4) Pertuzumab, approved June 8, 2012

Summary: No CMC or bioprocessing review or useful descriptive information retrievable in Drugs@FDA or the entire Web site!

Chemistry Review – The following screen-shot shows the "Drug Product Name/Code/Type" information from the introductory section.

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a)	Proprietary Name:	Pertuzumab
b)	Non-Proprietary/USAN:	Pertuzumab
c)	Code name:	rhuMab 2C4
d)	Common name:	Perjeta
e)	Drug Review Status:	Original Application
f)	Chemical Type:	
g)	CAS index/registry no.:	380610-27-5
h)	Internal systematic name:	MAB Humanized (IgG1k) ANTI P04626 (ERBB2_HUMAN)

But these names are substantially wrong! The correct Proprietary Name, as used elsewhere, is "Perjeta," not "Pertuzumab," which is the "Non-Proprietary/USAN" (properly reported) or establish name. "Perjeta" also is *not* the or a "Common Name" - it is the trade name, a registered trademark. The CAS Index/Registry Number refers only to the active agent/drug substance and only in the most generic sense, not the "Drug Product."

And what is this "Internal Systematic Name?" This petitioner has never seen mention of this before, nor does "Internal Systematic Name" retrieve anything in major search engines. If FDA has developed "Internal Systematic Names" for biologics, it needs to publically disclose these and information about this nomenclature system, including as part of addressing the requirements of this petition.

Overall, this "Drug Product Name/Code/Type" information is unacceptable, even misleading. This shows how even CMC reviewers and reviews, presumably subject to considerable internal peer review, are mixed-up when it comes to the most basic nomenclature for biologics. Note, there are no non-proprietary unique drug product or drug substances names/identifiers listed, which are what is needed here.

The following "Description of Pertuzumab (Perjeta) drug substance and drug product" section is rather useless. It does not even mention the expression system/host cell line, nor any other bioprocessing or quality-related information!

V. EXECUTIVE SUMMARY

A. Description of Pertuzumab (Perjeta) drug substance and drug product

Pertuzumab is a full length recombinant, humanized, immunoglobulin IgG1κ monoclonal antibody (rhuMAB 2C4; Omnitarg; 2C4) that is directed to subdomain II of the human epidermal growth factor receptor 2. Pertuzumab is comprised of two heavy chains (448 or 449 amino acid residues, dependent on the presence of a C-terminal lysine) and two light chains (214 amino acid residues), and contains an N-linked oligosaccharide. The total molecular weight of pertuzumab is approximately 148,000 Da, (b) (4)

The human epidermal growth factor receptor 2 (EGF-R2, HER2, c-erbB-2) is a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Amplification and/or overexpression of HER2 has been reported in 15-25% of breast cancers and is associated with increased tumor aggressiveness, higher rates of recurrence, and increased mortality. Pertuzumab is used in combination with trastuzumab and docetaxel to treat patients with HER2-positive metastatic breast cancer who have not already received anti-HER2 therapy or chemotherapy for metastatic disease.

Pertuzumab drug product is supplied as a sterile, preservative-free liquid formulation at 30 mg/ml. Pertuzumab drug product is formulated in 20mM L-histidine acetate, 120mM sucrose, and 0.02% (w/v) polysorbate 20, pH 6.0. (b) (4) As supplied, the solution of pertuzumab drug product has a clear to slightly opalescent, colorless to pale brown appearance. It is supplied in single-use, 20 ml vials containing 420 mg (nominal) pertuzumab for intravenous (IV) infusion. The extractable volume of each vial is 14 ml.

The intended long term storage temperature for pertuzumab drug product is 2-8°C.
The primary packaging components for pertuzumab drug product consist of a USP/Ph. Eur./JP (b) (4) 20 ml colorless glass vial that is sealed (b) (4) rubber stopper (b) (4) and crimped with a 20mm aluminum seal, then fitted with a slip off plastic cap.

The following Figure shows the “Summary of Pertuzumab Critical Quality Attributes” as being 100% redacted. How could “critical” quality attributes not include some public information?

Table 3.2.S.3.2-29 Summary of Pertuzumab Critical Quality Attributes

(b) (4)

And the following 100% redacted section:

With regard to control strategy, data provided by the Sponsor indicated the following links between product characteristics and activity:

(b) (4)

5) Brentuximab vedotin, approved Aug. 19, 2011

Summary: No CMC or bioprocessing review or useful descriptive information retrievable in Drugs@FDA or the entire Web site!

This is currently the only approved antibody-drug conjugate (ADC; immunotoxin). Yet, there is negligible information about the drug substance and drug product.

Chemistry Review – The following Figure was copied from the "Introduction" section

Chemical name Chimeric IgG1 cAC10 covalently linked to vcMMAE

Molecular formula [redacted] (b) (4) MW = 153,352 Da

How can a calculated molecular formula be proprietary or otherwise redactable?

The following 2 screen-shots show manufacturer identities for both the antibody and cytotoxin/drug portion of the molecule as being totally redacted. Besides manufacturers' identities, how could the definitions of the date of manufacture and expiration dates (and the data too) be proprietary or non-disclosable?

The cAC10 antibody is manufactured by [redacted] (b) (4) . Evaluation of the CMC information for cAC10 antibody was conducted by the Office of Biotechnology Products, which is the lead office for CMC review of this BLA.

SGD-1006 intermediate is manufactured by the [redacted] (b) (4). The ONDQA review evaluates the CMC information for SGD-1006 intermediate, relevant drug related information for SGN-35 bulk drug substance. There are no outstanding deficiencies from ONDQA. Approval is recommended.

and:

II. APPROVAL LETTER INFORMATION

The following information should be communicated to the sponsor in the approval letter:

Under this license, you are approved to manufacture the monoclonal antibody (cAC10) Intermediate for brentuximab vedotin at [redacted], and the SGD-1006 drug-linker intermediate at [redacted]. The brentuximab vedotin (Adcetris™) formulated bulk drug substance, SGN-35, will be manufactured at [redacted], and the SGN-35 final drug product will be manufactured at [redacted].

The expiration date for brentuximab vedotin (Adcetris™) drug product shall be 30 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of [redacted] of the formulated drug product. The expiration date for the drug substance shall be [redacted] when stored at [redacted]. The expiration date for the brentuximab vedotin cA10 Intermediate will be [redacted] when stored at [redacted]. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of the brentuximab vedotin drug substance and drug product and the cA10 Intermediate under 21 CFR 601.12. Data supporting extension of the expiration dating period should be submitted to the BLA Annual Report.

,

As shown in the screesnshots below, there is absolutely no discussion of bioprocessing, *never even mention of the expression system/cell line in the whole document*, and the identity of the manufacturer(s) is redacted.

SGN-35 Drug Substance

SGN-35 bulk drug substance is manufactured at [redacted] scale by a contract manufacturer, [redacted]. SGN-35 manufacturing starts with [redacted]

[redacted]

Structural characterization of SGN-35 has been conducted using a comprehensive set of methods. The data confirm that SGN-35 conjugation site is at the cysteine residues [redacted] resulting in many active forms with up to eight possible conjugation sites per antibody. Drug load distribution studies were conducted using HIC and RP-HPLC methods, The amount of various isoforms of drug antibody conjugates have been measured. And the relative abundance of the conjugation isoforms with respect to the average drug average drug load MR_D have been determined. Historical data for drug loading distribution and average drug load MR_D showed certain correlation.

These same redactions were repeated in the “Summary Review” document.

Conclusions

None of these sampled or other recent biologics approvals reviews-related public documents include in any way adequate disclosures of basic information about products and agents, including CMC, bioprocessing and quality-related aspects. In many cases, the few meager sentences included in product inserts are more informative (which is pretty bad)!

No useful, much less adequately descriptive, bioprocessing or CMC information is being disclosed. There is no public 'Bioprocessing" or real "CMC" reviews, Bioprocessing information is nearly universally absent from 'Chemistry Reviews;' and 'Microbiology Reviews' concern final product sterility issues. This generally includes no most basic information about bioprocessing, including no overall unit process or other flow diagrams; about bioreactor sizes, nature of bioprocessing (fed-batch, perfusion, etc.); chromatography technologies (e.g., conventional, radial, tangential flow filtration) and resin types used; whether recombinant antibodies are purified using newer recombinant or legacy non-recombinant Protein A products; use of additive enzymes, such as nucleases (e.g., Benzonase) for DNA/RNA removal; levels of protein aggregation and size distribution; any refolding processes applied; etc. This lack of bioprocessing/CMC information includes, for those few recently-approved products publicly known to be manufactured using single-use/disposable (plastics-based) bioreactors and other equipment, there being no mention of this, much less requisite associated information about leachates (and extractables), their identities, levels and safety assessments.

Among the 'Chemistry Reviews' examined (the non-redacted parts), none actually discuss drug substance or product chemistries! This includes no discussions of microheterogeneity, the normal expected distribution of molecular variations expected and allowed in products; glycosylation patterns and variants; by-products and contaminants; etc. 'Chemistry Reviews' (what is in the public documents) seem preoccupied with such things as shelf-lives and other largely formulation aspects. Also, none of the other reviewed documentation included useful information about purity, potency and how these were determined, with the one or a few sentences in product inserts' often disclosing more information than cumulatively disclosed in approvals-related review public documents. Only rarely are even just selective quality control and release testing criteria ever discussed.

No reviewed FDA documentation included any reference to, much less information and discussion, about the differences in bioprocessing and comparability or not between preclinical early trial, later trial and market products. This includes products where it is publicly known, e.g., disclosed in EMA EPAR documents, that products tested in early phases are significantly different, including not meeting comparability standards, compared to the approved product. This even includes where products in early development are known to have been manufactured using totally different expression systems and

methods than the approved product. Obviously, comparability of pre-commercialization products/agents with the marketed product is a major safety issue – without this information, preclinical testing and clinical trials information is useless or worse, substantially misleading.