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Selection Strategy for Shortlisting Potential Candidates for the Development of Biosimilars

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ABSTRACT

Biotherapeutics are revolutionary drugs used for the treatment of a plethora of life-threatening diseases. However, considering the expensive development process of these drugs, the accessibility to millions across the globe becomes a far cry. High cost of these drugs is attributed to their cost of production and patent status. Now that most of these biotherapeutics would be soon losing their patent protection, follow-on biologics like 'biosimilars' and 'biobetters' are poised to get accessible to patient. Several countries, like South Korea, European Union and Japan have already established markets for the production of biosimilars. India is considered to be an emerging market in this area and many pharmaceutical companies, such as Torrent Pharmaceuticals, are involved in the production of biosimilars for both domestic and global markets. To expand the base for development of biosimilars, it is important to identify viable biotherapeutics available in the market. In this study, we manually annotated the US-FDA Center for Drug Evaluation and Research (CDER) and Center

for Biological Evaluation and Research (CBER) lists, extracted biologics with therapeutic applications in humans, classified them on the basis of their patent status and biomolecule categories, and then checked for comparable biosimilars in the Indian market. With an aim to use a microbial expression system (instead of eukaryotic system which contributes towards the high cost) for the production of biosimilars, we eliminated products with extensive post-translational modification, and found enzyme such as Asparaginase, Collagenase, monoclonal antibody Ranibizumab and few others as suitable candidates for biosimilar development.

Keywords: Biosimilars, Biobetters, Biotherapeutics, CDER, CBER, EMA

INTRODUCTION

The advent of the modern, sophisticated tools and technology of Genetic Engineering have helped modern biopharmaceutical industry in the production of several life-saving drugs. In 1982, Genentech and Eli Lilly's recombinant human Insulin, Humulin, was the first biotech drug to be approved by FDA. Since then, at least a 100 more have been approved for the treatment of various life-threatening and chronic conditions (1). Biopharmaceuticals or bio-therapeutics are biological products (like proteins, blood derivatives, blood components, allergenic extracts, vaccines, cellular and gene therapies) which are sourced from mammalian cell culture, bacteria, mice, humans, transgenics and humans for the prevention, treatment or cure of diseases. Unlike small molecule drugs which have lower molecular weights and are synthesised using organic or chemical reactions, bio-therapeutics are medicinal products of biological origin with greater structural complexity and are difficult to characterise (2). This has important consequences for the development of their generic versions, which can be manufactured following patent expiration using non-proprietary technology at reduced costs.

Biotherapeutics have revolutionised the way we treat various life-threatening diseases, but being their cost being prohibitive, they remain out of reach of majority of patients around the globe. In comparison to the generic versions of small molecule drugs, generic bio-therapeutic drugs cannot be synthesized easily, owing to their complex structures and biological properties (3). How to make these life-saving drugs available

to patients is a pertinent question. Reference biologics are the Biotherapeutics approved by FDA for production and marketing for the treatment of diseases. With the expiration of patents on these drugs, follow-on biological products like biosimilars and biobetters are produced as promising alternatives to their cognate biotherapeutics. These are not exact replicas of, but are highly similar to the reference biologics, such that there are no clinically meaningful differences in terms of their efficacy, safety and purity (4).

Several guidelines are in place for the production and marketing of these drugs or their replicas. These guidelines vary from country to country. The European Medicines Agency (EMA) were the first one to release their regulatory guidelines for biosimilar development in 2005 followed by World Health Organisation (WHO) in 2009. US Food and Drug Administration (US FDA) also could place certain guidelines in 2012 (3). India being a major producer and exporter of chemical drugs actively involved in the production of biosimilars. In India, the Department of Biotechnology (DBT) and the Central Drugs Standard Control Organisation (CDSCO) released the guidelines on 'similar biologics' (terminology used for biosimilars in India) in the year 2012, which were further updated in 2016 (5).

Several other countries across the globe are also involved in the production and marketing of biosimilars, with some in preclinical and clinical development. In order to get profits in these markets, biosimilars companies in such countries will need to adopt a long-term strategy to provide affordable products and improved access to the public. In this paper, we have made an attempt to standardize a strategy in order to shortlist potential candidates for biosimilar and bio-better development. We used two-pronged approach, namely patent expiry and post translational modifications (PTMs). Using these two approaches, we shortlisted candidates as potential biosimilars which would be cost-effective and companies who wish to produce biosimilars would surely be benefitted by investing in these molecules.

METHODOLOGY

Workflow of the approach undertaken for the shortlisting of potential biosimilars which would be profitable for production by biopharmaceutical companies is schematically depicted in Figure I and the steps include:

Data extraction of biotherapeutics

Lists of biological products approved by the Center for Drug Evaluation and Research (CDER) and Center for Biological Evaluation and Research (CBER), U.S. FDA were retrieved from the Purple Book (last updated on 07-07-16 and 29-04-16) and are available on the following link:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.html.

A list of biosimilar products currently marketed in India was obtained from Generics and Biosimilars Initiative (GABI) Online, available on the following link:

http://www.gabionline.net/Biosimilars/General/Similar-biologics-approved-and-marketed-in-India.

All 126 products from the CDER list were considered, while from the CBER list which contains 296 products, 28 biologics with therapeutic applications in humans were extracted.

Candidate selection based on inclusion/exclusion criteria

These biologics from the CDER and CBER lists were then classified based on their year of licensure and exclusivity expiry date in the U.S. as: out of patent protection (inclusive) and within patent protection (exclusive), i.e. those licensed after 2009. Products found to be out of patent protection were considered for the next step.

Searching Indian market for comparable biosimilar

Searches were performed for the keywords '<proper name> biosimilar', <trade name> biosimilar in India' in Google News, Google Scholar as well as Google Web, so as to classify these reference products out of patent protection on the basis of whether a comparable biosimilar product was available in the Indian market. Those biologics with no comparable biosimilars were considered for the next step in the process.

Classification of reference biologics

These biologics that are out of patent protection and do not have a comparable biosimilar product in the Indian market were classified into: 'Blood factors, anticoagulants and thrombolytics', 'Antibodies', 'Hormones' 'EPO and Colony Stimulating factors', 'Interferons' and 'Others'(6). Those found to be cellular therapeutics or multi-protein drug formulations were excluded at this step.

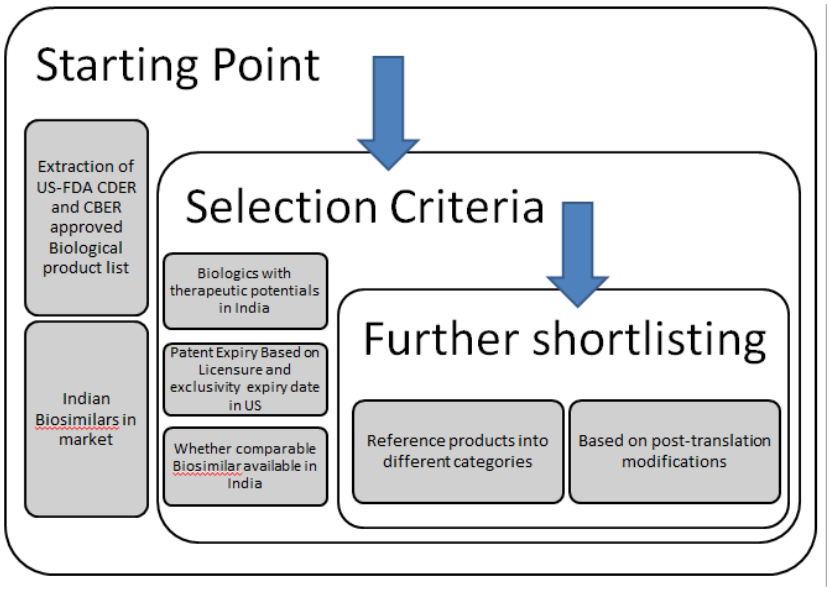

Figure I: Shortlisting process describing the exclusion/inclusion criteria applied

Identification of PTMs

Biopharmaceutical companies find it lucrative to invest in production of biosimilars with low production cost. We propose to identify candidate biosimilars which can be expressed with ease in bacterial systems since the yeast and mammalian systems are more expensive as expression system and hence add to the cost of production. Since

it is difficult to attain post-translational modifications (PTM) in prokaryotic expression systems, the CDER and CBER biologics were checked for the presence of PTMs in the screened biologics. Whether glycosylation was present (Yes/No) was determined, along with any other modifications using information from UniProt, DrugBank databases and the FDA prescription labels. Exact glycosylation positions were also noted using a combination of GlycoMine and Uniprot. Finally, the candidates meeting both our criterion (patent expiry by or before 2010 and absence of PTMs) were identified for biosimilar development.

RESULTS

Upon applying the inclusion/exclusion criteria (as described under methodology section) to the biologics of the CDER and CBER lists, a number of candidate biotherapeutics were obtained (Figure II and Supplementary Tables S1, S2 and S3). Candidate biotherapeutics of CDER list were selected based on patent expiry dates and the kind and degree of post-translational modification they possess. Out of the 24 biotherapeutics (whose patent had already expired: CDER List A, see Supplementary Table 1) shortlisted from the CDER list, seven were further shortlisted based on complete absence of glycosylation (or at least absence of glycosylation in the active site). Table 1 shows the exact glycosylation positions of some of the shortlisted biotherapeutics from the CDER list, determined by using GlycoMine and Uniprot.

Table I: Glycosylation positions of few shortlisted Biotherapeutics from CDER list

Drug	Glycosylation Position
Agalacsidase beta	96 (O-linked (Fuc) threonine)
Alteplase	152,219(N-linked (GlcNAc) asparagine)
Becaplermin	63 (N-linked (GlcNAc) asparagine)
Dornase alfa	40 (N-linked (GlcNAc) asparagine)
Interferon gamma-1b	48,120 (N-linked (GlcNAc) asparagine)
Laronidase	110,190,336,372,415,451(N-linked (GlcNAc) asparagine)
Peginterferon alfa-2a	129 (O-linked (GalNAc) threonine)
Sargramostim	22,24,26 (O-linked (GalNAc...) serine) 27 (O-linked (GalNAc) threonine) 44,54 (N-linked (GlcNAc) asparagine)

Fifteen (15) biotherapeutics were also selected from the CDER list with imminent patent expirations in the early 2020s (CDER List B, see Supplementary Table 2). Out of these15 candidates, four possible biosimilar candidates for biotherapeutics were shortlisted wherein the glycosylation pattern was found to be absent. Probably these would be important for biosimilar development in near future.

Using the CBER list, we shortlisted 28 biotherapeutics (as shown in Figure II and mentioned under supplementary Table 3) based on out of patent protection. These candidates were marked with NA under the header 'Exclusivity' in the Supplementary Table 3. No comparable biosimilars were found for these shortlisted 28 candidates in the Indian market. Some of the other biotherapeutics within patent protection were also included in this list because a knowledge-based assessment led to the conclusion that they could be interesting candidates for biosimilar development in the future.

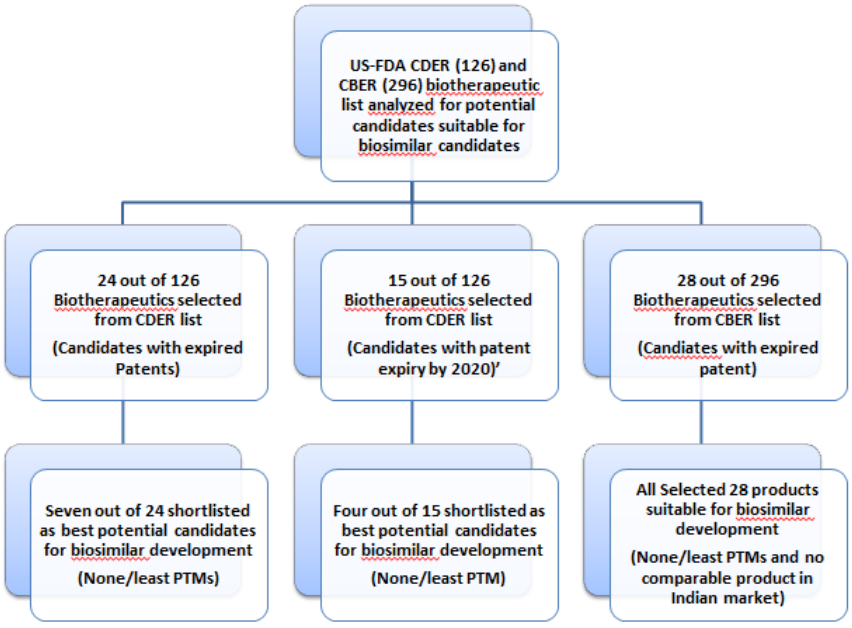

Figure II: Filtering out and shortlisting pipeline: Depicting number of shortlisted candidates suitable for biosimilar development

Developing cost-effective biosimilars is important to make them affordable to a large number of patients. It may be noted that while expressing a biosimilar in bacterial system can be cost effective, however besides PTMs, there could be other factors too that might not allow the correct expression/synthesis of the desired biotherapeutic in

an altered expression system. Nevertheless the data represented here would help pharmaceutical industries to choose and develop biosimilars (especially those which are in demand) in a cost-effective manner.

DISCUSSION

The first and a crucial step in the biosimilar/biobetter developmental pipeline is the identification of a reference biotherapeutic. Given the task of developing cost-effective biosimilars by using a microbial expression system for their production, we decided to systematically go through lists of approved biological products, eliminating products based on the aforementioned exclusion/inclusion criteria, to arrive at potential candidates that would be the most feasible to develop. Indeed, the results of this exercise show that there are many biotherapeutics for which follow-on biologics could possibly be developed even with level of competence of Indian Pharmaceutical Companies. By contributing to the development of cost-effective, good quality follow-on biologics, could help improve public health by making it accessible and affordable. Since approximately 70% of the country's population is rural and will always be worried about the cost of therapy – a 20-30% decrease on originator biologics would be beneficial for them.

India is emerging as a strong market for biosimilars development as patent expiry of many biological products is due in the coming years. India is considered to be one of the emerging players in biosimilar development across the globe. Indian companies have extensive experience with generics and have made in-roads in other countries as well through exports. It is estimated that its biosimilar industry would also boom in a similar manner with a whopping $80 billion profit in next few years. In order to maintain the quality of biosimilars, it would be important for Indian companies to strictly adhere to the guidelines laid down for biosimilar development by the regulatory authorities and partner with global pharmaceutical companies.

Indian companies are required to maintain their image of manufacturing safe and high quality drugs. This will hold true for biosimilars as well. They need to follow criteria's laid down by the following authorities concerned with the approval of biosimilar products; namely the Review Committee on Genetic Manipulation (RCGM), the Genetic Engineering Appraisal Committee and the Central Drug

Standard Control Organisation (CDSCO). The biosimilar approval pathway in India has to undergo the stages of product development, animal toxicity studies, clinical trials and licensure post approval formalities (5). However, the rigour of getting such biosimilar products approved and subsequently launched in the Indian market is less in comparison to developing a whole biotherapeutic from scratch.

Pharmaceutical companies have an inherent policy of carrying out routine market surveys for finding out drugs in demands. Such studies have helped in identifying drugs that might be important as lead molecules for development of biosimilars. The present study shortlists several candidates which could be important for developing biosimilars in a cost-effective manner. Among the possible biosimilar candidates shortlisted from the CDER list, based on those whose patents have already expired or is expiring soon and those which can be produced in prokaryotic systems, development of biosimilar of asparaginase holds great promise. It is witnessed that multiple asparaginase products (biologics) are available to patients in India with the costs ranging from Rs. 970 to 2210 per vial, with potencies of 5000 to 10,000 international units (IU) (7). A PEGylated (covalent attachment of the polymer polyethylene glycol moieties) form, called 'Pegaspargase' is also available, which is L-asparaginase covalently conjugated to mono-methoxy polyethylene glycol (mPEG). This modification increases the enzyme circulation time *in vivo* and decreases its toxic levels (8). Biosimilar version of the product reduces the cost to two-thirds among population.

Asparaginase is not only profitable to develop but is therapeutically important as well. Asparaginase which is bacterial enzyme L-asparagine amidohydrolase derived from *Escherichia coli*, is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukaemia (ALL). It primarily carries out the deamidation of the amino acid asparagine to aspartic acid and ammonia, as follows:

L-Asparagine + H_2O ↔ L-Aspartate + Ammonia.

It is thought to act by selectively killing leukemic cells by depleting asparagine in the plasma. Some leukemic cells are unable to synthesise asparagine because they lack

the enzyme asparagine synthetase and therefore depend on an exogenous source of asparagine to meet their requirements. Thus, depriving these cells of asparagine, by the use of L-asparaginase eventually kills the leukemic cells. Normal cells, however, are less affected by this as their asparagine biosynthesis is not impaired (9). Asparaginase derived from *Erwinia chrysanthemi* is used as an alternative in patients who develop hypersensitivity to the *E. coli*-derived asparaginase (10). Developing this drug as biosimilar would help ALL patients in their treatment, as this is the best drug available for them.

Another therapeutically important lead molecule would be Ranibizumab (shortlisted under CDER list) which when developed as a biosimilar would be of immense importance to patients considering its cost. Ranibizumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment (produced in an *E. coli* expression system) designed for intraocular use, and is indicated for the treatment of patients with neovascular age-related macular degeneration, macular edema following retinal vein occlusion, and diabetic macular edema. It binds to and inhibits the activity of human vascular endothelial growth factor A (VEGF-A) which prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation (11).

Ranibizumab is developed by Genentech, and has been available to patients since 2006 under the trade name Lucentis. In India, its price was as high as Rs. 45,000 per injection, which was recently brought down to Rs. 16,000 by its seller Novartis, after its cheaper clinical alternative, Avastin, was temporarily withdrawn from the market (12). In June 2015, Intas Pharmaceuticals became the first global company to launch a Lucentis biosimilar, Razumab, which was about 25% cheaper than imported Lucentis, resulting in an annual saving of about Rs. 35,000 per injection in the cost of treatment to the patient, depending on the number of injections used and the clinical condition of the patient. However, about 10% of patients who received product from the first three batches of the biosimilar experienced inflammation. Intas then introduced an additional filtration step to its manufacturing process and added fresh "ultrapure Polysorbate 20". From batch 4 onward, no such adverse events have been reported (13).

Ranibizumab is an anti-VEGF-A humanised Fab' antibody fragment. A biobetter version is thus proposed with reduced antigenicity and prolonged in vivo circulation time, which can be achieved by cysteine-specific PEGylation (covalent attachment of the polymer polyethylene glycol) of such Fab' antibody fragments. A similar strategy has been employed to improve the activity of the Fab' fragment of a humanized anti-TNF-monoclonal antibody, which is marketed as Cimzia (14).

The 28 biotherapeutics shortlisted from the CBER list could be also tapped for biosimilar development by the biopharmaceutical industries, knowing that these have remained untouched till date. Attempts are being made to experimentally produce these for therapeutic use. Further, we wish to work on biobetter versions of these drugs.

CONCLUSIONS

With the lapse of patent protection of biologics in the near future, it will be easier for companies to invest in biosimilar production, which would be cost-effective and economical for a developing country like India. In India and other developing countries, a cheaper alternative in the form of biosimilars as opposed to conventional biotherapeutics is much required and would be readily accepted. Leading biosimilar players have long been focussed on developed markets considering their future market potential. In the present study, we have shortlisted candidates that would be easy to produce in prokaryotic expression system, further reducing the cost of these drugs and making it affordable to patients of country like India.

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Supplementary Table 1: Seven shortlisted candidates (indicated in green) from the CDER list (CDER List A) with a high possibility of biosimilar development using prokaryotic expression systems

Product	Biosimilar Product in India	Therapeutic Category	Expression System	Glycosylation at the active site	Amino acid residue on the active site(s) modified?	Other PTMs
aldesleukin	No	Others (interleukin)	*Escherichia coli*	No	No, engineered to not contain N-terminal alanine residue, serine substituted for cysteine at position 125	http://www.drugbank.ca/drugs/DB00041
agalsidase beta	No	Others (enzyme)	Chinese Hamster Ovary cell line	Yes	No	http://www.uniprot.org/uniprot/P06280
alemtuzumab	No	Antibodies	Chinese Hamster Ovary cell line	Yes	Yes	http://www.drugbank.ca/drugs/DB00087
alteplase, cathflo activase	No	Blood factors, anticoagulants and thrombolytics	Chinese Hamster Ovary cell line	Yes	No	http://www.uniprot.org/uniprot/P00750
anakinra	No	Others (interleukin)	*Escherichia coli*	No	No, has the addition of a single methionine residue at its N-terminus	http://www.drugbank.ca/drugs/DB00026
asparaginase	No	Others (enzyme)	*Escherichia coli*	No	No	http://www.uniprot.org/uniprot/P37595
basiliximab	No	Antibodies	Murine Myeloma cell line	Yes	Yes	http://www.drugbank.ca/drugs/DB00074
becaplermin	No	Others (B chain of PDGF)	*Saccharomyces cerevisiae*	Yes	No	http://www.uniprot.org/uniprot/P01127
cetuximab	No	Antibodies	Murine	Yes	Yes	http://www.drugb

			Myeloma cell line			ank.ca/drugs/DB00002
collagenase	No	Others (enzyme)	*Clostridium histolyticum*	No	No	http://www.drugbank.ca/drugs/DB00048
daclizumab	No	Antibodies	Murine myeloma cell line (NS0)	Yes	Yes	http://www.drugbank.ca/drugs/DB00111
denileukin diftitox	No	Others (interleukin fused with diptheria toxin)	*Escherichia coli*	No	No	http://www.drugbank.ca/drugs/DB00004
dornase alfa	No	Others (enzyme)	Chinese Hamster Ovary cell line	Yes	No	http://www.uniprot.org/uniprot/P24855
interferon beta-1b	No	Interferons	*Escherichia coli*	No	No, substitutes serine for the cysteine residue found at position 17	http://www.drugbank.ca/drugs/DB00068
interferon gamma-1b	No	Interferons	*Escherichia coli*	Yes	No	http://www.uniprot.org/uniprot/P01579
laronidase	No	Others (enzyme)	Chinese Hamster Ovary cell line	Yes	No	http://www.drugbank.ca/drugs/DB00090
omalizumab	No	Antibodies	Chinese Hamster Ovary cell line	Yes	Yes	http://www.drugbank.ca/drugs/DB00043
onabotulinumtoxinA	No	Others (toxin)	*Clostridium botulinum* type A	No	No	http://www.uniprot.org/uniprot/P10845
oprelvekin	No	Others (interleukin)	*Escherichia coli*	No	No, is 177 amino acids in length whereas the natural IL-11 has 178	http://www.drugbank.ca/drugs/DB00038
palivizumab	No	Antibodies	Murine myeloma cell line (NS0)	Yes	Yes	http://www.drugbank.ca/drugs/DB00110
pegaspargase	No	Others (enzyme)	*Escherichia coli*	No	No, L-asparaginase is modified by covalently	http://www.drugbank.ca/drugs/DB00059

					conjugating units of monomethoxypolyethylene glycol (PEG) to the enzyme	
peginterferon alfa-2a	No	Interferons	*Escherichia coli*	Yes	No, covalent conjugate of recombinant alfa-2a interferon with a single branched bis-monomethoxy polyethylene glycol (PEG) chain	http://www.drugbank.ca/drugs/DB00008
rimabotulinumtoxinB	No	Others (toxin)	*Clostridium botulinum* type B	No	No	http://www.drugbank.ca/drugs/DB00042
sargramostim	No	EPO and colony-stimulating factors	*Saccharomyces cerevisiae*	Yes	Yes, substitution of arginine with leucine at position 23, and the carbohydrate moiety may be different from the native protein	http://www.drugbank.ca/drugs/DB00020

Supplementary Table 2: Five potential biosimilar candidates (indicated in green) obtained from the CDER list with imminent patent expirations in the early 2020s (CDER List B)

Product	Biosimilar Product in India	Therapeutic Category	Expression System	Glycosylation	Amino acid residue on the active site(s) modified?	Other PTMs/Reference
Bevacizumab	Yes	Antibodies	Chinese Hamster Ovary cell line	Yes	Yes	http://www.drugbank.ca/drugs/DB00112
certolizumab pegol	No	Antibodies	*Escherichia coli*	No	No, Fab' fragment conjugated (cysteine-specific) to an approx. 40 kDa branched polyethylene glycol	http://www.drugbank.ca/drugs/DB08904
Cetuximab	No	Antibodies	Murine Myeloma cell line	Yes	Yes	http://www.drugbank.ca/drugs/DB00002
Eculizumab	No	Antibodies	Murine Myeloma cell line	Yes	Yes	http://www.drugbank.ca/drugs/DB01257
Natalizumab	No	Antibodies	Murine Myeloma cell line	Yes	Yes	http://www.drugbank.ca/drugs/DB00108
Panitumumab	No	Antibodies	Chinese Hamster Ovary cell line	Yes	Yes	http://www.drugbank.ca/drugs/DB01269
Ranibizumab	Yes	Antibodies	*Escherichia coli*	No	No	http://www.drugbank.ca/drugs/DB01270
Abatacept	No	Others	Chinese Hamster Ovary cell line	Yes	Yes	http://www.drugbank.ca/drugs/DB01281
alglucosidase alfa	No	Others	Chinese Hamster Ovary cell line	Yes	Yes	http://www.drugbank.ca/drugs/DB01272
Galsulfase	No	Others	Chinese Hamster Ovary cell line	Yes	Yes	http://www.drugbank.ca/drugs/DB01279
Idursulfase	No	Others	HT1080 Human Fibrosarcoma cell line	Yes	Yes	http://www.drugbank.ca/drugs/DB01271, http://www.tandfonline.com/doi/full/10.3109/07388551.2015.1084266

methoxy polyethylene glycol-epoetin beta	No	EPO and colony-stimulating factors	Chinese Hamster Ovary cell line	Yes	Yes, amide linkage between either the N-terminal amino group or the ε-amino group of lysine, predominantly Lys 52 and Lys 45 and methoxypolyethylene glycol-succinimidyl butanoic acid	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000739/WC500033669.pdf
Palifermin	No	EPO and colony-stimulating factors	*Escherichia coli*	No	No, differs from endogenous human KGF in that the first 23 N-terminal amino acids have been deleted to improve protein stability	http://www.drugbank.ca/drugs/DB00039
Rilonacept	No	Others	Chinese Hamster Ovary cell line	Yes	Yes	http://www.drugbank.ca/drugs/DB06372
Romiplostim	No	Others	*Escherichia coli*	No	No, has no amino acid sequence homology to endogenous thrombopoietin	http://www.drugbank.ca/drugs/DB05332

Supplementary Table 3: Potential candidates obtained from the CBER list

Product	Exclusivity	Biosimilar Product in India	Therapeutic Category	Expression System/ Source	Glycosylation	Amino acid residue on the active site(s) modified?	Other PTMs/Reference	Remarks
Alpha-1-Proteinase Inhibitor (Human)	NA	No	Blood factors, anticoagulants and thrombolytics	Human plasma	Yes	Yes	http://www.uniprot.org/uniprot/P01009	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm051590.pdf
Antihemophilic Factor (Human)	NA	No	Blood factors, anticoagulants and thrombolytics	Human plasma	Yes	Yes	http://www.uniprot.org/uniprot/P00451	http://www.koate-dviusa.com/filebin/pdf/New_July2013_57210_Kedrion_PI_prf.pdf
Antihemophilic Factor (Recombinant)	NA	No	Blood factors, anticoagulants and thrombolytics	Chinese Hamster Ovary cell line	Yes	Yes	http://www.uniprot.org/uniprot/P00451	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM371094.pdf
Antihemophilic Factor (Recombinant), Fc Fusion protein		No	Blood factors, anticoagulants and thrombolytics	Human Embryonic Kidney cell line	Yes	Yes	http://www.uniprot.org/uniprot/P00451	http://www.eloctate.com/pdfs/full-prescribing-information.pdf
Antihemophilic Factor (Recombinant), Full Length		No	Blood factors, anticoagulants and thrombolytics	Baby Hamster Kidney cell line	Yes	Yes	http://www.uniprot.org/uniprot/P00451	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM491119.pdf
Antihemophilic Factor (Recombinant), PEGylate		No	Blood factors, anticoagulants and thrombolytics	Chinese Hamster Ovary cell line	Yes	Yes, covalently conjugated with one or more molecules	http://www.uniprot.org/uniprot/P00451	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM472594.p

d						of polyethylene glycol (MW 20 kDa)		df
Antihemophilic Factor (Recombinant), Plasma/ Albumin Free Method	NA	No	Blood factors, anticoagulants and thrombolytics	Chinese Hamster Ovary cell line	Yes	Yes	http://www.uniprot.org/uniprot/P00451	http://www.advate.com/pdf/advate_iri_pi.pdf
Antihemophilic Factor (Recombinant), Porcine Sequence		No	Blood factors, anticoagulants and thrombolytics	Baby Hamster Kidney cell line	Yes	Yes	http://www.uniprot.org/uniprot/P12263	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002792/WC500196884.pdf
Antihemophilic Factor (Recombinant), rAHF		No	Blood factors, anticoagulants and thrombolytics	Human Embryonic Kidney 293F cell line	Yes	Yes	http://www.uniprot.org/uniprot/P00451	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM461328.pdf
Antithrombin (Recombinant)		No	Blood factors, anticoagulants and thrombolytics	Genetically engineered goats	Yes	Yes, the glycosylation profile of is different from plasma derived antithrombin, which results in an increased heparin affinity	http://www.uniprot.org/uniprot/P01008	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM134045.pdf
Antithrombin III (Human)	NA	No	Blood factors, anticoagulants and thrombol	Human plasma	Yes	Yes	http://www.uniprot.org/uniprot/P01008	http://www.thrombate.com/documents/975812/975869/ThrombateIII_PI_3036431_Aug_2013.pdf/9337c369-130e-4e8b-98ea-

			ytics					1f5220fb0f34
Anti-thymocyte Globulin (Rabbit)	NA	No	Antibody	Rabbits immunised with human thymocytes	Yes	Yes	http://products.sanofi.ca/en/thymoglobulin.pdf	
C1 Esterase Inhibitor (Human)		No	Blood factors, anticoagulants and thrombolytics	Human plasma	Yes	Yes	http://www.uniprot.org/uniprot/P05155	http://www.fda.gov/downloads/%E2%80%A6/UCM186268.pdf
C1 Esterase Inhibitor (Recombinant)	7-16-2014	No	Blood factors, anticoagulants and thrombolytics	Milk of transgenic rabbits	Yes	Yes	http://www.uniprot.org/uniprot/P05155	http://shared.salix.com/shared/pi/ruconest-pi.pdf
Coagulation Factor IX (Human)	NA	No	Blood factors, anticoagulants and thrombolytics	Human plasma	Yes	Yes	http://www.uniprot.org/uniprot/P00740	http://labeling.cslbehring.com/PI/US/Mononine/EN/Mononine-Prescribing-Information.pdf
Coagulation Factor IX (Recombinant)	NA	No	Blood factors, anticoagulants and thrombolytics	Chinese Hamster Ovary cell line	Yes	Yes	http://www.uniprot.org/uniprot/P00740	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm093957.pdf
Coagulation Factor IX (Recombinant), Albumin Fusion Protein		No	Blood factors, anticoagulants and thrombolytics	Chinese Hamster Ovary cell line	Yes	Yes	http://www.uniprot.org/uniprot/P00740	http://labeling.cslbehring.com/PI/US/Idelvion/EN/Idelvion-Prescribing-Information.pdf
Coagulation Factor IX (Recombinant), Fc Fusion		No	Blood factors, anticoagulants and thrombolytics	Human Embryonic Kidney cell line	Yes	Yes	http://www.uniprot.org/uniprot/P00740	http://www.alprolix.com/pdfs/PrescribingInformation.pdf

Protein								
Coagulation Factor VIIa (Recombinant)	NA	No	Blood factors, anticoagulants and thrombolytics	Baby Hamster Kidney cell line	Yes	Yes	http://www.uniprot.org/uniprot/P08709	http://www.fda.gov/downloads/.../ucm056915.pdf
Coagulation Factor X (Human)		No	Blood factors, anticoagulants and thrombolytics	Human plasma	Yes	Yes	http://www.uniprot.org/uniprot/P00742	http://www.coagadex.com/download/Coagadex_PI_10-2015.pdf
Coagulation Factor XIII A Subunit (Recombinant)		No	Blood factors, anticoagulants and thrombolytics	*Saccharomyces cerevisiae*	Yes	Yes	http://www.uniprot.org/uniprot/P00488	http://www.novo-pi.com/tretten.pdf
Factor XIII Concentrate (Human)		No	Blood factors, anticoagulants and thrombolytics	Human plasma	Yes	Yes	http://www.uniprot.org/uniprot/P00488, http://www.uniprot.org/uniprot/P05160	http://labeling.cslbehring.com/PI/US/Corifact/EN/Corifact-Prescribing-Information.pdf
Fibrinogen Concentrate (Human)		No	Blood factors, anticoagulants and thrombolytics	Human plasma	Yes	Yes	http://www.uniprot.org/uniprot/P02671, http://www.uniprot.org/uniprot/P02675, http://www.uniprot.org/uniprot/P02679	http://www.fda.gov/downloads/Biolog...ionatedPlasmaProducts/ucm094006.pdf
Protein C Concentrate (Human)		No	Blood factors, anticoagulants and thrombolytics	Human plasma	Yes	Yes	http://www.uniprot.org/uniprot/P04070	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm119540.pdf
Thrombin topical (Recombinant)		No	Blood factors, anticoagulants	Chinese Hamster Ovary cell line	Yes	Yes	http://www.uniprot.org/uniprot/P00734	http://www.fda.gov/downloads/Biologi.../ucm120557.pdf

Thrombin, Topical (Bovine)	NA	No	Blood factors, anticoagulants and thrombolytics	Bovine origin	Yes	Yes	http://www.uniprot.org/uniprot/P00735	http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-biogen/documents/document/ucm256531.pdf
Thrombin, Topical (Human)		No	Blood factors, anticoagulants and thrombolytics	Human plasma	Yes	Yes	http://www.uniprot.org/uniprot/P00734	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm074092
von Willebrand factor (Recombinant)		No	Blood factors, anticoagulants and thrombolytics	Chinese Hamster Ovary cell line	Yes	Yes	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM476176.pdf	http://www.tandfonline.com/doi/abs/10.1080/17474086.2016.1214070?journalCode=ierr20