Available online on 15 Sept. 2019 at https://ijdra.com/index.php/journal

International Journal of Drug Regulatory Affairs

Published by Diva Enterprises Pvt. Ltd., New Delhi
Associated with Delhi Pharmaceutical Sciences & Research University

Review Article

Types of Biowaivers: A Discussion

Atreyee Sarkar*

Clinical Research Department, Micro Labs Limited. 58/3, Singasandra Post., Kudulu, Bangalore, India 560 068

Abstract

The aim of the present review is to discuss the different types of biowaiver applications. Waiving of In vivo bioequivalence studies is known as biowaiver. Types of biowaiver applications include BCS based biowaiver, well established use application, also known as bibliographical application and Literature based submission. Biowaiver is acceptable for both BCS class I as well as class III drug molecules. These kinds of applications are generally submitted to countries like US, European Union and Australia. Well established use application and literature based submission is acceptable if the drug product is available in the market for at least ten years. The latter are acceptable by Europe and Australia only. This review discusses various types of biowaiver applications accepted by the regulated markets.

Keywords: Biowaiver, Biopharmaceutics Classification System (BCS), bioequivalence, Bioavailability study, Bibliographic Application, Solubility, Permeability, Literature Based Submissions (LBS).

Article Info: Received 20 July 2019; Review Completed 06 Sept. 2019; Accepted 08 Sept. 2019

Cite this article as:
Sarkar A. Types of Biowaivers: A discussion. International Journal of Drug Regulatory Affairs [Internet]. 15 Sept 2019 [cited 15 Sept 2019]; 7(3):14-20. Available from: http://ijdra.com/index.php/journal/article/view/329

DOI: 10.22270/ijdra.v7i3.329
*Corresponding author Tel.: +91-8049516159;
E-mail address: atreyeesarkar@microlabs.in (A. Sarkar)

1. Introduction

Biowaivers are considered as the waivers of clinical bioequivalence studies. Bioequivalence studies are essential for drug development in order to prove the safety and efficacy of the product.

The advantages of using biowaiver is as follows:

- They circumvent expensive and sometimes unethically questionable human testing.
- Reduces time in launching product to the market.
- Reduces product cost. (1)

There are three types of biowaiver accepted by regulatory agencies.

i) BCS (Bio pharmaceutics Classification System) based biowaivers

ii) Well Established Use/Bibliographical applications

iii) Literature based submissions

BCS based biowaivers

The objective of the BCS classification of drugs is to predict *In vivo* performance of drug products from *in vitro* measurements of permeability and solubility. The purpose of BCS classification of drugs is to characterize products of those drugs which may be eligible for a biowaiver of *In vivo* bioequivalence studies. For drugs exhibiting high intestinal permeability rates, the major route of elimination in humans is via metabolism, while drugs exhibiting poor intestinal permeability rates are primarily eliminated in humans as unchanged form in the urine and bile. (2)

BCS based biowaivers helps in avoiding time consuming and costly pharmacokinetic studies using *in vitro* dissolution test as a surrogate test to evaluate the bioequivalence of a test and reference product. [1]

The BCS is an important tool for waiving the regulatory requirement for *In vivo* bioavailability and/or bioequivalence (BE) studies. This is acceptable by countries like USA, EU, Canada and Australia. (3)

Table 1 BCS classification of drugs (3)

Class I **High Solubility** **High Permeability** **Rapid Dissolution**	**Class II** **Low solubility** **High Permeability**
Class III **High Solubility** **Low Permeability**	Class IV Low Solubility Low Permeability

2. BCS based biowaiver criteria in US

When the In vivo dissolution of an Immediate Release (IR) solid oral dosage form is rapid or very rapid in relation to gastric emptying and the drug has high solubility, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal (GI) transit time. Under such circumstances, demonstration of In vivo bioavailability or bioequivalence may not be necessary for drug products containing class I drug substances, if the excipients used in the dosage form do not significantly affect absorption of the active ingredients.

The BCS approach covered by the US recommendation can be used to justify biowaivers for highly soluble and highly permeable drug substances (i.e., class 1) as well as highly soluble and low permeable drug substances (i.e., class 3) in IR solid oral dosage forms that exhibit rapid or very rapid *in vitro* dissolution using the recommended test methods.

Solubility

The solubility class boundary is based on the highest strength of an IR product that is the subject of a biowaiver request. A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media within the pH range of 1 - 6.8 at 37 ± 1°C. The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with an 8 fluid ounce glass of water.

Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic bioavailability) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, other systems capable of predicting the extent of drug absorption in humans can be used (e.g., *in situ* animal, *in vitro* epithelial cell culture methods). A drug substance is considered to be *highly permeable* when the systemic BA or the extent of absorption in humans is determined to be 85 percent or more of an administered dose based on a mass balance determination (along with evidence showing stability of the drug in the GI tract) or in comparison to an intravenous reference dose.

Intestinal Permeability Methods

The following methods can be used to determine the permeability of a drug substance from the GI tract: (1) *In vivo* intestinal perfusion studies in humans; (2) *In vivo* or *in situ* intestinal perfusion studies using suitable animal models; (3) *in vitro* permeation studies using excised human or animal intestinal tissues; or (4) *in vitro* permeation studies across a monolayer of cultured epithelial cells.

Dissolution

An IR drug product is considered rapidly dissolving when a mean of 85 percent or more of the labelled amount of the drug substance dissolves within 30 min, using United States Pharmacopeia (USP) Apparatus 1 at 100 rpm or Apparatus 2 at 50 rpm (or at 75 rpm when appropriately justified in a volume of 500 mL or less (or 900 mL when appropriately justified) in each of the following media:

(1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes;
(2) pH 4.5 buffer; and
(3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

An IR product is considered very rapidly dissolving when a mean of 85 percent or more of the labelled amount of the drug substance dissolves within 15 min, using the above mentioned conditions.

A minimum of 12 dosage units of the test and reference drug product for each strength should be evaluated to support a biowaiver request. Samples should be collected at a sufficient number of intervals to characterize the entire dissolution profile of the drug product (e.g., 5, 10, 15, 20 and 30 min).

When comparing the test and reference products, dissolution profiles should be compared using a similarity factor (f2).

$$f2 = 50 \bullet \log \{[1 + (1/n)\Sigma_{t=1}^{n}(Rt - Tt)^2]^{-0.5} \bullet 100\}$$

The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent of dissolution between the two curves; where n is the number of time points, R_t is the dissolution value of the reference batch at time t and T_t is the dissolution value of the test batch at time t.

Two dissolution profiles are considered similar when the f_2 value is ≥ 50. To allow the use of mean data, the coefficient of variation should not be more than 20 percent at the earlier time points (e.g., 15 min) and should not be more than 10 percent at other time points. Only one measurement should be considered after 85 percent dissolution of both products. In addition, when both test and reference products dissolve 85 percent or more of the label amount of the drug in 15 min using all three dissolution media recommended above, the profile comparison with an f_2 test is unnecessary.

For BCS class 1 drug products, the following must be demonstrated:

- The drug substance should be highly soluble
- The drug substance should be highly permeable
- The drug product (test and reference) should be rapidly dissolving and

- The product should not contain any excipients that will affect the rate or extent of absorption of the drug.

For BCS class 3 drug products, the following must be demonstrated:

- The drug substance should be highly soluble
- The drug product (test and reference) should be very rapidly dissolving
- The test product formulation should be qualitatively the same and quantitatively very similar.

Excipients

- BCS class 1 drug products: Excipients can sometimes affect the rate and extent of drug absorption. In general, using excipients that are currently in FDA-approved IR solid oral dosage forms will not affect the rate or extent of absorption of a highly soluble and highly permeable drug substance that is formulated in a rapidly dissolving IR product. To support a biowaiver request, the quantity of excipients in the IR drug product should be consistent with the intended function (e.g., lubricant). When new excipients or atypically large amounts of commonly used excipients are included in an IR solid dosage form, additional information documenting the absence of an impact on bioavailability of the drug may be requested by the Agency. Such information can be provided with a relative bioavailability study using a simple aqueous solution as the reference product. Excessive quantities of certain excipients, such as surfactants (e.g., polysorbate 80) and sweeteners (e.g., mannitol or sorbitol) may be problematic.
- BCS class 3 drug products: Unlike for BCS class 1 products, for a biowaiver to be scientifically justified, BCS class 3 test drug product must contain the same excipients as the reference product. This is due to the concern that excipients can have a greater impact on absorption of low permeability drugs. The composition of the test product must be qualitatively the same (except for a different colour, flavour, or preservative that could not affect the bioavailability) and should be quantitatively very similar to the reference product.

Prodrugs

Permeability of prodrugs generally depends on the mechanism and (anatomical) site of conversion to the drug substance. When the prodrug-to-drug (i.e., active moiety) conversion is shown to occur predominantly after intestinal membrane permeation, the permeability of the prodrug should be measured. When this conversion occurs prior to intestinal permeation, the permeability of the drug should be determined. Dissolution and pH-solubility data on both prodrug and drug can be relevant.

BCS-based biowaivers are not applicable for the following:

Narrow Therapeutic Index Drugs

The US guidance for BCS based biowaiver does not apply to narrow therapeutic index (NTI) drug products because of the critical relationship between the bioavailable dose and clinical performance.

Products Designed to be absorbed in the Oral Cavity

A request for a waiver of *In vivo* BA/BE studies based on the BCS is not appropriate for dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets). Similarly, a biowaiver based on BCS for an orally disintegrating tablet can be considered only if the absorption from the oral cavity can be ruled out. (4)

3. BCS based biowaiver criteria for EU

Applying for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form. However, it is not applicable for sublingual, buccal and modified release formulations. For orodispersible formulations the BCS-based biowaiver approach may only be applicable when absorption in the oral cavity can be excluded.

Requirements for biowaiver

BCS-based biowaiver are applicable for an immediate release drug product if

- the drug substance has been proven to exhibit high solubility and complete absorption (BCS class I) and
- either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) *in vitro* dissolution characteristics of the test and reference product has been demonstrated considering specific requirements and
- Excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred.

BCS-based biowaiver are also applicable for an immediate release drug product if

- the drug substance has been proven to exhibit high solubility and limited absorption (BCS class III) and
- very rapid (> 85 % within 15 min) *in vitro* dissolution of the test and reference product has been demonstrated considering specific requirements and
- Excipients that might affect bioavailability are qualitatively and quantitatively the same and other excipients are qualitatively the same and quantitatively very similar.

Solubility

The pH-solubility profile of the drug substance should be determined and discussed. The drug substance is considered highly soluble if the highest single dose administered as immediate release formulation(s) is

completely dissolved in 250 ml of buffers within the range of pH 1 – 6.8 at 37±1°C. This demonstration requires the investigation in at least three buffers within this range (preferably at pH 1.2, 4.5 and 6.8) and in addition at the pKa, if it is within the specified pH range. Replicate determinations at each pH condition may be necessary to achieve an unequivocal solubility classification (e.g. shake-flask method or other justified method). Solution pH should be verified prior and after addition of the drug substance to a buffer.

Absorption

The demonstration of complete absorption in humans is preferred for BCS-based biowaiver applications. For this purpose complete absorption is considered to be established where measured extent of absorption is ≥ 85 %. Complete absorption is generally related to high permeability.

Complete drug absorption should be justified based on reliable investigations in human. Data from

- absolute bioavailability or
- mass-balance

Studies could be used to support this claim.

***In vitro* dissolution**

Investigations related to the medicinal product should ensure immediate release properties and prove similarity between the investigative products, i.e. test and reference show similar *in vitro* dissolution under physiologically relevant experimental pH conditions. However, this does not establish an *in vitro*/*In vivo* correlation. *In vitro* dissolution should be investigated within the range of pH 1 - 6.8 (at least pH 1.2, 4.5 and 6.8). Additional investigations may be required at pH values in which the drug substance has minimum solubility. The use of any surfactant is not allowed.

Excipients

Although the impact of excipients in immediate release dosage forms on bioavailability of highly soluble and completely absorbable drug substances (i.e., BCS-class I) is considered rather unlikely it cannot be completely excluded. Therefore, even in the case of class I drugs it is advisable to use similar amounts of the same excipients in the composition of test like in the reference product.

If a biowaiver is applied for a BCS-class III drug substance excipients have to be qualitatively the same and quantitatively very similar in order to exclude different effects on membrane transporters. As a general rule, for both BCS-class I and III drug substances well-established excipients in usual amounts should be employed and possible interactions affecting drug bioavailability and/or solubility characteristics should be considered and discussed. A description of the function of the excipients is required with a justification whether the amount of each excipient is within the normal range.

Excipients that might affect bioavailability, like e.g. sorbitol, mannitol, sodium lauryl sulphate or other surfactants, should be identified as well as their possible impact on the following should be considered:

- gastrointestinal motility
- susceptibility of interactions with the drug substance (e.g. complexation)
- drug permeability
- interaction with membrane transporters (5)

4. WHO criteria for BCS based biowaivers

On the basis of solubility and permeability of the API, excipient nature, excipient content and dissolution characteristics of the dosage form, the BCS approach provides an opportunity to waive *In vivo* bioequivalence testing for certain categories of immediate release dosage forms. Oral dosage forms containing an API possessing a narrow therapeutic index are not eligible for a bio waiver based on the BCS approach.

High solubility

An API is considered highly soluble when the highest single therapeutic dose as determined by the relevant regulatory authority, typically defined by the labelling for the innovator product, is soluble in 250 mL or less of aqueous media over the pH range of 1.2-6.8. The pH solubility profile of the API should be determined at 37± 1°C in aqueous media. A minimum of three replicate determinations of solubility at each pH condition is recommended.

High permeability

An API is considered highly permeable when the extent of absorption in humans is 85% or more based on a mass balance determination or in comparison with an intravenous comparator dose. Ideally the mass balance study or comparison with an intravenous comparator dose should be conducted at the same dose as that used for the solubility classification.

Absolute bioavailability or mass balance study data obtained from published literature may be accepted as evidence if it can be clearly established that the data were derived from appropriately designed studies. In vivo intestinal perfusion in humans is an acceptable alternative test method.

Dissolution criteria

For exemption from an In vivo bioequivalence study, an immediate release, multisource product should exhibit very rapid or rapid in vitro dissolution characteristics, depending on the BCS properties of the API. In vitro data should also demonstrate the similarity of dissolution profiles between the multisource and comparator products.

Very rapidly dissolving

A multisource product is considered to be very rapidly dissolving when no less than 85% of the labelled amount of the API dissolves in 15 min at 37± 1°C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- pH 1.2 HCl solution or buffer;

- pH 4.5 acetate buffer;
- pH 6.8 phosphate buffer.

Pharmacopoeial buffers (e.g. International Pharmacopoeia monographs) are recommended for use at these three pH values. Surfactants should not be used in the dissolution media.

Rapidly dissolving

A multisource product is considered to be rapidly dissolving when no less than 85% of the labelled amount of the API dissolves in 30 min at 37±1°C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media

- pH 1.2 HCl solution or buffer;
- pH 4.5 acetate buffer;
- pH 6.8 phosphate buffer.

Surfactants should not be used in the dissolution media. Enzymes (pepsin at pH 1.2 and pancreatin at pH 6.8) may be used if the pharmaceutical product contains gelatin (e.g. capsules or caplets) due to the possibility of cross-linking.

A biowaiver based on the BCS as per WHO considers

(a) The solubility and intestinal permeability of the API (Active Pharmaceutical Ingredient);

(b) The similarity of the dissolution profiles of the multisource and comparator products in pH 1.2, 4.5 and 6.8 media;

Excipients

In all cases, well established excipients in usual amounts should be used in multisource products. Excipients that might affect the bioavailability of the API, e.g. mannitol, sorbitol or surfactants, should be identified and an assessment of their impact provided. These critical excipients should not differ qualitatively and must be quantitatively similar between the test product and comparator product.

For biowaiver for products containing Class 1 APIs there is some flexibility in the excipients employed, with the exception of critical excipients as discussed above. It is recommended that the excipients employed be present in the comparator product or be present in other products which contain the same API as the multisource product and which have marketing authorizations in ICH associated countries.

For biowaiver for products containing Class 3 APIs all excipients in the proposed product formulation should be qualitatively the same and quantitatively similar to that of the comparator product, as defined by the WHO quality limits on allowable quantitative changes in excipients for a variation. (6)

Table 2 Comparison of BCS based biowaivers between US, EU and WHO (4-6)

Criteria	US	EU	WHO
BCS class	I and III	I and III	I and III
Solubility	High solubility within pH range of 1 - 6.8 at 37 ± 1°C	High solubility within pH range of 1 - 6.8 at 37 ± 1°C	High solubility within pH range of 1.2 - 6.8 at 37 ± 1°C
Permeability	Systemic BA or the extent of absorption in humans is determined to be 85 percent or more	extent of absorption is ≥ 85 % or more	extent of absorption in humans is 85% or more
Dissolution media	(1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes	(1) pH 1.2; (2) pH 4.5 buffer; (3) pH 6.8 buffer	(1) pH 1.2 HCl solution or buffer; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes
No. of dosage units required	Minimum 12	12	At least 12
NTI Drugs	No	No	No
Products getting absorbed from oral cavity	No	No	Not specified
Use of surfactant for *in vitro* dissolution testing	Not allowed	Not allowed	Not allowed

5. Well Established Use/Bibliographical applications

These kinds of Applications are accepted in the European Union.

According to Article 10a of Directive 2001/83/EC, as amended it is possible to replace results of pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substances of a medicinal product have been in well-established medicinal use within the Union for at least ten years, with recognized efficacy and an acceptable level of safety.

The following criteria for the demonstration of such well-established use should be taken into account:

- The time over which a substance has been used with regular application in patients; quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods;
- The degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments;

For such applications, the provisions of the Annex I to Directive 2001/83/EC apply in like manner. They are considered as full and independent applications. The Modules 1, 2 and 3 as described in Part I of Annex I to Directive 2001/83/EC should be submitted for this kind of application. For Modules 4 and 5, a detailed scientific bibliography shall address all required pre-clinical and clinical characteristics and should be summarised in Module 2. As with any other full application, if parts of the dossier are incomplete, particular attention must be paid to justify such absences in the non-clinical and clinical overviews.

It should be noted that, if well-known substances are used for entirely new therapeutic indications, it is not possible to solely refer to a well-established use and additional data on the new therapeutic indication together with appropriate pre-clinical and human safety data should be provided. (7)

6. Literature Based Submissions (LBS)

This kind of applications is accepted by Australian TGA. These rely solely, or predominantly, on bibliographic data (i.e. based on published literature) to support the safety and efficacy claims.

The acceptance and evaluation of a LBS is considered by the TGA on a case-by-case basis according to the regulatory and clinical history of the medicine, both in Australia and overseas (especially in the UK, USA, Sweden, Canada, the Netherlands and New Zealand).

LBS for New Chemical Entity (NCE) applications

Under exceptional circumstances, a LBS (including a mixed application) may be accepted for the registration of a new chemical entity (NCE) in Australia where it has been marketed in other countries for many years.

The quality (Module 3) component must be a conventional dossier.

LBS (or a mixed application) is not accepted for applications to register a NCE where the marketing in other acceptable countries has been less than ten years, except where:

- The NCE has been designated in Australia as an Orphan Drug, or
- There is no medicine registered and available in Australia that is registered for the same or (in the view of the TGA) essentially the same indication.

Countries currently identified as acceptable are:

- Canada
- Sweden
- Netherlands
- United Kingdom
- United States of America
- New Zealand

LBS is not acceptable in the following cases:

- Applicants should not routinely submit literature based data sets where sufficient company study reports are available. If the set of data generated from company study reports is incomplete, applicants may supplement the data with literature-based data.
- LBS are generally not appropriate for applications to change the clinical trials section of a medicine's product information (PI). Applications to change this section usually require the submission of full study reports of the relevant clinical trials.
- Literature-based data sets are not suitable for the quality (Module 3) component of an application as published reports rarely include sufficient validation information. A conventional Module 3 dossier should be submitted for all applications with a quality component. (TGA for Literature based submission). (8)

7. Conclusion

All the types of biowaivers viz. BCS based biowaiver, Bibliographical or well established use Application and Literature based submission have been discussed in detail in the above review. Hence, it may be concluded that bioequivalence studies are not necessary always for generic drugs provided the respective country regulatory guidelines are met.

Acknowledgements

I am highly thankful to Clinical Research Department of Micro Labs Limited for allowing me to carry out the review work.

Financial Disclosure statement: The author received no specific funding for this work.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

References

1. Abilash. N and Chandramouli. R. Biowaivers - an updated review, Journal of Pharmaceutical Research [Internet]. 2017 [cited 2019 Jun 16]; 16(3). Available from: http://www.journalofpharmaceuticalresearch.org/index.php/kpc/article/view/118768
2. Leslie Z. Benet. The Role of BCS (Biopharmaceutics Classification System) and BDDCS (Biopharmaceutics Drug Disposition Classification System) in Drug Development, Journal of Pharmaceutical Sciences [Internet]. 2013 [cited 2019 Jul 11]; 102(1): 34-42. Available from: https://jpharmsci.org/article/S0022-3549(15)31278-8/fulltext
3. Barbara M. Davit Isadore Kanfer, Yu Chung Tsang, and Jean-Michel Cardot. BCS Biowaivers: Similarities and Differences among EMA, FDA and WHO Requirements,

American Association of Pharmaceutical Scientists [Internet]. 2016 [cited 2019 Jul 22]; 18(3). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5256598/

4. FDA [Internet]. Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System Guidance for Industry, U.S. Department of Health and Human Services Food and Drug Administration. Centre for Drug Evaluation and Research (CDER); 2017 [cited 2019 Jul 13]. Available from: https://www.fda.gov/media/70963/download
5. European Medicines Agency [Internet]. Guideline on the Investigation of Bioequivalence, Committee for Medicinal Products for Human Use (CHMP); 2010 [cited 2019 Jul 21]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf
6. WHO Expert Committee on Specifications for Pharmaceutical Preparations, Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability, Annex 6 [Internet]. WHO; 2017 [cited 2019 Jul 13]. Available from: http://apps.who.int/medicinedocs/documents/s23245en/s23245en.pdf
7. EMA [Internet]. European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure; 2019 Apr [cited 2019 Jul 15]. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-pre-authorisation-procedural-advice-users-centralised-procedure_en-0.pdf
8. Australia TGA guideline for Literature Based Submission [Internet]. TGA; 2003 [cited 2019 Jul 21]; 10:3. Available from: https://www.tga.gov.au/publication/literature-based-submissions