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Review Article

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Regulatory perspective of Drug Repurposing: Methods, Regulatory pathways and Hurdles

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Abstract

Drug repurposing is a phenomenon that aims at utilising an established and approved drug product or drug substance for an additional clinical indication apart from the one that it was intended for. The reprofiling of drug formulations creates an extensive arsenal of therapeutic options for drug products, thus making the practice a desirable and forthcoming procedure. There are several techniques and methods that have been adopted over the years to evaluate the various possibilities for the repurposing of drugs in search of a wider range of chemical therapeutics.

The repurposing of drug products has provided, over the course of time several different advantages to the pharmaceutical industry, and yet remains an uncomprehended and over-looked procedure. The following paper attempts to identify the different benefits that are to be gained from the repurposing of drug products along with the approaches that have been used for the same. Additionally, the paper also discusses the regulatory perspective of drug repurposing, emphasising on the incentives that are available for various pharmaceutical sponsors as well the hurdles that are to be faced during the repurposing of a drug product or drug substance.

Keywords: Drug repurposing, Drug reprofiling, Repurposing approaches, Regulatory aspect of repurposing, Hurdles in repurposing

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1. Introduction

Rapid advancement in the various technological aspects has effectively influenced the pharmaceutical sector. Development and invention of medication and other pharmaceuticals is now being constantly viewed with more consideration for both time of development as well as the finance that the development would require. As various pharmaceutical giants are limited on both ends, drug development has become a cumbersome and draining task. On the other hand, the constant need for better developed medication and more effective therapeutic options is the need of the hour. With such circumstances, various pharmaceutical industries turn to the new age method that has gained much popularity, especially after the onset of a pandemic in 2020, i.e., drug repurposing. 1

Drug repurposing/ repositioning is a term that is coined for a phenomenon when a particular drug product is utilised for a clinical indication other than the one that the drug was initially intended for. Repurposing of pharmaceuticals implies the presence of an opportunity to rediscover a clinical indication for a drug that was not otherwise specified during the first stages of drug development. The different therapeutic significance that may be present in any formulation may be discovered intentionally through extensive screening methods or may be stumbled upon through a serendipitous course of action. 1 Oftentimes, a clinical indication for a formulation, which is further established as therapeutically significant for a drug product, may have been thought of as an idiosyncrasy at the initial framework.

Drug repurposing may prove to be an advantageous proposition for many organisations. The basis for repurposing of a pharmaceutical formulation is that the Active Pharmaceutical ingredient as well as the Drug Product that is to be scrutinised must have already been studied by other clinical investigators for a different therapeutic outcome. This would mean that the formulation has been proven to be safe for administration by the clinical investigators through several clinical as well as non-clinical trials. Consequently, when the same formulation is being studied for another clinical indication the drug sponsors

may by-pass these stages and move on to efficacy studies without delay, thus saving several costs to the organisation as well as reducing a substantial amount of time in drug development process for the repurposed drugs. 3 This becomes especially a defining parameter when an organisation wants to work on chemical therapies for rare or orphan diseases.

Owing to the several advantages that drug repurposing presents to the pharmaceutical sector, several major industries have taken a great interest in the procedure. This, however, poses a problem to the innovators of the formulation or API that is to be repurposed. If a new indication is being discovered by an organisation for a formulation, the original patentee of the formulation may pose a threat. The investigators involved in drug repurposing of a patented formulation may face several challenges when it comes to the regulatory perspective of a repositioned drug. In different regions repurposed drugs are dealt with differently as these drugs prove to be part of a legal grey area since several of the guidelines that are published by different regulatory authorities do not emphasise on the repurposing of a drug, which ultimately leads to several conflicts of interest. This paper intends to shed some light on the various regulatory guidelines that may be followed in different regions when it comes to the registration of repurposed drugs as well as the various regulatory restrictions that organisations may have to face while working on commercialization of repurposed drugs.

Defining repurposed drugs

Repurposing of a drug product is a procedure where any formulation that has been or is in the process of development for any one clinical indication, may prove to be useful in another therapeutic outcome. The key to repositioning of any drug would be the addition of a new therapeutic significance to the drug formulation's arsenal. For every new indication that is detected in the pharmaceutical product, the drug is said to be repurposed or reprofiled. This situation may arise in some cases where any particular drug substance that has been utilised in the making of a formulation is known to affect different drug targets which may ultimately lead to different pharmacological outcomes. 4

On the other hand, there may be times when a particular drug product that is known to theoretically provide a therapeutic action does not perform as expected. The drug product may be shown to produce a particular undesirable effect that may be a required action in a different situation. In such cases drug repurposing may be done serendipitously, where an unplanned occurrence may lead to the invention of a new or relatively new method of treatment.

Another situation where drug repurposing may occur is when a particular formulation that is being studied for a therapeutic indication through various clinical trials, despite proving to be safe for administration, is ineffective in the actual treatment. In several cases, the formulations that fail at the therapeutic efficacy trial stages, that is the Phase III of a clinical trial, are shelved and further developmental studies are discontinued. 5 However, this may lead to the loss of several funds that were invested in development of formulation and the safety and quality trials that had already taken place and proved to be satisfactory. Such formulations that are evidently safe for administration in a particular dosage form are prime candidates for repositioning. Numerous organisations and investigators opt to study such formulations to discover any other clinical indications that the formulation may possess through various thorough screening procedures.

Moreover, various cases of repurposing are reported after the formulation has been approved for sale to the general public. During post-market surveillance studies adverse events may be recorded that in some cases may bring about new data that was uncovered during clinical trials due to lack of sampling diversity. The data thus obtained may be used for repositioning of the formulation through various drug development approaches.

Additionally, in many situations drug repurposing of various approved drugs is already underway by many clinicians. This is the case when any specific drug is prescribed for an 'off-label' use, which essentially means using a formulation for a purpose other than the one that it was intended or instructed for. While off-label use of drugs is prohibited and frowned upon, it is prevalent in many situations. The greatest disadvantage that this would bring is that the off the label use of drugs for the treatment of any pathophysiology may cause more harm than benefit to the patient as these have not been clinically tested. While off-the-label uses of a drug may bring about desirable effect, it may just be a surrogate outcome and not the actual treatment that would be required for full internal recovery.

2. Adopted repurposing approaches 6

There are a number of methods that have been predetermined over the course of the years for the reprofiling and repositioning of any drug product. While a serendipitous approach is always welcome and expected for drug repurposing, other procedures have also been adopted by major pharmaceutical industries to add on to the existing clinical indications of a formulation. A variety of approaches for drug repurposing have been reported to bring about desirable results to various sponsors, among which a computational approach plays a major role in repurposing, especially with the ardent development that the scientific industry has seen with regards to bioinformatics. In addition to that, sponsors and investigators have also given due credit to more traditional methods of repurposed drug development which would include various hit-and-trial experiments. The various approaches that are being followed for the repositioning of drug products are listed as follows:

Computational approaches

This method of repurposing utilises bioinformatics as its core to help understand any chemical formulation and its interaction with the human body in a greater depth. This is possible with the immense amount of data that has been collected over the years in genetic mapping. This

method can further be classified into the following categories:

a. *Genomic approach:* Genetic profiles that have been generated and are the base of bioinformatics can provide a basic framework for the repositioning of any drug product or formulation. Transcriptomic data can be used to evaluate how a particular compound might react to any target receptor in a virtual environment thus leading to the discovery of a possible new pharmacological outcome

b. *Phenotypic approach:* This technique implies the observation of outward symptoms to detect a pharmacological effect of the body. Clinical outcome of any formulation may be deduced by the careful assessment of the phenotypic reaction that has been produced after administration of any drug product, thus leading to repurposing opportunities

Physiochemical structures

The complete knowledge of the physical, chemical as well as the biological aspects of any chemical product is essential in any repurposing technique applied. This may help evaluate a particular drug product's possible reaction in the target organ through biochemical data that has been thoroughly studied by the investigators. This procedure relies on the fact that a particular compound after the interaction with a receptor must react in a certain way, and that would be applicable on all active moiety that are in the same category with similar functional groups. Investigators in this case rely on their ability in assessing the similarities between different active pharmaceutical ingredients to gain this particular outcome that may advance to the reprofiling of a drug product.

Combination approach

Administering a combination of drugs for a particular pathological problem in a patient has been an age old chemical therapeutic strategy. Oftentimes the desirable outcome for both curative measures as well as to provide comfort to the patient cannot be possibly done through a single dose of a formulation. In such cases, clinicians may look to a combination of drug products and study their effects together. These methods are also approaches to reprofiling as the pharmacological effect that a drug product produces on its own may be vastly different from the effect that it produces when administered in the presence of another formulation. However, this approach is largely being done as an off the label method and has little room for regulatory approvals and hence does not provide much incentive for further investigational or confirmatory studies.

3. Discussion

Reasons for Drug Repurposing

New Market:

Repurposing of drug products till date remains an unconventional technique. Nevertheless, the procedure may provide the sponsors of drug products with several benefits in the long run. Repositioning of a drug involves investigators to include an undiscovered and non-obvious clinical indication to the profile of a pharmaceutical product. This situation would eventually lead to two different benefits. First, if the drug product in question clinically proves to provide an additional clinical benefit to any patient group, then the commercialisation of the drug product may be exponentially increased, leading to a financial benefit to the sponsors of the pharmaceutical formulation. Second, the studies that sponsors conduct for the repurposing of the drug would provide an overall health benefit to the society, as a new therapeutic outcome becomes available to the general public. [3]

Utilisation of shelved API [5]

In several cases, chemical formulations are prepared through computational screening based on the disease or targets that the drug is intended to attach with. However, the in vivo studies for such cases may prove to be a completely different matter. The chemical formulations may align with the desired target but may not bring about the desired outcome. This leads to the discontinuation of all developmental activities which may cause huge losses to the pharmaceutical company. Drug repurposing, however, would provide an additional opportunity for the active chemical moiety. With various computational techniques the drug substance can be studied with additional variability and lead to a reprofiled drug.

Development of Orphan Drugs

Repurposed techniques may also be used as an incentive for several pharmaceutical companies to study the cure or therapeutic options for various rare or orphan diseases. [5] Rare diseases or orphan diseases are pathological conditions that occur in a minor section of the demographic. Due to the reduced amount of use of the drug products that are to be used in the treatment of orphan diseases, pharmaceutical organisations are less inclined to use the company funds for the development of drug products for their treatment. However, these formulations would still remain a necessity in society. In that case, repurposing can come as a great and effective solution. Since the drugs that are repurposed are already declared to be safe for administration, the investigators can avoid the entire lengthy drug development procedure and focus only on the efficacy studies. This may provide the organisations an inclination to devote the study of helved drugs for the treatment of rare or orphan diseases. Also, several government schemes would also support the development procedure for the repurposed drug if it is proved to be an effective therapeutic strategy for an orphan disease.

Emergency treatment/Surrogate outcomes [5]

Urgent or life threatening, or debilitating situations may lead to the utilisation of repurposed drugs for an off the label clinical indication. An emergency approval for pharmaceutical products may be provided to the clinician if it is essential in a life-or-death situation. While off label uses are not supported, they may be practiced with caution in cases where no other options are available. This may be the case where a particular formulation with a different clinical indication may produce a

pharmacological effect as an idiosyncrasy that may be desirable in a different situation. These outcomes are usually termed as surrogate effects, i.e. outcomes that are desirable in the current situation to reduce outward symptoms temporarily but may not provide an actual cure. This may help stabilise the situation of a patient for some given amount of time which gives the physician an opportunity to re-administer the required treatment.

Personalised medication

While developing any drug product for the commercialization of a drug, a sample population is carefully selected for the evaluation of the finished drug product before its complete market authorization approval. The sample population is selected with precision, keeping in regard the various diverse groups that are part of a demographic.5 However, even the most accurate of selected samples cannot account for the variability in genetic makeup that may be present in even the most similar patient groups. Genetic polymorphism is a parameter that most sponsors developing drug products fail to consider, mostly due to the complications that it may bring to the evaluation studies. In such cases, physicians opt for repurposing of the drugs that are administered in order to suit the polymorphic forms of the receptors of a similar target organ group. Repurposing is the most practical and reasonable approach for dealing with personalised therapeutics.

Economic Feasibility

Repurposing of drug products does not incorporate any sort of modifications or reformulation activities to the drug product. Due to such reasons, during the safety and efficacy assessment that are to be done for the drug product, several of the safety trials may be by-passed as the safety and toxicological profile for the drug substance and drug product has previously been established which allows the sponsors or investigators to save up on a considerable amount of capital. The registration and approval of the additional clinical indication only requires the dose compatibility studies and proof of pharmacological action. 5 Many of the documents that would be usually required for the registration of any drug product with a regulatory authority for a marketing approval grant, are not to be required to be developed again in case of repurposed drugs and hence saves the sponsors a decent number of resources. 4

Regulatory aspects of drug repurposing

Repurposed drugs are an advancing trend in the field of pharmaceuticals and one in which a lot is yet to be clarified. While major regulatory authorities of the world have established a certain amount of legislation for the inclusion and regulation of new indications to an approved drug product, a lot is yet to be defined when it comes to repurposing. Guidelines of regulatory agencies do not deal with the repurposing of drug products in a clear and concise manner, which provide various pharmaceutical organisations with loopholes for the establishment of such drugs.

Repurposing of therapeutic agents can be a challenging task from a regulatory point of view as well. 7 Repositioning is dealt with drug products or drug substances that were previously registered or established for different therapeutic uses. The investigators or sponsors that are involved in the repurposing developmental studies need to face several legislative barriers as they are utilising products that are legally bound to different entities. The use of such products may lead to infringement charges and a long, exhausting battle for intellectual rights of the pharmaceutical product, which shall be detrimental to both the investigators developing the drug as well as to the patient groups that hope to benefit from the new indication.

In addition to that, the new indication that is eventually discovered also needs to be registered through an application or submission to the regulatory authority of the region where the investigator or sponsor wishes to market the product. This would again provide the investigators with yet another hurdle, as registration route for repurposed drugs in various regulatory authorities is not decisive. This leads to yet further conflict during the review and registration process between the regulatory agency and the applicant.

Owing to the various difficulties that the investigators of new repurposed drugs face, several well-established regulatory authorities are promoting the incentivisation of repositioning of drugs as, complicated as they may be, they prove to be beneficial in not just improving the general health of the public by providing alternative therapeutic routes but also provide an economical advantage to the sponsors and manufacturers who opt to invest in such programmes. The purpose of this section is to emphasise on some of the regulatory considerations and schemes that have been developed over the years to allow the repurposing of pharmaceutical products in the drug market.

Government Agencies for Repurposing

The repurposing of drugs, has time and again, proven its worth through various incidents in the recent years. Especially with the recent pandemic that hit the world equally, government officials were forced to make some decisions to overcome the severe adversities that they were faced with. With such a predicament, drug repurposing was the technology that helped provide various regions with the necessary therapeutic alternatives, that may not have provided the necessary cure, but were effective in providing a surrogate outcome and benefit to the general public.

Repurposing of drug products has always been a topic of great interest for the pharmaceutical industries as well the government organisations. This interest in development of existing drug products has led several government authorities to establish organisations that incentivise the repurposing of existing drugs in their regions and demographics. These organisations help provide financial aid to the various investigators and sponsors who have held an interest in the repurposing of drug products. One of the major organisations that works with repurposed drugs, is the organisation under the USFDA (Food and Drug Administration), i.e., the National Centre for Advancing Translational Service (NCATS). 1,8 The principal objective of this

organisation is to aid various investigators working on the repurposed drug products and provide them with the essential financial aid in the development of new indications and therapeutic benefits from the existing drug markets. They are also known to be prevalent in the implementation and incentivisation of novel therapeutics that are developed by the sponsors under this organisation. In addition to that, the organisation also finds responsibility in surveying the effects of the repurposed drug in the region it was marketed to provide a post-marketing response to help evaluate the repurposed drug in a better way and to provide as much information about it as possible to the general public.

In Canada, the regulatory authority, Health Canada along with the Ministry of Health have also come up with a similar sister organisation, the Canadian Institute of Health Research (CIHR) that functions with the same principles in mind. 1 The organisation is also established in the country with the aim of providing efficient and beneficial repurposed drugs to the patient groups in the country. The organisation works in tandem with the organisation functioning under the European Medicines Agency (EMA) to fund and provide all necessary support to organisations and establishments that work with the repurposing of drug products in their respective regions. Similarly, the Medical Research Council (MRC) that was established under the UK (United Kingdom) provided similar incentives to investigators in their nations. 6

Regulatory considerations for repurposing of drugs

It is now an established fact that the repurposing or repositioning of pharmaceutical products can be carried out in several ways to provide innumerable benefits to all parties that may be involved. This leads us to the regulatory considerations that must be taken note of when establishing such a drug product in the market for commercialisation. Some of the well-established nations have opted to devise legislative rules and regulations for the marketing, manufacturing and even development of repurposed drug products and drug substances. These regulatory provisions are necessary to ensure the safety and quality of the products before they are made available for dispensing and to also assess whether the efficacy of the new therapeutic ingredient would out-weigh the risks that it may pose and also to verify if that benefit has any advantage to the therapeutic options that are already commercially available in that particular demographic region.

One of the biggest and dominant drug regulatory authorities in the world, the US FDA, has established certain provisions that must be followed by the various organisations in order to register the repurposed drugs and to gain any exclusivity privileges for their particular pharmaceutical product. The registration pathway for approval of repurposed drugs in US FDA would be through the 505 (b) (2) registration pathway as this registration process provides an opportunity for the drug product sponsors and applicants to file a dossier which may include studies that have been conducted from a different organisation, if the data is necessary for providing verification of safety, quality and efficacy of the drug product. 1 Another peculiarity in this pathway of drug product approval is that the application that contains details about an existing approved drug, must provide some amount of novelty for it to applied for again, i.e. the product that is submitted through this dossier must be incorporated with a new route of administration, dosage form or a new clinical indication. This proves to be in sync with the requirements of a registration application that may be needed for a repurposed drug as the proposed drug product is being reprofiled with the addition of a new therapeutic outcome. The registration of drug products through this pathway may also gain some amount of market exclusivity in the region that they were registered, as in this pathway any drug product may gain a market exclusivity of up to five commercial years starting with the point of registration of the drug product, and an additional three years of marketing benefit may be granted, provided a new indication is added within this period. 1 This pathway thus promotes the repurposing development studies of drug products even after the registration and marketing approval of pharmaceutical products.

On the other hand, if any pharmaceutical organisation wishes to market their drug products in the European countries, with the intention of reprofiling the drug product in the later stages of manufacturing and development, they must opt for the pathway and registration procedure that is established by the Article 10 Directive 2001/83/EC, which is a registration pathway that provides the sponsors of various drug products to file and market any novelties and additions that they may have made to the existing reference listed drugs in the European Medicine Agency (EMA).1 This registration and approval procedure provide the sponsors and investigators with an exclusivity period of a total of eight years, starting from the registration of the drug product, and also provide the sponsors with an opportunity to gain an additional two years of exclusivity if the sponsor can opt for the inclusion of an additional clinical indication to the existing profile of the drug product. 1

Moreover, various regional regulatory authorities provide incentives to the sponsors and investigators associated with pharmaceutical industries for the development of repurposed drug products through different methods. One such method that has been employed by several regulatory authorities is providing ‘Indication-specific market exclusivity’. 3 This term implies that for every drug formulation that may be registered for approval in any regulatory authority, the marketing exclusivity rights would be granted to not the formulation, but to the therapeutic indication that the formulation is intended for. This promotes the repurposing of the chemical compounds that are available in the market as with every new indication that may be added to a drug product’s arsenal, additional market exclusivity rights would be granted to the sponsor. This type of registration may also be termed as a ‘Second-indication Patent’ and is prevalent in many regions for the approval of repurposed or reprofiled drug products. 7

Regulatory barrier to Drug Repurposing

Despite the different provisions that have been provided to pharmaceutical investigators to promote the development of repurposed drugs, many sponsors are likely to face several challenges and hurdles while attempting to register and regulate such drug products. Most of the restrictions in repurposing and reprofiling arise from the lack of information that the sponsors have when it comes to dealing with a second indication in any pharmaceutical product. Drug regulation of reprofiled drugs is extremely difficult because many organisations find it convenient to allow physicians to utilise the drug for a second indication through off-label prescription i.e., the physicians prescribe a drug product for a therapeutic effect that the formulation was not originally intended for. 3 For most generic drugs, off-label use of drug products proves to be the biggest hurdle when considering repurposing of drugs. The off-label use of pharmaceuticals is discouraged by regulatory authorities as the effects have not been studied in complete detail and could cause unknown or unexpected results. Therefore, repurposing in such a manner may violate regulation policies.

On the other hand, repurposing studies are significantly lower in number as regulation for the repurposing of generic drugs is not a convenient process. The reason for this is simply that the revenue that any drug product may generate by its repurposing is not equivalent to the amount of capital that would be required to clinically study the second indication through laboratory studies and experiment. Also, the regulation of the repurposed drugs defines several registration pathways for the repurposed drugs, however, the process of registration of any second indication is cumbersome to pharmaceutical organisations and hence an unattractive option for establishments and sponsors.

The patent rights and the intellectual property consideration for the original drug that is being repurposed may present yet another hurdle to the repurposing of drug products. For instance, if a drug formulation has been registered with any regulatory authority for any one indication, it receives a certain amount of market exclusivity in that particular region that may be violated in case of repurposing. The repurposed drug products affect the market exclusivity of the original product especially if the reprofiling or registration of a second indication is done by an organisation different from the one that registered the original drug formulation. This provides conflicts with the regulatory authorities as to who shall gain the profit that comes from the commercialisation of drug products for a second indication. This conflict becomes much more difficult to resolve as in case of drug repurposing the chemical composition of the drug formulation does not change at all. If in case any establishment chooses to change the formulation in the slightest to provide a difference or an edge as compared to the existing therapeutic options, then the sponsor has deviated for the repurposing route and would require to use a different pathway of submission of drug product as compared to the pathway that may be used for repurposed drugs. This in turn would be yet another entirely different process and the investigators lose the advantage that may have while developing a repurposed drug.

Another hurdle that investigators may face when it comes to repurposing is the existence of patents for the various Active Pharmaceutical Ingredients that have been developed by the manufacturers. If any establishment or a sponsor were to register an active ingredient or a drug substance and obtain a patent for the same, then it discourages repurposing. This is because a patent on the drug substance will prohibit any research and development activities that may be conducted. Only the pharmaceutical organisation that has obtained the patent right for the precise API may be permitted to submit any additional therapeutic indications in order to re-profile the drug substance. 1 Also, the discovery of the existence of any new clinical indication that the particular molecular compound may show during any research and developmental studies may be credited only to the entity or organisation who possesses the patent right for that particular compound regardless of who was involved in the research for the same. In such cases also, investigators do not have much to gain from the repurposing of the drug purposes, effectively hampering the reprofiling process. The same situation would be applicable in case of ‘shelved API’ which may propose to be an ideal candidate for repurposing but are let down for such studies as the sponsors and investigators for repurposing studies are likely to face conflicts with the original patent holder of the API. 5

In some cases, lack of sufficient provisions and incentives from the government may hamper the repurposing of drug products. There are many regulatory authorities of varying countries that have no provisions to provide any support for the drug products that are repurposed by investigators. Many regulatory authorities have yet not developed any specifications for the registration of any new indications to a drug product. In these countries, the formulation and composition of the drug product itself is registered for the grant of a marketing approval and hence any new indication that may be developed at later stages do not have an advantage of market exclusivity in the country. The regulatory authorities in such cases demand the development of a different dosage form or a different dosage strength in order to validate the reprofiled drug substance but that would immediately deviate from repurposing which the sponsor was originally aiming for. 8

4. Conclusion

The repurposing of a drug product may prove to be a valuable procedure for any sponsor or investigator as it provides a much easier ground for the drug development and research activities. Due to the rise in the several approaches that have been developed over the years for the reprofiling of drug products, repurposing has become increasingly convenient. However, it must be noted that the regulatory pathway of drug products and drug substances are yet to be clarified. The repurposed drug products have several regulatory pathways that may be used for the registration and approval of the additional indication. The governmental agencies have also

attempted to provide the sponsors with different incentives to aid in the repurposing of the drug formulation, yet the sponsors of such developmental projects are liable to face several hurdles. The solution for the regulatory hurdles that a sponsor is likely to face in the repurposing of a drug formulation are yet to be definite and is something that many organisations are aiming to rectify.

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