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Literature review: Determination and role of pharmacy personnel in providing information of beyond use date

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ABSTRACT

One of the pharmaceutical jobs that are closely related to the quality control of pharmaceutical preparations is ensuring drug stability. Drug stability must be guaranteed not only in pharmaceutical manufacturers but also continue until the product is handed over to patients/consumers or health workers. In daily practice, it is common for errors to occur regarding the limit of use of drugs after the packaging is opened or beyond the use date and expiration date. Many people in the general public assume that drugs that have been opened and used have the same use limit as the expiration date. Products that have been repackaged or whose original packaging has been opened due to repeated use may have a risk that the preparation lacks the potency, efficacy, and safety of the product in its original sealed packaging. Many factors affect drug stability and quality, including temperature, solvents, storage techniques, and other factors. Various studies have also examined how information and education provided by health workers are related to drug stability. To what extent does the research impact changes in community behavior, and what needs to be developed so that an understanding of drug stability can be successfully implemented in the community. This literature review is expected to provide an overview and input related to the use of drugs to ensure the quality of pharmaceutical preparations.

Keywords: *Beyond Use Date, in-use stability, quality control, expired date, efficacy*

INTRODUCTION

The expiration period is the time limit when a preparation can no longer be used. The expiry date in pharmaceutical preparations is known as the Expired Date (ED) and Beyond Use Date (BUD). BUD and ED are similar in that they signify an expiration date, but the time is different. ED is the expiration date of the drug that determined by the manufacturer, where the product or drug can still be used until the time limit stated on the drug packaging as long as the drug has not been opened from the original packaging and as long as it is stored in the right place1,2. Beyond use date (BUD) is the expiration date or time limit for using drugs that have been opened from their packaging / dispensed /mixed / dissolved 1–3. The difference between BUD and ED can be seen in table 1 below.

TABLE 1: The difference between BUD and ED

Parameters	Expired Date (ED)	Beyond Use Date (BUD)
Definition	Expiration period when the drug has not been opened from its primary packaging and while it is stored in the right place	Expiry date when the drug is opened from the original packaging or mixed or has been dissolved or transferred to another container (re-packing)
Time determination	The time listed on the drug packaging and determined by the manufacturer based on long term or accelerated stability study	The time is determined since the primary packaging is opened/mixed/re-packed based on guideline and in use stability study

Quality management

The quality management of a drug does not only rely on approval from BPOM and pharmaceutical industries, but quality assurance must also continue until the product reaches the patient/consumer4. The low quality of the drug affects the therapeutic efficacy, side effects and unwanted reactions. The criteria for drug quality include several parameters including purity, potency, dosage form uniformity, bioavailability, and stability. This aspect of quality is influenced by the process of raw materials becoming the final product, including the process of manufacture, packaging, storage, and other factors. Low drug quality will produce substandard therapeutic effects which can cause side effects and toxic effects. There are several quality control activities that can be carried out by pharmacists, such as:

Organoleptic Control

Changes in drug quality can be observed visually, namely changes in color, smell, and shape. If from visual observation it is suspected that there is damage that cannot be determined by organoleptic but the quality of the drug is suspected to have a degradation, then a sample must be taken for laboratory testing.

Changes in drug quality can be suspected by various changes, including

1. Tablet dosage forms: changes in color, smell, and taste. Damage in the form of stains, spots, holes, chipped, broken, cracked and/or contains foreign objects, becomes powder and damp, and damaged cans or bottles, which can affect the quality of the drug
2. Capsule dosage forms: changes in the color of the capsule shell, capsules soften, changes in the contents of the capsules, capsules open, empty, damaged or attached to one another
3. Coated tablet dosage forms: discoloration, wet and sticky to one another. Cans or bottles are damaged, causing physical abnormalities
4. Liquid dosage form : change in liquid to become cloudy or precipitate, consistency changes, color or taste changes, plastic bottles are damaged or leaking
5. Ointment dosage form: discoloration of ointment, consistency, broken or leaky pot or tube and change in odor
6. Injectable dosage form, can be marked by the presence of leaking containers (vials, ampoules), the presence of foreign particles in the injection powder
7. The solution that should be clear looks cloudy or there is a precipitate, the color of the solution changes

Beyond Use Date Determination
USP and BPOM

Products that are formulated or mixed or dissolved must be guaranteed for their characteristics, potency, purity and quality to fullfill the standards until the product is used by patients 5. The functions of BUD information are:

- Indicates the time in which the drug or preparation must be used before it is at risk of experiencing physical, chemical

degradation and contamination by microorganisms
- As a warning to health workers or consumers that mixed or opened preparations from their primary packaging may no longer be used from the date stated in the BUD

There are various ways to obtain information related to beyond use date, by looking at information on packaging leaflets, reading the guidebooks issued by the USP and BPOM, as well as from various studies related to stability.

- To determine BUD, preparations are divided into two categories 2,6
- Non-sterile preparations, including powder and capsule preparations, tablets, syrups, suspensions, emulsions, ointments, creams, gels, lotions, nose drops, and ear drops.
- Sterile preparations, including eye drops, eye ointments, injection preparations.
- If there is no reference, BUD can be determine based on BPOM5
- Tablets/capsules that have been opened and packaged in plastic medicine clips: 2 months expiration
- Syrup and liquid for external medicine, ointment/cream in a tube: Six (6) months after the package is opened or according to the expiration date (ED) printed on the package, see which one is faster, if the ED is faster according to the ED time, BUD same with EDs
- Ointment/cream in a sealed pot: Three (3) months after opening or according to the expiration date printed on the packaging, see which one is faster, if ED is faster according to ED time, BUD is the same as ED
- Ear drops, nose drops, nasal and ear sprays: Three (3) months after the drug is opened, unless stated otherwise based on the rules stated on the drug packaging
- Powder: If the powder is not used or is not needed, it is advisable to throw it away, don't store it
- Insulin: If it hasn't been opened, then BUD is the same as ED for medicinal preparations and stored in the refrigerator. If insulin has been opened, BUD insulin for 28 days and stored at room temperature.
- Suppositories and inhalers: According to the time or expiration date stated on the leaflet/medicine packaging

Pharmaceutical Industry

Before a product is marketed, Pharmaceutical Industry conducts a series of stability tests such as long-term stability tests, intermediate and accelerated stability tests. The purpose of this stability test is to provide evidence of how the quality of the drug compound or product is affected by temperature, humidity and light. Stability test also conduct to determine the re-test period for the drug compound or the shelf life (expired date) of the product and recommendations for storage7. In addition to the stability test, products that are used repeatedly (multiple use) will also be tested for in-use stability. The purpose of this stability test is to determine the length of time during which a product can be used with acceptable quality according to specifications after opening the container or primary packaging. In the registration process, this use stability test needs to be included in the registration document or justification for not conduct the in-use stability test8. In use stability test is listed in EMEA 2001, Asean Guideline on Stability Study of Drug Product (R1), WHO Annex 10, dan FDA Guidance Document 2020 (only for animal injection products) 9–11.

The use stability test is carried out on a minimum of two batches of pilot batch. Products are packaged in primary packaging that is equivalent to the packaging that will be marketed. The test procedure is designed to simulate the use of the product respect to product volume and dilution or reconstitution prior to use. Sampling was carried out on the conditions of use. Parameters tested were physical (color, clarity, integrity of packaging, particulate matter, particle size), chemical (level of active substance, preservatives, antioxidants, amount of degradants and pH) and microbial. The evaluation process is carried out using a validated method.

The use stability test is carried out for each product due to its different characteristics either to the environment or changes in the formula

(dilution or reconstitution). The long-term stability test was carried out on the primary packaging, so when the packaging is removed, this study should be carried out. This is because each package has different characteristics such as 12:

- Permeation, the ability to transmit oxygen and water vapor
- Leaching, the process of migrating packaging components into drug products
- Absorption of drug components into the packaging
- Chemical reactivity between packaging components and drug products
- Physical and chemical modification of packaging materials due to drug products

Constraints In Determining Beyond Use Date

According to EMEA 2001, the in-use shelf life should be stated on the label, leaflet and secondary packaging. However, in accordance with PerKaBPOM HK.03.1.23.06.10.5166, drug product labels in Indonesia are not yet required to include this information. Regarding the date that must be stated, only the expiration date in month and year format10. The period of drug use and storage conditions after the drug is opened must be stated on products circulating in the USA and EU and listed on the label. Likewise, Korea is obliged to include this in the section on precautions of use13. This shows that there is a gap between the tests that have been carried out by the pharmaceutical industry and information for consumers that cause by regulations limitations.

Research Related Beyond Use Date

Many studies have been conducted to examine problems related of people's behavior towards drugs that have been opened or drugs whose packaging has been moved. Based on a study conducted on 88 participants, regarding BUD, it was found that the majority of participants (88.64%) had never heard of BUD from the media. In addition, 97.73% of participants did not know BUD was the time limit for drug use after the drug was dispensed or opened from the packaging, and 100% of participants or all participants stated that health workers had never provided information regarding drug BUD 14. The latest survey conducted on 20 respondents in North Jakarta regarding the level of knowledge of people of productive age (20-37 years) found that health workers never provide information or counseling related to BUD. From this research it can be concluded that information related to BUD has not been conveyed properly to the public. Research related to BUD is still lacking and not much conduct in Indonesia15.

In the Guidelines for Good Drug Manufacturing Practices (GMP), it is stated that the expiration date of the drug stated on the original packaging cannot apply to drug products that have been moved or repackaged in a different container or place, due to the risk that the container does not provide equivalent protection or the container is not compatible with the preparation, so the expiration date of the drug is not as stated on the original packaging. The expiration date of drugs that have been dispensed or moved from their original packaging is determined by considering the physicochemical properties of the drug, the characteristics of the container and storage conditions4. However, unfortunately, from various studies conducted on health workers, many of them are not provide information to patients and the public regarding use limits. This is shown in various studies conducted. From the research of Fonny C et al (2019), data were obtained regarding BUD perceptions in 6 sub-districts located in the North Jakarta area in the period September-November 2021. From 60 informants who were recruited using purposive sampling, the results obtained were that the majority of informants (97%) did not know about BUD, and all informants (100%) never received BUD information from pharmacists. Some of the informants have the perception that the BUD is the same as the expiration date on the factory packaging15.

In fact, one of the responsibilities of the pharmacist is to provide information on the time limit for drug use after the package is opened so that the drug used has guaranteed drug stability in terms of its effectiveness and safety16,17. Information and education provided by health workers to the community can significantly increase public knowledge regarding the Beyond

Use Date. This is shown by research conducted by Baiq et al (2022), Anis et al (2022), Ikhwan et al (2020), Godelive et al (2021), Ratna et al (2019). Increasing public knowledge regarding the Beyond Use date will certainly reduce safety risks in drug use, and maintain drug efficacy by storing and disposing of drugs properly 18–21. Unfortunately, due to time constraints, it is common for pharmacists when dispensing drugs do not accompany important information related to BUD, which provides understanding to patients and their families, how to store drugs properly, and how to identify drugs that have been damaged and past their expiration date so that patients do not store and use drugs that have been damage and dispose of them in the right way.

TABLE 2: Research on Health Workers Related to BUD

Reference	Research Purpose	Result
Beyond Use Date Education for Iismakes, Mataram City18	Knowing the effect of providing drug information with leaflets on the increasing public knowledge related to BUD	There was an increase in participants' insights about BUD after providing education with an increase in knowledge of 13.71%
Beyond Use Date Education on Household Medicines in Demangan Gondokusuman Village19	Knowing the effect of BUD knowledge after mentoring and education	The percentage of increase in knowledge and understanding of PKK groups related to Beyond Use Date of household medicines is 62.8%.
The Beyond-Use Date Perception of Drugs in North Jakarta, Indonesia 15	To see the perceptions of the people at North Jakarta regarding BUD, and to know the role of pharmacists in providing BUD information	Of the 60 informants recruited, it was found that the majority of informants (97%) did not know about BUD, and all informants (100%) had never received BUD information from pharmacists.
Increase Community Understanding of Beyond Use Date in Kecepit Village, Punggelan District, Banjarnegara Regency20	To find out the public's understanding regarding the safety and use of drugs related to Beyond Use Date	Increased knowledge of 25 of 32 respondents after being given information and education about BUD
Analysis of the Level of Public Understanding Regarding Drug Management and Beyond Use Date21	To find out people's knowledge regarding Storage, Disposal of drugs and BUD	Respondents' understanding was significant before and after providing counseling in the BUD domain as well as drug storage and disposal
Description of Community Knowledge About Beyond Use Date at Suhio Housing, Lamongan Regency	To find out the description of community knowledge regarding storage and BUD	There is good knowledge about beyond use date, namely 36 people (81.8%) and a small portion of sufficient knowledge, namely 8 people (18.2%)

DISCUSSION

Drugs have effectiveness and safety according to standards when their stability is maintained during storage until they are finally used by users (patients/health workers). A drug product is said to be stable if during storage until use, it has physical, chemical, microbiological, toxicological and therapeutic characteristics that remain the same (do not change) from the specifications set by the manufacturer based on regulation2,3. Thus, when the stability of the drug decreases, there will be a risk of decreasing the drug's efficacy and safety. Drug stability is correlated with expiration date. Unfortunately, until now, there is no prevalence data on how the safety of drug use is related to stability and BUD.

In daily practice, sometimes there are requests to make dispensing of several medicinal preparations in mixed form. As an example is parenteral preparations. For this case, stability can be obtained from several primary literature studies, using search engine (Google Scholar,

Pubmed etc) that can be carried out with the keywords Stability And Beyond Use Date And Parenteral Nutrition. Several things need to be considered, when searching the literature, it is better to use more than one source, at least 2 (two), the more the better, and if possible, adjust it to the type of product you are looking for. This is because one literature may differ from another, because the components of the preparation studied may differ from one literature to another. In addition, it is necessary to consider the microbiological stability of the preparation, especially for parenteral or sterile preparations. Even though according to the literature the physical and chemical stability of drug preparations is quite far when compared to microbiological stability, the BUD time still follows the provisions of microbiological stability. For microbiological stability of sterile preparations, refer to the BUD guidelines according to revised USP <797>. The complexity of establishing BUD is of course a challenge for pharmacists in providing information and education to the public. To ensure that the information and education provided is correct, of course, pharmaceutical staff must complete with competence. Competence can be increased by participating in training related to the stability and quality of pharmaceutical preparations. In addition to sufficient competence, the number of pharmaceutical staff also needs attention. If the number of pharmacy staff is sufficient, of course the provision of information and education will go well, because officers have time to carry out and provide information correctly. Other factors such as facilities and infrastructure in information and educational services related to BUD also need to get adequate attention22. With so many factors influencing the success of providing education and information from pharmaceutical staff to the community, of course this opens up opportunities for researchers to explore further how Optimization of the provision of BUD education and information is carried out well, so that the goal of administering drugs can be achieved, namely having efficacy with guaranteed quality and safety.

CONCLUSION

Beyond use date and expiration date are two different parameters that should be listed on the packaging of the finished product. Both are parameters to ensure the quality of the product that can impact efficacy and safety for the consumers. Pharmacists or any health workers that contact directly to consumers during the medicine counseling or transfer process should explain the expiration date and beyond use date. But before the application services related to BUD, health workers also should have sufficient knowledge about that parameter. This knowledge can be obtained through seminars, training or during formal education programs. Beyond use date determination can be considered based on guidelines or in use stability study that conducted by manufacturers. Indonesian government should push this parameter to be one of the list information stated on the finished product.

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