# Supporting Statement

# Antiparasitic Drug Use and Antiparasitic Resistance Survey

# OMB Control No. 0910-NEW

**Part A. Justification**

1. **Circumstances Making the Collection of Information Necessary**

The Center for Veterinary Medicine (CVM) faces unique challenges while making decisions regarding the conditions of approval for drugs to treat and control animal parasites. Although the agency’s decisions to approve new antiparasitic drugs are based on information provided by drug companies, CVM does review the relevant antiparasitic drug resistance literature and is the final authority of the information and concerns listed in the labeling and the Freedom of Information Summary. The mission of the Office of New Animal Drug Evaluation (ONADE) within CVM is to expeditiously approve quality, safe, and effective new animal drug products through a science-based approach in a regulatory environment. We are charged with and committed to communicating with our stakeholders (including but not limited to the public/end user and industry) and understanding the forces that affect them.  Ultimately our goal is to protect human and animal health and to promote a safe and abundant food supply.

Antiparasitic drugs with demonstrated effectiveness against a broad spectrum of parasite species are vital to the animal health industry in the United States and around the world. Parasitism is detrimental to the health and welfare of domestic animals and causes significant production losses in food-producing species. The development of resistance to antiparasitic drugs poses a significant threat to the health and productivity of food-producing animals worldwide and has become a major concern among veterinarians, parasitologists, and animal owners globally. Numerous reports have documented antiparasitic drug resistance in small ruminants, cattle, and horses outside the United States over the past 15 years (Getachew et al 2007; Leathwick et al 2008; Leathwick et al 2009; Molento et al 2011; Skuce et al 2010; Sutherland and Leathwick 2010; Watson and Hosking, 1990) and more recently within the United States (Gasbarre et al 2009a,b; Edmonds et al 2010; Garretson et al 2009; Ballweber and Baeten 2011; and Wolstenholme and Kaplan 2011). The level of awareness of the issues associated with antiparasitic drug resistance, including detection and mitigation strategies, among the different sectors of the veterinary community in the United States is unknown.

We anticipate that this survey will be an important tool for us to be able to fulfill our charge to better communicate with our stakeholders and guide the development of best practices to expeditiously approve safe and effective antiparasitic drugs. While a focus group might seem ideal for asking the same questions and collecting similar information, focus groups involving a wide range of scientists and practicing veterinarians in many diverse regions would be cost prohibitive to the agency. Alternatively, a survey is more appropriate than a focus group for our concerns because it allows CVM to document individual responses to individual questions.

Survey Objectives

The survey includes specific questions designed to address the following knowledge gaps identified above:

1. The current level of awareness and concern regarding antiparasitic drug use and antiparasitic drug resistance in U.S. veterinarians and parasitologists;
2. The commonly used strategies for detecting, monitoring, and/or managing antiparasitic drug resistance; and
3. The types of information that would best assist end users in the safe and effective use of antiparasitic drugs.

In conclusion, the mission of ONADE within CVM is to expeditiously approve safe and effective, properly labeled, quality manufactured new animal drugs through a science-based approach in a regulatory environment. This collection is necessary for the proper performance of CVM’s mission because it will help CVM gather information to appropriately label antiparasitic drugs and, thereby, enhance the sustainability and continued availability of approved antiparasitic drugs. The information collection is consistent with ONADE’s mission and mandate to approve new animal drugs within the following regulatory framework:

21 CFR 514.1(b)(8), “Evidence to establish safety and effectiveness,” states that a New Animal Drug Application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the new animal drug is safe and effective for use as suggested in the proposed labeling. The effectiveness must be demonstrated by substantial evidence as defined in 21 CFR 514.4.

21 CFR 514.4(c)(3), “Other combination new animal drugs,”requires sponsors to demonstrate by substantial evidence, as defined in 21 CFR 514.4, that the combination new animal drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling and that each active ingredient or animal drug contributes to the effectiveness of the combination new animal drug.

This information collection is not related to the American Recovery and Reinvestment Act of 2009 (ARRA).

This survey was given an exemption approval under 45 CFR 46 101 (B)(2) under RIHSC number 11-020V (See attached).

1. **Purpose and Use of the Information Collection**

The purpose of this survey is to gauge the level of awareness and concern surrounding antiparasitic drug resistance issues among veterinarians using antiparasitic drugs in many types of clinical practice and production settings, as well as among academic parasitologists and scientists involved in drug research and development. The survey will investigate participants’ experiences with antiparasitic drug use in clinical practice, including the empirical use of antiparasitic drugs either individually or as combinations of existing antiparasitic drugs, as well as methods used to detect, monitor, and manage parasites and antiparasitic drug resistance. The results of the survey will help CVM’s understanding of practitioners’ and parasitologists’ perceptions of the types of information that would best assist appropriate use of antiparasitic drugs in the field to prevent or slow the development of antiparasitic drug resistance.

Information regarding how veterinarians and parasitologists decide which drugs to recommend or use or which diagnostic tools to recommend or use is important in the process of designing better labeling and education outreach programs for the sustainability of effective antiparasitic drugs. The loss of efficacious antiparasitic drugs through the development of resistance is a direct concern of CVM and can result in a measurable economic impact. For example, *Cooperia punctata* is one parasite that infects cattle. Infected cattle have been shown to consume less feed and have reduced weight gain compared to uninfected cattle (Stromberg et al 2012). In the United Kingdom, reported cases of parasitic gastroenteritis in sheep quadrupled four fold from 1975 to 2005 (van Dijk et al 2009) and financial losses due to reduced growth, coupled with treatment costs associated with gastrointestinal nematodes in lambs, were estimated to amount to ₤84 million annually to UK sheep farmers (Nieuwhof and Bishop 2005). In the NAHMS Beef 2007-2008 Survey, 82.3% of beef cattle operators either agreed or strongly agreed that intestinal parasites are a significant problem for the U.S. beef industry, 53.4% agreed or strongly agreed that internal parasites had an economic impact on the operations, and 56.7% of operators also agreed or strongly agreed that resistance to anthelmintics was a significant problem for the U.S. beef industry (USDA 2011). CVM seeks to safeguard the safety and effectiveness of approved antiparasitic drugs for all users by examining this issue in a proactive manner.

Use and Expected Outcome

The survey will be used to provide information to the agency on the perceptions in the veterinary community about the current awareness of antiparasitic drug resistance, the use patterns of antiparasitic drugs, and the measures being employed in the field to detect and slow the development of antiparasitic drug resistance.

This survey is not designed to provide data on the prevalence of antiparasitic drug resistance or frequency or amount of antiparasitic drugs used. The collection of such data would require a multi-year, multi-site study of parasite resistance and antiparasitic drug use in multiple species in diverse geographic regions throughout the country. Such a study would be prohibitively expensive, complicated, and outside the scope of this survey. However, the design of the current survey is appropriate for a descriptive qualitative study to gain insight into awareness of the issues of antiparasitic drug resistance and to provide a basis for further research and communication with our stakeholders. Using the methods described in Section B, the information will be collected, maintained, and used in a manner consistent with the Office of Management and Budget’s information quality guidelines for utility, integrity, and objectivity, as well as the agency’s own information quality guidelines.

It is important to note that this survey will not directly relate to the creation of new policies and will not be used as the sole means by which CVM makes any regulatory decision. CVM will continue to gather information from currently used sources, including scientific meetings, consultation with outside experts, and comprehensive literature searches. However, the survey will permit CVM to consider the opinions of a more diverse cross-section of the community of decision makers in veterinary parasitology regarding the current state of antiparasitic drug resistance, the use patterns of combinations of individual antiparasitic drugs, and measures being employed in the field to detect and slow the development of antiparasitic drug resistance.

1. **Use of Improved Information Technology and Burden Reduction**

The survey announcement, method of access, and instrument will use standard internet and email platforms. The CVM-authored survey (approved by Human Research Subject Committee – April 11, 2011) will be hosted by SurveyMonkey.com, LLC (“SurveyMonkey”) to decrease the burden of response for individuals and for ease of collecting and collating data. One hundred percent of responses will be collected by the use of the web-based survey. Although a relatively new tool to facilitate data collection, use of SurveyMonkey has been documented in many peer-reviewed scientific studies (Coen et al 2011; Freedman et al 2011; Hauk and Nogan 2011; Hussain et al 2010; Morgan and Worsley, 2011; Parsons et al 2006; Stefandis, Richardson and Fanelli 2010; Swaminath et al 2011).

1. **Efforts to Identify Duplication and Use of Similar Information**

This information is not being gathered elsewhere by the Federal government, nor has similar information been collected and published by any academic institution. The proposed survey is designed to elicit veterinarian and parasitologist opinions and experiences with antiparasitic drug usage to supplement other completed surveys. While the National Animal Health Monitoring System (NAHMS) has implemented surveys of producers to monitor antiparasitic drug use in beef cattle, horses, sheep, and goats (USDA 1999, 2000, 2003, 2010, 2012), there are no similar published surveys to acquire corresponding information from veterinarians or veterinary parasitologists in the United States. Other industry organizations such as American Horse Publications also perform industry-wide surveys on multiple facets of production, including antiparasitic drug use. These surveys are directed towards private owners and not veterinarians (Stowe 2010). There are some published studies of veterinary practices and recommendations in other countries outside the United States (Nielsen, Monrad and Olsen 2006). The published literature concerning antiparasitic drug use and antiparasitic drug resistance in the United States, however, is limited to studies of antiparasitic drug resistance in groups of animals and case reports of resistant parasites (*see for example* Gillespie et al 2010; Gasbarre et al 2009a,b; Grosz et al 2013; Howell et al 2008; Lyons et al 2011). Finally, the survey does not attempt to obtain the same data as that obtained through post-market surveillance and adverse event reporting. The survey is not designed to yield data or reports of adverse drug reactions, lack of effectiveness, or product defects which is obtained as part of post-market surveillance.

1. **Impact on Small Businesses or Other Small Entities**

This information collection does not involve small businesses.

1. **Consequences of Collecting the Information Less Frequently**

The information is being collected once.

1. **Special Circumstances Relating to the Guidelines of 5 CFR 1320.5**

All of the reporting requirements are consistent with 5 CFR 1320.5.

1. **Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency**

On July 13, 2012, CVM scientists and reviewers consulted with Dr. Martin Nielsen regarding CVM’s consideration of implementing a survey of veterinarians and veterinary parasitologists on the topic of antiparasitic drug use and resistance. Dr. Nielsen responded with enthusiastic support for the survey as the information that CVM hopes to acquire is not currently available and would be useful to his work. Dr. Nielsen has performed similar surveys in the past, including a survey of Danish equine veterinary practices on veterinary antiparasitic drug usage and helminth parasites. He is currently analyzing data from a web-based survey of equine owners. He concurs that response rate is an issue with surveys designed to be accessed in this manner, but stated that any bias from collecting in this manner can be adjusted for during statistical analysis.

Design and statistical analysis of the survey included consultation with subject matter experts, statisticians, and epidemiologists. Consulted individuals included:

| Table 1. Consulted individuals |  |  |
| --- | --- | --- |
| FDA/CVM |  |  |
| Name | Title | Phone Number |
| Lynne Boxer, DVM | Veterinary Medical Officer | (240) 276-8321 |
| Laura Hungerford, DVM, PhD | Senior Science Advisor, Epidemiologist | (240) 276-8232 |
| Michele Kornele, DVM | Veterinary Medical Officer | (240) 276-8355 |
| Janis Messenheimer, DVM | Supervisory Veterinary Medical Officer | (240) 276-8348 |
| Sanja Modric, DVM, PhD | Veterinary Medical Officer, Pharmacologist | (240) 276-8339 |
| Anna E. O'Brien, DVM | Veterinary Medical Officer | (240) 276-8343 |
| Aimee Phillippi-Taylor, DVM, DABVP (Equine) | Veterinary Medical Officer | (240) 276-8335 |
| Prajwal R. Regmi, DVM, PhD | Staff Fellow | (240) 276-8353 |
| Emily R. Smith, DVM | Veterinary Medical Officer | (240) 276-8344 |
| Anna Nevius, PhD | Supervisory Mathematical Statistician - Biomedical | (240) 276-8170 |
| Cynthia Bashore, DVM, MPH | Veterinary Medical Officer | (240) 276-8207 |
| Cindy L. Burnsteel, DVM | Supervisory Veterinary Medical Officer | (240) 276-8341 |
| External subject matter experts/pre-testers |  |  |
| Thomas Craig, DVM, MS, PhD | Parasitologist, Texas A&M University | (979) 845-9191 |
| Louis Gasbarre, PhD | Gasbarre Consulting, Buffalo, Wyoming | (307) 684-5292 |
| Timothy Geary, PhD | Director, Institute of Parasitology, McGill University | (514) 398-7954 |
| Ray Kaplan, DVM, PhD | Research Parasitologist, University of Georgia College of Veterinary Medicine | (706) 542-5670 |
| Dave Leathwick, PhD | Scientist, AgResearch Grasslands, Palmerston North, New Zealand | +64 6 351 8085 |
| Roger Prichard, PhD | Research Parasitologist, Institute of Parasitology, McGill University | (514) 398-7929 |
| Martin K. Nielsen, DVM, PhD | Gluck Equine Research Center, University of Kentucky | (859) 218-1103 |

During late December 2012 to January 2013, the survey was pre-tested by seven individuals. Comments received from the pre-testers resulted in minor changes to a few of the questions.

In accordance with 5 CFR 1320.8(d), FDA published a 60-day notice for public comment in the FEDERAL REGISTER dated December 3, 2012 (77 FR 71603). Nine comments were received (eight from one source).

(Comment 1) The first comment stated that the collection is not necessary for the proper performance of FDA’s functions.

(CVM Response) The mission of the Office of New Animal Drug Evaluation (ONADE) within CVM is to expeditiously approve safe and effective, properly labeled, quality manufactured new animal drugs through a science-based approach in a regulatory environment. This collection is necessary for the proper performance of FDA/CVM’s mission because it will help CVM gather information that can be used to appropriately label antiparasitic drugs and, thereby, enhance the sustainability and continued availability of approved antiparasitic drugs.

(Comment 2) The second comment stated that while assessing the current situation in the field is important, the information to be gained from the survey will have little practical utility because the data will be of opinions held by an extremely small sample size.

(CVM Response) The target population for this survey is the subset of veterinarians and parasitologists who have a direct opportunity to observe and assess the antiparasitic resistance issues in the field. CVM understands that a part of the target population, namely veterinarians with training and experience with large animals, are diminishing in numbers in some areas of the United States (https://www.avma.org/KB/Resources/Reference/Pages/Food-Supply-Veterinary-Medicine-Data-Maps.aspx). While a wider and more general sampling of veterinarians would provide a larger sample size, such sampling would then include those who have opinions on the topic of antiparasitic resistance but not direct experience with the animal populations of interest. CVM designed the survey with input from subject matter experts, statisticians, and epidemiologists to reach the largest and most representative sample of this target population. Sample size, as well as total survey error, was considered in the design.

(Comment 3) The third comment stated that there are numerous variables involved in the field; thus, measuring resistance by observational methods has questionable validity. Re-infection is a significant confounder which could mimic resistance. Resistance should be determined more scientifically, such as through a challenge model.

(CVM Response) The survey is not designed to measure antiparasitic resistance, but rather collect information from clinical experts who diagnose and treat the relevant animal populations and to provide a basis to assist CVM in the design of labeling for approved antiparasitic drug products and the design of educational outreach programs.

Data from laboratory-based, experimental models is extremely important for characterizing antiparasitic resistance. For successful translational research, both “bench” research, such as challenge models, and research from clinical or field settings, such as collecting the observations of clinicians treating and monitoring real animal patients are needed (http://commonfund.nih.gov/clinicalresearch/overview-translational.aspx).

(Comment 4) The fourth comment stated that many antiparasitic drugs are available as over-the-counter drugs. Inappropriate or inconsistent administration could produce a perceived resistance.

(CVM Response) CVM has not designed the survey to estimate the prevalence of resistance and agrees with the comment that the survey should not be used to draw conclusions about potential causes of resistance. The collection of such data would require a multi-year, multi-site study of parasite resistance and antiparasitic drug use in multiple species in diverse geographic regions throughout the country. Such a study would be prohibitively expensive and complicated and is outside the scope of this survey. However, the survey is appropriately designed to gauge the level of awareness and concern about antiparasitic drug resistance issues among veterinarians using drugs in different clinical practice and production settings, as well as among academic parasitologists and scientists involved in drug research and development. In addition, the survey is designed to investigate methods currently used by veterinarians to detect, monitor, and manage parasites and antiparasitic drug resistance.

(Comment 5) The fifth comment stated that FDA’s efforts regarding drug safety and efficacy are vital. The survey could potentially yield a small glimpse of conditions in the field; however, the information to be gathered seems to be an ill fit with post-market surveillance as well as adverse event reporting.

(CVM Response) CVM agrees that the survey should not attempt to obtain the same data as that obtained through post-market surveillance and adverse event reporting. The survey is not designed to yield data or reports of adverse drug reactions, lack of effectiveness, or product defects which is obtained as part of post-market surveillance.

Information regarding the current state of awareness and concern about antiparasitic drug resistance issues in the field is important because it will assist CVM in the enhancement of appropriate labeling for the safe and effective use of approved antiparasitic drug products. The survey is one tool in a comprehensive antiparasitic resistance management strategy within CVM which is aimed at facilitating collaboration with CVM stakeholders on the issues related to antiparasitic resistance.

(Comment 6) The sixth comment stated that recommendations regarding the management or reduction of antiparasitic resistance are aspects of medical management and preventative herd health within the practice of veterinary medicine. Such recommendations are based upon veterinary expertise combined with several factors including animal owner capabilities, animal species and health, and the parasitic risks. The respondent questioned FDA’s reasoning and intended regulatory use in gathering such information from responders, especially since such recommendations are available in scientific literature.

(CVM Response) The proposed survey is not a replacement for the review of scientific research in published literature or the recommendations of expert veterinary parasitologists. As evidenced by CVM’s recent Public Meeting on Antiparasitic Drug Use and Resistance in Ruminants and Equines (77 FR 7588, February 13, 2012; Docket No. FDA-2012-N-0102), CVM is committed to accessing and highlighting the current research associated with the development and management of antiparasitic resistance in the United States. The survey is not designed to lead to any new recommendations regarding the management or reduction of antiparasitic resistance or provide recommendations related to the practice of veterinary medicine, but rather obtain information regarding the awareness and use of a variety of available strategies for detecting, monitoring, and/or managing antiparasitic resistance. CVM will not use this information to interfere with the efforts of other organizations to provide science-based recommendations regarding the management or reduction of antiparasitic resistance. Rather, the information obtained from the survey will be used by CVM to ensure properly labeled, safe and effective antiparasitic drugs are available to veterinarians. In doing so, CVM will be providing the best array of options for veterinarians to choose from as they serve their patients and will be fulfilling its mission to protect human and animal health.

(Comments 7 and 8) Comment seven suggested that if a survey is to be done, that it be redesigned so that while it may still gather opinions, it focuses on obtaining pertinent scientific information and more accurately targets respondents possessing the appropriate expertise on this particular subject. Comment eight stated that the incorporation of a scientific literature review may be beneficial in addressing some of the questions proposed.

(CVM Response) CVM believes that there are other more appropriate ways to obtain specific scientific information regarding antiparasitic resistance, including the recent Public Meeting on Antiparasitic Drug Use and Resistance, direct consultation with experts in the field of veterinary parasitology, and a review of the vast amount of published literature available on the subject. The survey is not designed to obtain the same information; rather it is designed to obtain information on the levels of awareness and concern related to antiparasitic resistance issues among veterinarians, a key stakeholder for CVM.

1. **Explanation of Any Payment or Gift to Respondents**

There are no payments or gifts to respondents.

1. **Assurance of Confidentiality Provided to Respondents**

Information will be kept confidential in accordance with 18 USC 1905 and 21 USC 331(j), as well as section 301(j) of the Act.

The survey was provided an exemption approval by the Research in Human Subject Committee (Exemption approval #11-020V, dated April 11, 2011).

All responses will be kept confidential. No identifying information will be collected from respondents. All responses will be reported in aggregate. While the online survey instrument will store network IP addresses used to access the survey, this information is used only to determine that duplicate surveys are not completed. The IP addresses will not be included in the results obtained by FDA employees for data analysis. SurveyMonkey has a security infrastructure in place for all survey data, including procedures to address user, data center, network, storage, and organizational security, availability of data, and software usage. This includes, but is not limited to, use of Secure Sockets Layer (SSL) technology for authentication and data encryption, a staffed and surveilled SAS70 Type II certified facility, redundant IP connections, intrusion detection systems, and encrypted back up. All data are stored on servers located in the United States. A complete list of SurveyMonkey’s privacy and security procedures and policies is attached. As noted in the privacy policy, SurveyMonkey complies with the US-EU and US-Swiss Safe Harbor Frameworks developed by the U.S. Department of Commerce.

All data will be downloaded to the Agency informational technology network for storage. This information will be available to FDA ONADE employees directly involved with the project including agency employees listed in Part B, Question 5.

1. **Justification for Sensitive Questions**

This information collection does not contain questions pertaining to sexual behavior, attitude, religious beliefs, or any other matter commonly considered private or of a sensitive nature.

1. **Estimates of Annualized Burden Hours and Costs**

a. Estimated burden remains as follows:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Table 2. -- Estimated Annual Reporting Burden | | | | | |
| Portion of Study | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Average Burden per Response | Total Hours |
| Pre-test | 7 | 1 | 7 | 0.5 | 3.5 |
| Survey | 650 | 1 | 650 | 0.5 | 325 |
| Total | | | | | 328.5 |

FDA calculated the total annual responses by multiplying the number of respondents by the annual frequency. FDA calculated the total hours by multiplying the estimated hours per response (30 minutes = 0.5 hours) by the number of respondents.

12b. Annualized Cost Burden Estimate

|  |  |  |  |
| --- | --- | --- | --- |
| Type of Respondent | Total Burden Hours | Hourly Wage Rate1 | Total Respondent Costs |
| Veterinarian | 328.5 | $40.61 | $13,340 |

328.5 x $40.61 = $13,340.39.[[1]](#footnote-1) Median hourly income for veterinarians, times total hours equals total annual cost burden to respondents.

1. **Estimates of Other Total Annual Cost Burden to Respondents and Record Keepers**

There are no capital costs or operating and maintenance costs associated with this collection of information.

1. **Annualized Cost to the Federal Government**

For the fiscal years 2012 and 2013, the total cost of this information collection is $50754.75 resulting in an annualized cost to FDA of $25377.38

The annual costs were determined as follows:

FY 2012:

Overhead: $23,135

Agency staff: [($48.35 x 15 hrs) x 6 (GS13/5)] + [($57.13 x 15 hrs) x 2 (GS14/5)] + [$67.21 x 15 hrs] x 2 (GS15/5) + [($29.93 x 300 hrs) x 1 (GS11/5)] = $17,060.7

FY2013:

Cost of survey instrument: $19.95 X up to 3 months = 59.85

Overhead: $17,399

Agency staff: [($48.35 x 20 hrs) x 7 (GS13/5)] + [($57.13 x 15 hrs) x 2 (GS14/5)] + [($67.21 x 15 hrs) x 2 (GS15/5)] = $10,499.2

1. **Explanation for Program Changes or Adjustments**

This is a new collection.

1. **Plans for Tabulation and Publication and Project Time Schedule**

The survey period will begin within four weeks of OMB approval. The tabulation and analysis of the data will occur after the survey period has closed and should take approximately two months following the survey period. Within one year from completion of the data analysis, CVM will develop a research paper for publication or final report to be available through the CVM website. The target audience will be veterinarians, veterinary parasitologists, and researchers practicing in equine, food animal, and small ruminant medicine, and members of industry and the general public interested in antiparasitic drug use and resistance. The report will include methods of survey development, collection, descriptive tables of relevant study content for the overall and subgrouped data, methods of analysis, discussion of statistical significance, and comparison of study data with other published data. The data collection is descriptive in nature and appropriate methods for categorical data analysis will be utilized as determined by the data distribution. Logistic regression analysis will be performed as warranted to explore associations of study outcomes with respondent characteristics. A detailed analysis plan is included with the survey question mapping document attached.

1. **Reason(s) Display of OMB Expiration Date is Inappropriate**

Display of the OMB Expiration Date is appropriate.

1. **Exceptions to Certification for Paperwork Reduction Act Submissions**

There are no exceptions to certification.

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